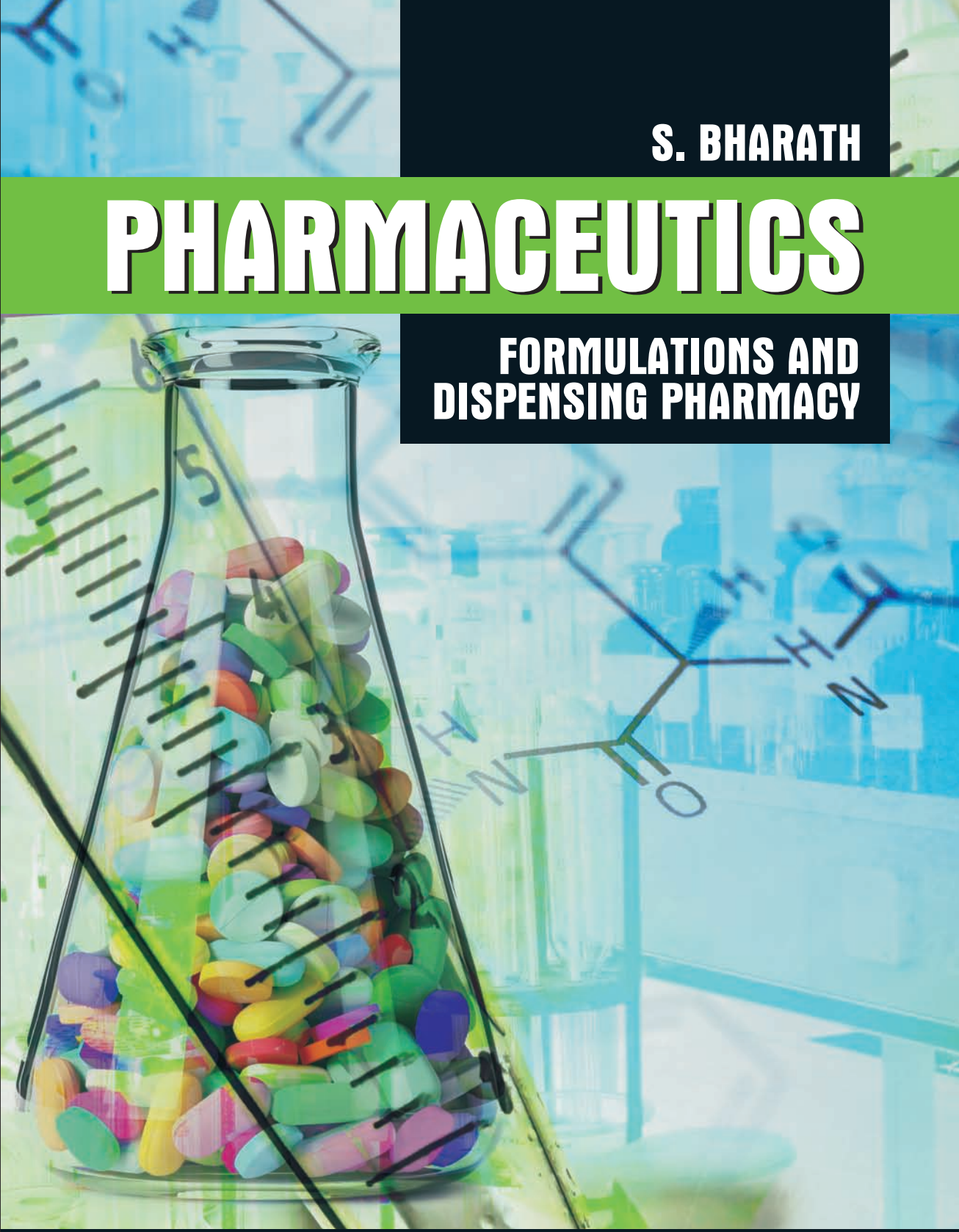
S. BHARATH

PHARMACEUTICS

FORMULATIONS AND DISPENSING PHARMACY



ALWAYS LEARNING

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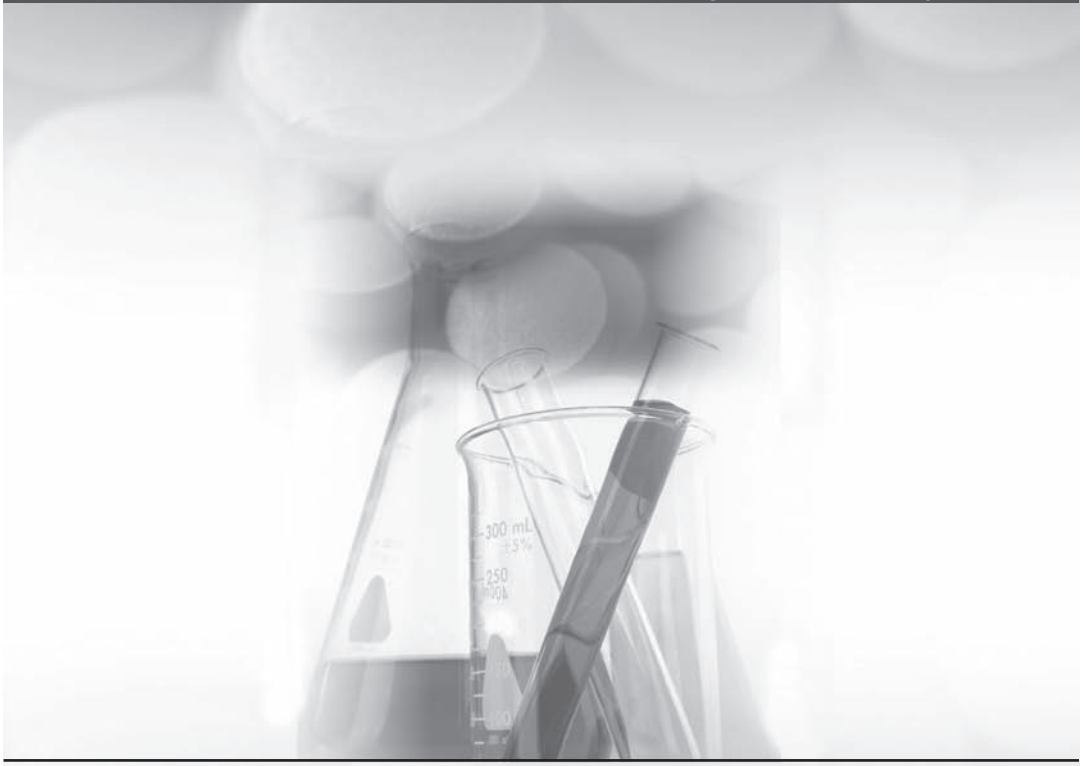
Pharmaceutics

Formulations and Dispensing Pharmacy



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Preface

Pharmaceutics is the art and science of preparing and dispensing dosage forms safely and effectively to patients. The overall effectiveness of a formulation is determined by stringent application of fundamental aspects ranging from the basics of prescription reading to patient acceptance of medications. Formulation designing and dispensing is a discipline that provides a better and cost-effective drug therapy to the convalescent community, making pharmacy an indispensible arm of the health sciences.

The pharmacy profession has grown by leaps and bounds, with great improvements in drug-manufacturing technologies. Likewise, pharmacy education has also been continuously upgraded to suit current professional needs.

Pharmaceutics: Formulations and Dispensing was conceived after reviewing the pharmacy curriculum provided by different universities across the country. It aims to sensitize the students of pharmacy to the core concepts of pharmaceutics and impart integrated information on converting a drug into suitable dosage forms. The book provides elaborate information on the fundamental theoretical aspects of various dosage forms while presenting the concepts in a simple and lucid language to enable students gain a firm foundation in the subject.

I am confident that this book, spread across 12 chapters, will cater to the academic needs of pharmacy graduate students of most Indian universities. The chapters on prescription, posology, solid dosage forms, liquid dosage forms and semisolid dosage forms have been dealt with comprehensively. Likewise, the chapters on sterile dosage forms, surgical aids, herbal formulations and aerosol technology give a deep insight into the role of these specifics in therapy.

I place on record the valuable contribution of my co-authors and research scholars for their literary help. I am indebted to the authors and editors of the various books and scientific articles that I have used for reference while writing this book. I thank Dr V. Madhavan, Principal, M. S. Ramaiah College of Pharmacy, for his encouragement and moral support. I am obliged to the ever-supporting and inspiring management of Gokula Education Foundation (Medical). I appreciate the immense interest and commitment of the team at Pearson Education, which contributed to make this venture a big reality. Special thanks to Ms. Dheepika and Ms. Pavithra.

There is always a scope for improvement, and I welcome the valuable comments and recommendations from readers for better structuring of the subsequent editions.

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Introduction to Pharmacy

The term pharmacy is derived from the Greek word *pharmakon,* which means "medicine" or "drug." Pharmacy can be defined as the art and science of preparing and dispensing medications and providing drug and related information to the public. The concept of pharmacy involves interpreting prescription, compounding, labeling and dispensing drugs and drug-related devices, counseling and monitoring the patients by giving important information related to the usage of the medicament.

Pharmacy in the field of the health profession links chemical sciences with the health sciences, and it ensures safe and effective use of the pharmaceutical drugs.

The present approach of professional practice in a rational way is referred as "pharmaceutical care." According to this concept, an important role of the pharmacists is "the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve patient's quality of life."

DRUGS IN THE HUMAN LIFE

Learning Objectives

- Introduction to pharmacy profession
- Importance of pharmacists
- Introduction, scope and progress of the pharmacy profession in the world

Human beings always have an intense urge of treating physical and mental ailments. From the time of evolution of human beings, an existing practice is identification of active constituents, collection, processing and incorporation into suitable dosage forms. Drugs have made the human life better and longer. They have played a vital role in scientific discovery, arts, commerce and political thinking of mankind. Medicaments such as antibiotics, chemotherapeutic agents, insulin, etc., have saved people and kept them alive from fatal diseases.

PREHISTORIC PHARMACY

In the prehistoric time, the use of medicinal plants was frequent and on daily basis. The earliest known compilation of medicinal substances as per Ayurveda was the *Sushruta Samhita*. There are evidences supporting the fact that prehistoric people used extracts from plants for medicinal purposes. The knowledge of the plant extracts as a healing substance grew among people and was widespread among the folks. Thus, drugs were regarded as both simple tool and special substances with nearly supernatural powers. Even though early people discovered only a few effective drugs, the concept of influencing bodily functions via an outside force or source must be considered as one of the humanity's greatest achievements. The further progression of this concept required the explorative skills of civilization. To survive, rational medical therapy was needed and the required tools were provided by defined domains—writing, systems of exchange, weights and measures.

PREHISTORIC TIME

In the prehistoric era, there were evidences of pharmacists being respected more than the physicians. In the highly stable hierarchy of royal family of Japan (538–710 B.C.), the pharmacists were assigned superior status when compared to physicians and acupuncturists. Records from the Egyptian medical practices indicate sophisticated pharmaceutical techniques, where many descriptive formulae were used for compounding dosage forms. Drugs from the plant sources, laxatives and enemas were used more prominently.

The expertise of Theophrastus, a student of Aristotle, in combining information from scholars, root diggers, midwives and traveling physicians was emulated 300 years later by Dioscorides. The collected information became the physician's summary of knowledge and the standard encyclopedia of drugs known as *Materia Medica*.

Galen, a Greek physician, practiced pharmacy in Rome in the second century A.D. He devised a treatment that attempted to balance the tumors of an individual who is ill by using drugs that have contrary nature, for example, treating an external inflammation by the use of cool and wet drug galenicals and liquid extract of different drugs obtained from natural source. The influence of Galen was so strong that his basic healing approach guided the commoners in their own treatment of ailments.

REVIVAL OF PHARMACY IN EARLY MODERN WORLD

A series of change in radical events were resulted during the European middle ages because of Renaissance. New drugs were introduced into the modern world, which removed the outdated concepts of Galen. With the invention of printers, the medical and pharmaceutical concepts and works were printed. The printing had an important effect for the growth of pharmacy, by illustrating the study of the natural drugs during this period. This era also led to the publication of pharmacopoeias with the cooperation of government bodies.

The scientific contributions by the pharmacists helped in the elevation of the image of pharmacists in the society during the nineteenth century. A major shift over occurred during this period in different professions, and conflicts and court cases erupted during the same time. Confusions and misunderstanding within the British health community, led to the development of American profession of pharmacy.

PHARMACY IN INDIA

The Indian traditional systems of medicine have been Ayurveda, Siddha and Unani. Ayurveda and Siddha originated in India, whereas Unani, the Greco-Arabic medical system, came from West Asia. The European colonizers brought the western system of medicine to the country. During the colonial period, the new pharmacy system, referred to as allopathy got firmly established. After independence, many investigators chose to explore the history of modern pharmacy in India and related aspects of the span covering the last several centuries.

The earliest pharmaceutical companies in India are Bengal Chemicals, East India Pharmaceutical Works Limited, IDPL, etc., which exist even today as one of the five government-owned drug-manufacturing units. The government started to encourage the growth of drug manufacturing by Indian companies in the early 1960s, along with the implementation of Patents Act in 1970. The industry oriented pharmaceutical research started in late 1980s, with the support from the University Grants Commission, New Delhi and subsequently sponsorship continued from the Indian National Science Academy, New Delhi.

However, economic liberalization in 90s enabled the growth of the industry to become what it is today. The Patent Act removed the composition patents from food and drugs. Though it retained process patents, the duration was shortened to a period of five to seven years. The lack of patent protection made the Indian market undesirable to the multinational companies that had dominated the market and they streamed out. Indian companies carved a niche in both the Indian and world markets with their expertise in reverse engineering, yielding new processes for manufacturing drugs at low costs. Although some of the larger companies have taken initiative towards drug innovation, the industry as a whole has been following this business model until the present.

DIFFERENT PHARMACY PRACTICE AREAS

Learning Objective

- Different types and areas of pharmacy profession across the globe

Clinical Pharmacy

The pharmacists who are involved with direct patient care services dealing with use of medication, promoting health and disease prevention are called as clinical pharmacists. The practice of clinical pharmacy began with clinics and hospitals. For a better drug therapy and improved patient care, clinical pharmacists should have coordination with physicians and nurses in various medical and surgical areas. Clinical pharmacists are now an integral part of the interdisciplinary approach to patient care.

Hospital Pharmacy

The pharmacies located within the hospital premises, are hospital pharmacies. The pharmacists in hospital pharmacies deal with clinical management issues when compared to community pharmacies. The hospital pharmacists have a broad horizon where they deal with complex factors related to medications such as specific indications, effectiveness of treatment regimens, safety of medications and patient compliance issues.

Hospital pharmacies usually stock a larger range of dosage forms, including more specialized medications, than would be feasible in the community pharmacy setting. Most hospital medications are unit-dose or a single dose of medicine. There are also trained pharmacy technicians who compound non-sterile and sterile products for patients including total parenteral nutrition (TPN). This is a complex process that requires adequate training of personnel, quality assurance of products and adequate facilities. Several hospital pharmacies also outsource high-risk preparations and some other compounding functions to specialized manufacturing companies.

Community Pharmacy

Community pharmacies usually consist of a retail store with a dispensary where medications are stored and dispensed. The dispensary is subject to pharmacy legislation with requirements for storage conditions, compulsory texts, equipment, etc., as specified in legislation. All pharmacies, practicing community pharmacy should have qualified and trained pharmacists. A community pharmacist should spend more time in communicating with patients who have drug-related issues.

Consultant Pharmacy

Consultant pharmacy practice focuses more on medication regimen review than on the actual dispensing of drugs. The consultant pharmacists work in nursing homes and some medical and paramedical institutions. They are independent working professionals and as per the recent trends, the consultant pharmacists work directly with patients.

Compounding Pharmacy

Compounding pharmacy deals with preparing and converting the drugs in to a suitable dosage form which is more acceptable to the patients. If the patients come across any kind of inconvenience with the drug form, then those drug forms can be modified to make it more convenient for the patients. The pharmacists in compounding pharmacies should have more theoretical knowledge and practical skills in modifying drug dosage form.

Internet Pharmacy

Internet pharmacies or online pharmacies are practiced worldwide. These pharmacies serve the patients online. Patients or customers find this method more convenient than traveling all along to a medical store. Moreover, privacy is maintained in this method, whereas in a medical store, the presence of other customers may embarrass the patient while revealing the name of the medications.

Most internet pharmacies sell prescription drugs and require a valid prescription by the medical practitioner. However, some patients prefer taking medications from internet pharmacy without a valid prescription. This practice has been strongly criticized as potentially dangerous with the possibility of patients developing a self-medication habit.

Nuclear Pharmacy

Nuclear pharmacy deals with the use of radioactive substances for diagnostic tests and for treatment of certain diseases. The pharmacists who deal with nuclear pharmacy should undergo specialized training in handling the radioactive substances.

Veterinary Pharmacy

Veterinary pharmacies are for keeping a stock of medicines used for animal use. They fall into the categories of retail pharmacy, hospital pharmacy, etc. Veterinary pharmacies and products comply with regulations on veterinary medicines and are not for human use.

MAJOR PHARMACEUTICAL AND MEDICAL SYMBOLS

Learning Objective

- An explanation of different signs and symbols used in pharmaceutical and medical field

The following are some of the major pharmaceutical and medical symbols:

1. **The Recipe:** It has been suggested that the recipe sign (Figure 1.1) is the astronomical sign of the planet Jupiter, the Greek god of healing. The sign appears at the start of prescriptions. The sign is universally accepted as abbreviation of the Latin word *recipe*, which means "take thou."

Figure 1.1 Recipe

2. **The Mortar and Pestle:** It is the basic tool of pharmacy used in preparation of several formulations (Figure 1.2). It has long been used as a pharmaceutical symbol in Britain.

Figure 1.2 Mortar and Pestle

3. **The Green Cross:** The Royal Pharmaceutical Society of Great Britain declared the Green Cross (Figure 1.3) as a symbol for British pharmacy and was used after 1984.

Figure 1.3 Green Cross

4. **The Serpent of Epidaurus on the Staff of Asclepius:** Asclepius was one of the Greek gods of medicine, usually depicted carrying a staff with a snake coiled around it. The snake symbolizes wisdom, immortality and healing. The serpent of Epidaurus on the staff of Asclepius is shown in Figure 1.4.

Figure 1.4 Epidaurus on the Staff of Asclepius

5. **The Bowl of Hygeia with the Serpent of Epidaurus:** The bowl with a snake coiled around it is called the *bowl of Hygeia with the serpent of Epidaurus* (Figure 1.5). Hygeia was the daughter of Asclepius, the god of medicine. While Asclepius was directly associated with healing, Hygeia was associated with the prevention of sickness and continuation of good health. She was considered as the divinity of health, cleanliness and sanitation.

Figure 1.5 Bowl of Hygeia with the Serpent of Epidaurus

6. **The Caduceus:** It is the symbol of two snakes on a staff containing wings (Figure 1.6). Since the nineteenth century, it has been adopted as a symbol of medicine in the West. The wings on the staff is that of Hermes, Greek god of commerce.

Figure 1.6 Caduceus

7. **The Serpent around a Palm Tree:** This symbol was introduced in the nineteenth century and was used by French and Portuguese pharmaceutical bodies. The palm tree represents the kingdom of vegetables, the snake represents the animal kingdom and the rocks at the base of the palm tree represent the mineral kingdom. The serpent around a palm tree is shown in Figure 1.7.

Figure 1.7 Serpent Around a Palm Tree

8. **The Carboy:** The term carboy (Figure 1.8) was originated from the Persian word *qarabah*, meaning "large flagon." It is a glass vessel with a globular base tapering to a narrow neck, filled with differently colored liquids. It was showcased in pharmacy shop windows.

Figure 1.8 Carboy

REVIEW QUESTIONS

Answer in Detail

1. Explain in detail the origin and history of pharmacy.

Answer in Brief

1. Write a note on the evolution of Indian pharmaceutical industry.
2. Explain the development of pharmaceutical industry in India.
3. Discuss the different signs and symbols related to pharmacy field.
4. Explain the importance of different signs used in the medical field.

Answer in One or Two Sentences

1. Write in brief about the evolution of pharmacy in India.
2. Write a brief note on compounding pharmacy.
3. List the major pharmaceutical and medical symbols.
4. Write in brief about mortar and pestle as a sign in pharmacy.

Multiple Choice Questions

1. The earliest pharmaceutical companies in India are _____.
   (a) Bengal Chemicals (b) IDPL
   (c) East India Pharmaceutical Works Limited (d) All of these
2. Which one of the following is not among the pharmacy practice areas?
   (a) Hospital pharmacy (b) Nuclear pharmacy
   (c) Internet pharmacy (d) Mobile pharmacy

3. Compounding pharmacy is _____.
   (a) the practice of pharmacy online
   (b) the use of radioactive substances for treatment
   (c) preparing and converting the drug into dosage form
   (d) consisting of retail store to dispense medication
4. The Greek god of medicine depicted carrying a staff with a snake coiled around it is _____.
   (a) the bowl of Hygeia
   (b) the serpent of Epidaurus on the staff of Asclepius
   (c) the Caduceus
   (d) the recipe
5. The term derived from the Greek word *pharmakon* is _____.
   (a) medicine (b) drug (c) *drogue* (d) pharmacy

ANSWERS TO MULTIPLE CHOICE QUESTIONS

1. (d) 2. (d) 3. (c) 4. (b) 5. (d)

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Prescription

2

Prescription is a written order issued by a registered medical practitioner, physician, dentist, or veterinarian or any other licensed practitioner to dispense or supply a specific medication at a particular time. The prescription order is a part of the professional relationship between the prescriber, pharmacist, and patient.

ROLE OF A PHARMACIST

Learning Objective

- Role of a pharmacist in filling a prescription

A pharmacist has the following responsibilities:

1. Be accurate in manual aspects of filling the prescription order.
2. Provide the patient with necessary information related to the prescribed medication to ensure the patient's compliance.
3. Advise the prescriber of drug sensitivities and medication history of the patient in order to ensure the effectiveness and safety of the prescribed medication.
4. Maintain appropriate records of health status and medication history of the patients.
5. Maintain secrecy about the patient's medication and illness.

OTC DRUGS AND PRESCRIPTION DRUGS

There are two broad legal classifications of medicines:

Learning Objective

- Over-the-counter drugs and prescription drugs

1. Non-prescription/over-the-counter drugs, which may be purchased without a prescription
2. Prescription drugs or medications, which may be dispensed legally only if prescribed. These drugs are regulated by legislation to require a medical prescription.

Prescriptions are written by the prescriber and given to the patient for presentation at the pharmacy. They may also be communicated directly over telephone to the pharmacist. Prescriptions received orally on telephone must be written down immediately.

FORM OF A PRESCRIPTION ORDER

Prescriptions are usually written on printed forms that contain blank spaces for the required information. These forms are called prescription blanks. Figure 2.1 is an example of a prescription blank.

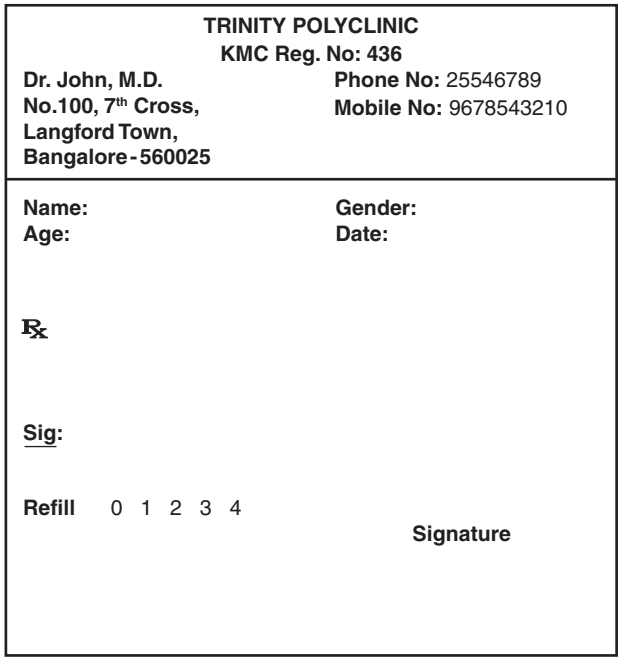

Figure 2.1 Prescription Blank

Prescription blanks are imprinted with the name of the physician, address and telephone number of the practice site, for example, hospital or clinic, and the Medical Council registration number and other relevant information of the physician.

PARTS OF A PRESCRIPTION

Learning Objectives

- Different parts of a prescription and their significance
- Latin terms used in prescription writing

The following are the parts of a prescription:

1. Prescriber's information (address, contact numbers, and other relevant information)
2. Patient information

3. Date
4. Superscription
5. Medication prescribed or inscription
6. Subscription
7. Signa or Signatura
8. Renewal or refilling instructions
9. Prescriber's signature

Patient Information

It includes the name, age, sex, and address of the patient. It is important to check the age of the patient to ensure that the prescribed dose is correct. Weight can also be mentioned to calculate the appropriate dose.

Date

Prescriptions are dated at the time of writing them. It is an important factor in establishing the medication record of the patient. Date is also important to a pharmacist in filling prescriptions for controlled substances. It helps to prevent the patient from producing the prescription repeatedly at later dates.

Superscription

This is denoted by the symbol ℞, which is an abbreviation of the Latin verb "recipe," meaning "take thou" or "you take." Some historians believe the symbol originated from the sign of Jupiter, the god of healing. It was the custom of the Roman physicians to begin a prescription with an invocation to Jupiter to bless their remedies.

Inscription

This is the body or principal part of the prescription order. It includes the medication prescribed and contains the names and quantities of the prescribed drugs. Today, a majority of prescriptions are written for medications that are already formulated into dosage forms by industrial manufacturers. The medications may be prescribed under their brand names or generic names. Pharmacists are required to dispense the trademarked product when prescribed, unless the substitution of an equivalent product is permitted by the prescribing physician and the patient.

Prescription orders requiring the pharmacist to mix the ingredients are termed as compounded prescriptions. Such prescriptions contain the names of the ingredients and their quantities. The quantities of ingredients used may be indicated in metric or apothecary system of weights and measures.

Subscription

This part of the prescription contains directions to the pharmacist for preparing the prescriptions and for dispensing them. In a large majority of prescriptions, the subscription merely serves to indicate the

dosage form (tablets, capsules, syrup, etc.) and the number of dosage units to be supplied. The following are a few examples of directions to the pharmacist:

M. ft. caps. d.t.d. no. xxiv (Mix and make capsules. Dispense 24 such doses.)
Ft. sup. no. xii (Make 12 suppositories.)
M. ft. ung. (Mix and make an ointment.)

Signatura

This is usually abbreviated as "Signa" or "Sig," meaning "mark thou." In this portion of the prescription, the prescriber indicates directions to the patient regarding the use of the medication. The directions are usually written using abbreviated forms of English or Latin terms or in combination (see Table 2.1). The directions are transcribed by the pharmacist onto the label of the container of the dispensed medication. It is advisable for the pharmacist to reinforce the directions to the patient while dispensing the medication.

Table 2.1 Some Important Latin Terms and Abbreviations

Latin Term	*Abbreviation*	*English Meaning*
	Dosage Forms	
Auristillae	auristill.	Ear drops
Capsula	caps.	Capsule
Capsula amylacea	caps. amylac.	Cachet
Cataplasma	cataplasm.	Poultice
Charta	chart.	Powder
Collutorium	collut.	Mouthwash
Collyrium	collyr.	Eye lotion
Cremor	crem.	Cream
Emplastrum	emp.	Plaster
Emulsio	emul.	Emulsion
Gargarisma	garg.	Gargle
Gelatina	gelat.	Jelly
Guttae	gtt.	Drops
Haustus	ht.	Draught
Inhalatio	inhal.	Inhalation
Injectio	inj.	Injection
Insufflatio	insuff.	Insufflation
Linctus	linct.	Linctus
Linimentum	lin.	Liniment

(*Continued*)

Table 2.1 Continued

Latin Term	*Abbreviation*	*English Meaning*
	Dosage Forms	
Liquor	liq.	Solution
Lotio	lot.	Lotion
Mistura	mist.	Mixture
Naristillae	narist.	Nose drops
Nebula	neb.	Spray
Oculentum	oculent.	Eye ointment
Pasta	past.	Paste
Pessus	pess.	Pessary
Pilula	pil.	Pill
Pulvis	pulv.	Powder
Suppositorium	suppos.	Suppository
Tabella	tab.	Tablet
Unguentum	ung.	Ointment
Vapor	vap.	Inhalation
	Method of Administration	
Addendus	addend.	To be added
Applicandus	applicand.	To be applied
Capiendus	capiend.	To be taken
Dandus	dand.	To be given
Deglutiendus	deglut.	To be swallowed
Infricandus	infricand.	To be rubbed in
Inhaletur	inhal.	Let it be inhaled
Instillandus	Instilland.	To be dropped in
Miscendus	miscend.	To be mixed
Signa	sig.	Label
Sugendus	sugend.	To be sucked
Sumendus	sum.	To be taken
	Time of Administration	
Semel in die	sem.in die	Once a day
Bis in die	b.i.d.	Twice a day
Ter in die	t.i.d.	Three times a day
Quater in die	q.i.d.	Four times a day

(*Continued*)

Table 2.1 Continued

Latin Term	*Abbreviation*	*English Meaning*
	Time of Administration	
Primo mane	prim.m.	Early in the morning
Omni mane	o.m.	Every morning
Jentaculum	jentac.	Breakfast
Prandium	prand.	Dinner
Nocte	n.	At night
Omni nocte	o.n.	Every night
Omni hora	o.h.	Every hour
Anti cibos	a.c.	Before meals/food
Post cibos	p.c.	After meals/food
Inter cibos	i.c.	Between meals/food
	Parts of the Body	
Dexter	dext.	Right
Laevus	Laev.	Left
Part affectae applicandus	p.a.a.	To be applied to the affected part
Brachio	brach.	To the arm
Capiti	capiti.	To the head
Cruri	–	To the leg
Sterno	stern.	To the chest
Auri	auri	To the ears
Gutturi/Jugulo	gutt./jug.	To the throat
Naso	–	To the nose
Oculus	ocul.	To the eye
	Other Terms	
Mitte	mitt.	Send
Phiala prius agitata	p.p.a	Shake the bottle before use
Mitte Tales	miit. tal.	Send such
Dolore urgente	dol. urg.	When pain is severe
Modo dicto	m.d.	As directed
Pro re nata	p.r.n.	Occasionally
Statim	stat.	Immediately. At once
Tussi urgente	tuss. urg.	When cough is troublesome

Renewal or Refilling Information

The number of authorized refills should be indicated on each prescription by the prescriber. This is especially important for prescriptions containing narcotic and habit-forming drugs to prevent their misuse.

Signature of the Prescriber

This is a necessary part of the prescription and is required to validate the prescription order.

Figure 2.2 shows an example of a model prescription.

TRINITY POLYCLINIC
KMC Reg. No: 436

Dr. John, M.D.
No.100, 7th Cross,
Langford Town,
Bangalore - 560025

Phone No: 25546789
Mobile No: 9678543210

Name: Ms. Ann **Gender:** Female

Age: 21 yrs **Date:** 17/01/2012

℞

Paracetamol tablets-500mg

Dispense 4 tablets

Sig: Take one tablet every 4 hours or when pain is severe.

Refill 0 1 2 3 4 5

Signature

Figure 2.2 A Model Prescription

PROCESSING THE PRESCRIPTION ORDER

Learning Objective

- Different steps involved in processing a prescription order

The primary responsibility of a pharmacist is to safely and properly dispense medication to the patients. The manner in which a pharmacist processes a prescription order is an important aspect of his/her professional responsibilities. The important steps in processing a prescription order are described as follows:

1. **Receiving the prescription:** It is desirable that the patient present the prescription to the pharmacist directly. This enhances the patient–pharmacist relationship. The individual receiving the

prescription should be trained to accept the prescription in a professional manner. While receiving or reading the prescription, the pharmacist should not show any signs of confusion or surprise, as it may cause anxiety in the patient.

2. **Reading and checking the prescription:** The prescription order should be read completely and carefully in the privacy of the prescription department. Any doubt regarding the prescription should be cleared by consulting a fellow pharmacist, the prescriber, or even by checking the posological table.

   A pharmacist should never guess the meaning of a distinct word or unrecognized abbreviation. If any important data is omitted, it should be verified by contacting the prescriber.

   Sometimes, the prescriptions are received by a senior pharmacist over telephone. In such cases, the prescription should be immediately written down and should be verified by repeating it. This is important because there are a number of drugs with the same pronunciation, for example, Digoxin and Digitoxin.

3. **Collecting and weighing the ingredients:** Once the procedure for the formulation is decided, the pharmacist assembles the necessary materials in a single location on the prescription counter. As each ingredient is used, it is transferred to another location away from the workstation. The use of this technique provides the pharmacist with a mechanical check on the introduction of each ingredient.

   Through this process, the pharmacist has the opportunity to read the label of each ingredient three times—once when the container is removed from the shelf, again when the contents are weighed and measured, and finally when the container is returned to the shelf.

4. **Preparing the prescription:** After reading and checking the prescription, the pharmacist should decide on the exact procedure to be followed in dispensing or compounding the ingredients.

   Most prescriptions call for dispensing medications already formulated into dosage forms by pharmaceutical manufacturers. Care must be exercised by the pharmacist to ensure that the product dispensed is of the prescribed dosage form, strength, and number of dosage units.

   The pharmacist should verify the manufacturer's label by comparing it with the prescription order before and after filling the order to ascertain its correctness. Products that show signs of poor manufacturing, have undergone deterioration, or have crossed the expiry date as stated on the label should never be dispensed.

   For prescriptions that need compounding, the pharmacist must acquire and maintain the knowledge and skills necessary to accurately prepare them. The pharmacist should also take into consideration the compatibility of all the ingredients, the right order of mixing, the need for special adjuvants/additives or techniques, and the mathematical calculations to be followed.

   Any calculations or compounding information that would be useful in refilling the prescription at a later date should be noted on either the face or back of the prescription order. The adjuvants used in the formulation, order of mixing, quantity of each ingredient, capsule size used, type and size of the container, name and product identification number of the manufacturer, auxiliary labels used, clarification of illegible words or numbers, price charged, and any special notations should be recorded. Failure to do this may result in difference in the appearance of the prescription when refilled and possibly create doubt and apprehension in the mind of the patient.

5. **Packaging:** In filling a prescription, the pharmacist may select a container from among various shapes, sizes, mouth openings, colors, and compositions. Selection is based primarily on the

type and quantity of medication to be dispensed and the method of its use. Table 2.2 illustrates a few examples for container selection.

Table 2.2 Types of Containers for Different Products

Type of Container	*Type of Product*
Round vials	Solid dosage forms such as tablets and capsules
Prescription bottles	Liquids of low viscosity
Wide-mouthed bottles	Bulk powders, large quantities of tablets and capsules, and viscous liquids
Dropper bottles	Ophthalmic, nasal, ear, or oral liquids to be administered by drop
Ointment jars and collapsible tubes	Semisolids such as creams and ointments

Most of the prescription containers are usually available in colorless or amber-colored glass or plastic containers. However, amber-colored containers are most widely used because they provide maximum protection to their contents against photochemical deterioration.

6. **Labeling:** The prescription label is usually prepared by the pharmacist. The label should be aesthetic and professional in appearance. The size of the label should be appropriate to the size of the container and should be written or typed in indelible ink.

   The label contains the following information:

   - Name and address of the pharmacy
   - Prescription number
   - Prescriber name
   - Patient's name, directions for use, and the date of dispensing

   Directions should be written as clearly as possible. Auxiliary labels should be used to emphasize a number of important aspects of the dispensed medication, including its proper use, handling, storage, refill status, necessary warnings, or precautions. Figure 2.3 gives a few examples of auxiliary labels.

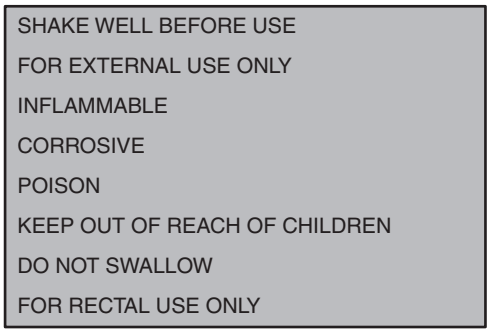

Figure 2.3 Auxiliary Labels

7. **Rechecking:** Every prescription should be rechecked and the ingredients and amounts verified. All details on the label should be rechecked to verify the directions given, patient's name, prescription number, date, and prescriber's name.
8. **Dispensing and patient counseling:** While delivering the prescription to the patient, the instructions on the label should be reinforced to the patient.
9. **Recording and filing:** A record of all the dispensed prescriptions should be maintained in the pharmacy by using prescription files.

PRICING THE PRESCRIPTION

Learning Objective

- Different methods used for calculating the price of a prescription

The pharmacist should effectively manage the financial aspects of his/her practice. Each pharmacy should have a method for pricing prescriptions, which is applied by every pharmacist practicing in that pharmacy. A pricing method that ensures profitable operation of the prescription department should be established.

The cost applied to the prescription should cover the following:

1. Cost of ingredients, including the container and label
2. The time devoted by the pharmacist
3. Cost of inventory maintenance and other operational costs of the department
4. A reasonable margin of profit on investment

Pricing Schedules

The following are the most common methods of pricing:

1. **Percentage markup:** In this method, the price is calculated as follows:

   Cost of ingredients + (cost of ingredients × percentage markup) = Dispensing price

   The desired percentage markup is taken of the cost of the ingredients and added to the cost of the ingredients to obtain the dispensing price. For example, if the ingredients in a prescription cost ₹100 and if the pharmacist wishes to apply 40% markup on the cost, he/she would add ₹40 to the cost of the ingredients and the dispensing price would be ₹140.

   The percentage markup applied may be varied depending on the cost of the ingredients. Lower markup is generally used for prescription items of higher cost and higher markup for ingredients of lower cost.

2. **Percentage markup + minimum fee:** According to this method, the price is calculated in the following manner:

   Cost of ingredients + (cost of ingredients × percentage markup)
   + minimum fee = Dispensing price

Here, a minimum fee is added to the cost of ingredients apart from a percentage markup. The markup used in this method is generally lower than the one used in the percentage markup method.

A minimum fee is established to recover the combined cost of the container, label, overhead, and professional services. Overhead expenses include rent, heater, refrigeration, electricity, taxes, insurance, depreciation on equipment, deterioration of drugs, interest on investment, delivery service, and other miscellaneous expenses. In computing the average overhead cost per prescription, the total overhead expenses of the prescription department are divided by the total prescription dispensed over a specific period of time. It is computed annually.

3. **Professional fee:** The pricing of a prescription in this method is as follows:

   Cost of ingredients + professional fee = Dispensing price

   This method involves the addition of a specified professional fee to the cost of the ingredients used in filling a prescription. The professional fee includes the dispensing cost and professional remuneration. A true professional fee is independent of the cost of the ingredients. Some pharmacies use a variable or sliding professional fee method. Here, the magnitude of the fee is varied with the cost of the ingredients.

   A common fee for all prescriptions is the true basis of the professional fee method. The fee represents payment for the professional service rendered in filling a prescription and is the same irrespective of the cost of the ingredients.

   A pharmacy may determine its professional fee by averaging the amount previously charged, above the cost of the ingredients, for prescriptions dispensed over a specific period of time or by using the cost analysis method.

4. **Summation:** In this method, the pricing is determined as follows:

   Sum of all costs + profit = Dispensing price

   Each component cost is determined individually for each prescription and totaled. This equals the break-even point. To this, a profit is added to obtain the dispensing price. The method is equitable and economical, but it has the disadvantage of being complicated, cumbersome, and time-consuming.

REVIEW QUESTIONS

Answer in Detail

1. List the different parts of a prescription with their significance.
2. Give a detailed description of the handling of a prescription order.
3. Explain the different pricing schedules used in calculating the price of a compounded medication.

Answer in Brief

1. Draw a neat labeled diagram of a prescription.
2. What is the role of a pharmacist in filling a prescription order?
3. Write a few Latin terms and their abbreviations used in prescriptions.

Answer in One or Two Sentences

1. What are OTC drugs?
2. What are prescription drugs?
3. What is the role of a pharmacist in filling a prescription?
4. What is the significance of inscription in a prescription?
5. What is the significance of subscription in a prescription?
6. What is the significance of signatura in a prescription?
7. Give the English meaning for the following:
   (a) Cremor (b) Cataplasma (c) Haustus (d) Charta
   (e) Mistura (f) Pulvis (g) Addendus (h) Applicandus
   (i) Sumendus (j) Bis in die (k) Ter in die (l) Post cibos
   (m) Nocte (n) Mitte (o) Statim
8. What is the significance of renewal or refilling information in a prescription?
9. What is the importance of choosing a suitable container in packaging the product?
10. Give examples for some auxiliary labels.
11. List the different pricing schedules used in pricing of a prescription.

Multiple Choice Questions

1. Drugs that can be obtained without a prescription are called _____.
   (a) prescription drugs (b) physician samples
   (c) OTC drugs (d) placebo
2. Drugs dispensed only if prescribed are called _____.
   (a) prescription drugs (b) nonprescription drugs
   (c) pediatric formulations (d) veterinary drugs
3. The part of the prescription that means 'take thou' is _____.
   (a) subscription (b) inscription
   (c) superscription (d) signatura
4. The part of the prescription that contains the medication prescribed with their quantities is _____.
   (a) signatura (b) inscription
   (c) subscription (d) superscription
5. The part of the prescription containing the directions to the pharmacist regarding the preparation of the medication is _____.
   (a) procedure (b) subscription
   (c) inscription (d) superscription
6. Signatura contains _____.
   (a) directions to the pharmacist (b) directions to the physician
   (c) directions to the patient (d) signature of the prescriber
7. 'Cataplasm' is a _____.
   (a) draught (b) capsule (c) cream (d) poultice
8. 'Haustus' is a/an _____.
   (a) mouthwash (b) gargle (c) draught (d) inhalation

9. ‘Charta’ means _____.
   (a) powder (b) injection (c) linctus (d) insufflations
10. ‘Auristill’ is a/an _____.
   (a) powder (b) injection (c) linctus (d) eardrops
11. ‘Nebula’ is a/an _____.
   (a) spray (b) injection (c) linctus (d) insufflations
12. ‘Twice a day’ is abbreviated as _____.
   (a) b.i.d (b) q.i.d (c) t.i.d (d) sem.in.die
13. ‘Before meals’ is abbreviated as _____.
   (a) Anti cibos (b) Post cibos (c) Inter cibos (d) Omni hora
14. ‘After meals’ is abbreviated as _____.
   (a) Anti cibos (b) Post cibos (c) Inter cibos (d) Omni hora
15. Dropper bottles are preferred for _____.
   (a) topical preparations (b) ophthalmic preparations
   (c) solid dosage forms (d) viscous liquids

ANSWERS TO MULTIPLE CHOICE QUESTIONS

1. (c)	2. (a)	3. (c)	4. (b)	5. (b)
6. (c)	7. (d)	8. (c)	9. (a)	10. (d)
11. (a)	12. (b)	13. (a)	14. (b)	15. (b)

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Posology

The term posology is derived from the Greek words "posos," meaning how much, and "logos," meaning science. It is a branch of medical science that deals with the dose or quantity of drugs that needs to be administered to a patient to get the desired pharmacological action.

Dosing of drugs in infants and children requires thorough consideration of the differences in the pharmacokinetics and pharmacology of a specific drug. The variation in the body composition and the maturity of liver and kidney functions are the potential sources of differences in pharmacokinetics with respect to age. One of the most arduous tasks in pediatric therapy is the calculation of dosage for children, particularly newborn babies, premature babies, infants, and very young children.

Various methods have been reported to calculate the dosage for children and infants, all of which calculate the child's dose as a fraction of the adult dose. In general, the formulas used to calculate the child dose use the following criteria:

1. Age of the child
2. Body weight of the child
3. Body surface area of the child

FORMULAS BASED ON AGE

Learning Objective

- Important formulas used to calculate dose on the basis of age, body weight, and body surface area

The following formulas are based on the age of the child:

1. **Young's formula**

$$\text{Child dose} = \frac{\text{Age (in years)}}{\text{Age (in years)} + 12} \times \text{Adult dose}$$

2. **Dilling's formula**

$$\text{Child dose} = \frac{\text{Age (in years)}}{20} \times \text{Adult dose}$$

3. **Cowling's formula**

$$\text{Child dose} = \frac{\text{Age (in years)} + 1}{24} \times \text{Adult dose}$$

(or)

$$\text{Child dose} = \frac{\text{Age at next birthday}}{24} \times \text{Adult dose}$$

4. **Fried's formula (for infants)**

$$\text{Child dose} = \frac{\text{Age (in months)}}{150} \times \text{Adult dose}$$

5. **Bastedo's formula**

$$\text{Child dose} = \frac{\text{Age at next birthday} + 3}{30} \times \text{Adult dose}$$

6. **Augsberger's formula**

$$\text{Child dose} = \frac{4(\text{Age at next birthday}) + 20}{100} \times \text{Adult dose}$$

7. **Brunton's formula**

$$\text{Child dose} = (0.4)(\text{Age at next birthday})(\text{Adult dose})$$

8. **Fried's formula**

$$\text{Child dose} = (0.08)(\text{Age at next birthday})(\text{Adult dose})$$

9. **Martinet's formula**

$$\text{Child dose} = (0.05)(\text{Adult dose})$$

FORMULA BASED ON BODY WEIGHT

Clark's formula uses the body weight of the child to determine the dose and is calculated as follows:

$$\text{Child dose} = \frac{\text{Weight (in pounds)}}{150} \times \text{Adult dose}$$

(or)

$$\text{Child dose} = \frac{\text{Weight (in kg)}}{70} \times \text{Adult dose}$$

(70 kg = 150 pounds is the average weight of an adult.)

FORMULA BASED ON BODY SURFACE AREA

Crawford Terry Rourke method uses the body surface area of the child to calculate the dose:

$$\text{Child dose} = \frac{\text{Body surface area of a child } (m^2)}{1.73\ m^2} \times \text{Adult dose}$$

(1.73 m^2 is the average body surface area of an adult.)

FACTORS AFFECTING DOSE SELECTION

Learning Objective

- Factors affecting dose selection.

The following are the factors that affect the selection of dose for a patient:

1. **Age:** In determining the dose of a drug, the age of the patient is of great importance, especially in the case of children and the elderly. The lower age group patients such as infants and children have striking physiological differences from adults. This is because the organs liver and kidney, which are responsible for biotransformation and excretion, are immature and still in the generative stage. The hepatic drug metabolizing system is inadequate in newborns—for example, chloramphenicol can produce gray baby syndrome. The blood–brain barrier is more permeable and drugs can attain a higher concentration in the central nervous system (CNS). Drug absorption may be altered in infants because of lower gastric acidity and slower intestinal transit. Growing children are more vulnerable to special adverse effects of drugs, for example, suppression of growth due to corticosteroids and discolouration of teeth due to accumulation of tetracycline.

   In the case of geriatrics (elderly patients), the liver and kidney functions progressively decline and the organs exhibit impaired ability to inactivate or excrete drugs. Due to lower renal and metabolic clearance, the elderly are more prone to develop cumulative toxicity while receiving prolonged medication. Absorption will be slow due to reduced blood flow and motility of intestines. The elderly are also likely to be on multiple drug therapy for hypertension, ischemic heart disease, diabetes, arthritis, and so on, which increases the chances of drug interactions.

   Therefore, the dose of drugs should be adjusted for pediatrics and geriatrics keeping in mind the physiology of the patients and the pharmacokinetic parameters of the drug.

2. **Body weight:** The recommended adult dose is based on the normal body weight of 70 kg but such a dose will be very less for a muscular person weighing about 100 kg and will be very high for a lean patient weighing about 40 kg. Child doses are usually calculated on the basis of body weight.
3. **Sex/Gender:** In general, women require lesser dose than men because of their smaller body size and also because they are more responsive and sensitive to certain drugs. Many drugs should be avoided or monitored carefully during menstruation, pregnancy, and lactation. The following precautions need to be taken while determining the dose for women:
   (a) Strong purgatives should be avoided during menstruation.
   (b) Drugs that induce contraction of uterus must be avoided during pregnancy (as it may lead to abortion or miscarriage).
   (c) During pregnancy, drugs such as barbiturates, narcotics, anesthetics, and alcohol, which readily cross the foetal circulation, should be avoided.
   (d) In lactating mothers, drugs such as tetracycline, antihistaminics, and morphine should be carefully prescribed.
   (e) A number of antihypertensives (such as clonidine, methyldopa, and β blockers) interfere with the sexual function in men but not in women.
   (f) Gynecomastia is a side effect of drugs such as ketoconazole, metoclopramide, and chlorpromazine that occurs only in men.
   (g) Androgens are unacceptable to women and estrogens to men.
4. **Route of administration:** The route of administration influences the efficacy of a drug in terms of drug response. Absorption of drugs is more rapid and complete by parenteral administration than by oral route. Drugs that are administered by parenteral route require lesser dose when compared to oral doses.

   A single drug may exhibit varied uses through different routes. For example, magnesium sulfate on oral administration results in purgative action, whereas it produces CNS depression and hypotension when given intravenously.
5. **Time of administration:** Drugs that are absorbed rapidly should be given on empty stomach, whereas drugs that are irritant to the gastrointestinal tract should be given after meals. For example, fatty meals enhance the absorption of griseofulvin, whereas food interferes with the absorption of ampicillin.
6. **Presence of disease/Pathological conditions:** It is not only drugs that modify disease processes, but the presence of diseases can also influence drug disposition and drug action. For example, gastrointestinal diseases can alter the absorption of orally administered drugs. Liver diseases can increase the bioavailability of the drugs that normally undergo high first pass metabolism. Kidney diseases can alter the clearance of drugs.
7. **Environmental factors:** Alcohol is better tolerated in a cold environment than in hot summer. The dose of sedative required to induce sleep during the day is more than that required in the night. Hypnotics taken at night and in quiet, familiar surroundings may work more easily.
8. **Genetic makeup:** Variations in response of different individuals to the same dose of a drug are sometimes due to differences in genetic makeup.
9. **Rate of elimination:** If age or disease impairs liver function, the breakdown of drugs may be delayed, whereas if the kidney activity is reduced, the excretion of drugs will be incomplete.

Both the situations cause greater and prolonged activity of medicaments with a risk of toxic reactions.

10. **Idiosyncrasy:** This is a genetically determined abnormal reactivity to a chemical. This term is used to indicate exceptional and individual intolerance towards certain drugs. The drug interacts with some unique feature of the individual, not found in majority of subjects, and produces the uncharacteristic reaction. The following are some examples:
    (a) Quinine and quinidine causes cramps, diarrhea, and asthma in some patients.
    (b) The adverse effects of penicillin (seen in 0.1–1% of patients) include rashes, fever, vomiting, erythema, dermatitis, angioedema, seizures (especially in epileptics), and pseudomembranous colitis (which is the cause of antibiotic-associated diarrhea (AAD) and is an infection of the colon).
    (c) Large doses of quinine cause tinnitus (ringing in the ears).
    (d) Barbiturates cause excitement and mental confusion in some individuals.
11. **Tachyphylaxis:** This is defined as the rapid development of tolerance on repeated doses of a drug in quick succession with a marked reduction in clinical response. (Tolerance refers to the requirement of a higher dose of a drug to produce a given response.) When certain drugs are administered repeatedly at very short intervals, the cell receptors get blocked by which the pharmacological response to that particular drug is decreased. Under such circumstances, even if the dose is increased, the necessary pharmacological response is not obtained. If the administration of the drug is stopped for a certain period of time and continued again, the response is observed. Examples of such drugs are ephedrine and nicotine.
12. **Species and race:** Differences in therapeutic efficacy to drugs are quite evident in different species or races.

    For example, in the case of human beings, blacks require higher concentrations of atropine and ephedrine to dilate their pupil, whereas Mongolians require lower concentrations for the same.
13. **Synergism:** When the action of one drug is promoted or enhanced by the other, the drugs are termed as synergistic in nature and the phenomenon as synergism. In a synergistic pair, both the drugs can show action in the same direction or one may be inactive but still enhance the action of the other when given together. The following are some examples of synergism:
    (a) Aspirin + paracetemol is used as an analgesic/antipyretic.
    (b) Amlodipine + atenolol is used as an antihypertensive.
    (c) Glibenclamide + metformin is used as a hypoglycemic.
14. **Antagonism:** Antagonism is a phenomenon in which one drug decreases or blocks the action of another. In an antagonistic pair, one drug is inactive as such but antagonizes the effect of the other. The following are some examples of antagonism:
    (a) Charcoal adsorbs alkaloids and can prevent their absorption—used in alkaloidal poisoning.
    (b) Potassium permanganate oxidizes alkaloids—used for gastric lavage in poisoning.
    (c) Tannins + alkaloids—insoluble alkaloidal tannate is formed.
    (d) Chelating agents (calcium disodium edetate) form complexes with toxic metals such as lead and arsenic.
15. **Psychological factors:** Patient's beliefs, attitudes, and expectations remarkably affect the efficacy of the drug, especially in the case of centrally acting drugs. For example, a nervous and anxious patient needs more general anesthetic.

REVIEW QUESTIONS

Answer in Detail

1. Discuss the factors affecting dose selection.
2. List out all the formulas used for calculating child dose.

Answer in Brief

1. Calculate the child dose for a nine-year-old boy and a child weighing 25 pounds if the adult dose is 350 mg.
2. Write short notes on idiosyncrasy and tachyphylaxis.
3. Name the formulas that are used to calculate the child dose on the basis of age.

Answer in One or Two Sentences

1. Define posology.
2. Write Fried's formula for dose calculation.
3. Define idiosyncracy and tachyphylaxis.
4. Which formula would you use to calculate dose on the basis of body surface area?

Multiple Choice Questions

1. Clark's formula is used to calculate dose on the basis of _____.
   (a) age (b) body weight (c) body surface area
2. Which one of the following factors is not considered for dose selection?
   (a) Time of administration
   (b) Tachyphylaxis
   (c) Height of the patient
3. Development of tolerance due to repeated drug dosing is called _____.
   (a) antagonism (b) tachyphylaxis (c) synergism
4. Which formula can be used to calculate the dose on the basis of the patient's age?
   (a) Crawford Terry Rourke method
   (b) Clark's formula
   (c) Dilling's formula
5. Which formula can be used to calculate the dose for an infant?
   (a) Young's formula (b) Fried's formula (c) Bastedo's formula

ANSWERS TO MULTIPLE CHOICE QUESTIONS

1. (b) 2. (c) 3. (a) 4. (c) 5. (b)

Introduction to Dosage Forms

4

Learning Objectives

- The most common medication dosage forms
- The different types of dosage forms
- The different routes of administration of each dosage form
- The need for dosage form development

A drug is defined as an agent intended for use in the diagnosis, mitigation, treatment, cure, or prevention of disease in humans or in animals. Drugs are not administered as such and they are converted into a palatable form, which is called as "dosage form." Dosage form contains both active and inactive ingredients (excipients or additives). They act as a carrier by which drug molecules are delivered to sites of action within the body. Inactive ingredients give shape to the formulation; increase its efficacy, stability, and palatability; and impart elegance to the preparation. The route of administration for drug delivery is dependent on the dosage form of the drug substance. Various dosage forms may exist for a single drug, since different medical conditions need different routes of administration.

A drug is converted into a dosage form for the following reasons:

1. To protect the drug from oxidation, hydrolysis, reduction, and other environmental factors
2. To protect the drug from the destructive effects of the gastric juice of the stomach after oral administration; for example, enteric coated tablets
3. To provide a safe and convenient delivery of accurate dosage
4. To mask the bitter, salty, or obnoxious taste or odor of a drug substance
5. To provide the optimum drug action through a suitable therapy; for example, inhalation aerosols and inhalants
6. To administer the drug into one of the body cavities; for example, rectal suppositories
7. To deliver maximum drug action from topical administration sites; for example, creams, ointments, and ophthalmic preparations

8. To provide sustained and controlled release action, thereby reducing dosing frequency; for example, sustained release tablets, capsules, and suspensions
9. To provide liquid dosage form of the drugs soluble in a suitable vehicle, for example, solutions.

CLASSIFICATION OF DOSAGE FORMS

Dosage forms are classified into four types on the basis of the following aspects:

1. **Physical state**
   (a) Solid
   (b) Liquid
   (c) Semisolid
   (d) Gas
2. **Route of administration**
   (a) Oral
   (b) Parenteral
   (c) Rectal
   (d) Nasal
3. **Site of application**
   (a) Skin
   (b) Eye
   (c) Tooth
   (d) Hand
   (e) Foot
   (f) Hair
   (g) Nose
   (h) Buccal
4. **Use**
   (a) Internal
   (b) External

Figure 4.1 shows the classification of dosage forms.

Powders

Powders are preparations consisting of solid, loose, and dry particles of varying degrees of fineness. They are smooth to touch and nonirritating to skin. Powders generally range from 0.1 microns to 10 microns in size and are either swallowed or may be administered with water. They are marketed as single-dose and multidose powders. Each dose is packed in a separate container, called a sachet or vial. An example is the eutectic powder.

Granules

Granules are solid dosage form of medicament in which the powdered drug or drugs are mixed with sweetening, flavoring, and coloring agents. A granulating agent is added to moisten the powder and

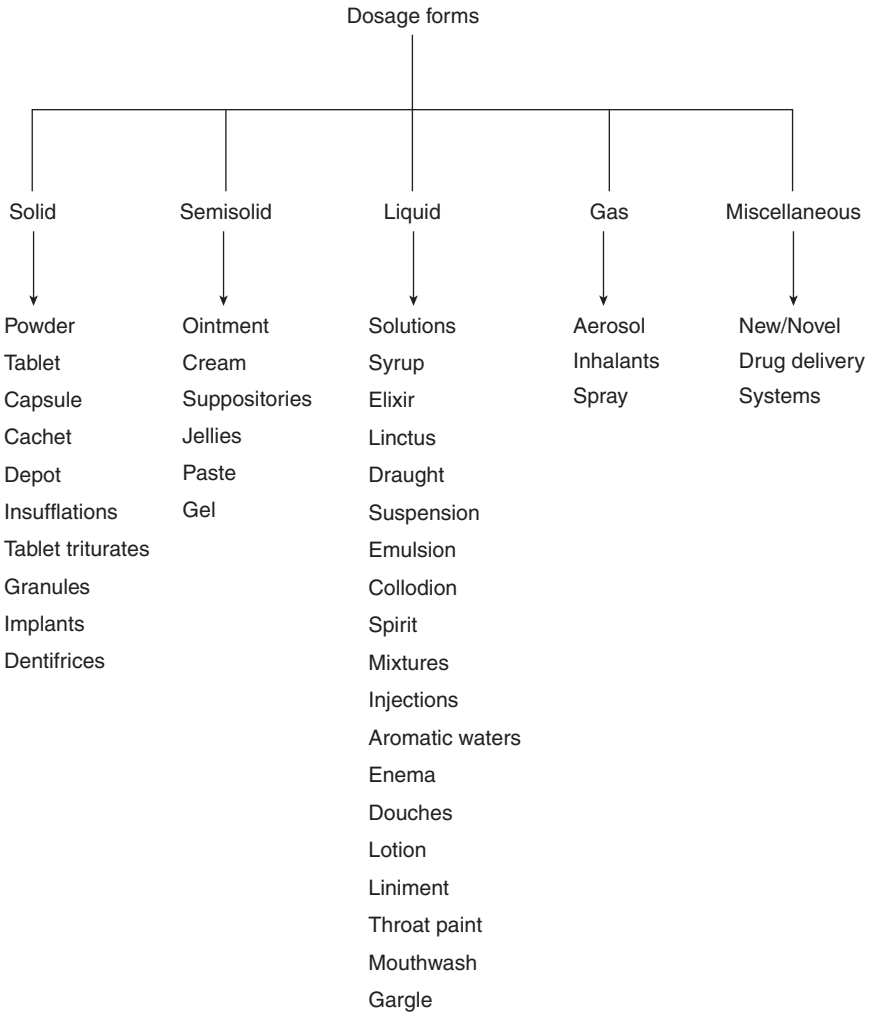

Figure 4.1 Classification of Dosage Forms

mixed thoroughly. The wet mass is passed through a suitable sieve and the granules are dried at a temperature of 60°C. They are supplied in glass containers and the patient is asked to add sufficient freshly boiled and cooled water to constitute a liquid preparation. These are specially prepared solid dosage form of medicament that is meant for internal use. Effervescent granules are examples of such dosage form.

Tablet Triturates

Tablet triturates or molded tablets are small, cylindrical, molded, or compressed tablets containing small amounts of potent drugs, which are produced by tablet compression process. Tablet triturates

are completely soluble in water. A mixture of powdered lactose with sucrose is used as the base for molded tablets. Minimum amount of pressure should be applied in preparation of such molded tablets. They are administered by oral and sublingual route, or they are administered after filling them into a capsule. An example is the nitroglycerine tablet triturates.

Cachets

Cachets offer a means of administering comparatively large amounts of disagreeable powders, but they offer very little protection from light, moisture, or mechanical handling. They are also large to swallow and must be moistened by immersion in water immediately prior to swallowing with water. Cachets vary in size from three-fourth of an inch to one-eighth of an inch in diameter and consist of two concave pieces of wafer made of flour and water. One part is filled with the required quantity of drug and then sealed by pressing both the margins tightly after moistening them. When moistened with water, they become soft, elastic, and slippery. The shells of cachets are molded from rice paper and are used to enclose quantities of medium density dry powder of fill weight between 200 mg and 2 g. Cachets are used to administer drugs with an unpleasant taste in a tasteless form.

Tablets

Tablets are solid preparations containing a single dose of one or more active ingredients with or without excipients and prepared by compressing uniform volumes of particles. Tablets are intended for oral administration. They are either swallowed, chewed, dissolved, or dispersed in water before administration. Tablets are generally prepared by three methods, namely dry granulation (slugging), wet granulation, and direct compression. Different types of tablets for oral use are compressed tablets, film-coated tablets, enteric-coated tablets, sugar-coated tablets, buccal tablets, sublingual tablets, and chewable tablets.

Capsules

Capsules are unit solid dosage forms in which the drug is enclosed within a hard or soft soluble container or shell usually made up of gelatin. The medication incorporated may be a powder in case of hard gelatin capsules and a solid/liquid/semisolid mass in soft gelatin capsules. Capsules are usually intended to be administered orally by swallowing them. Occasionally, capsules may be administered for ophthalmic, rectal, or vaginal use as well.

Dentifrices

These are bulk solid powder or granules, generally containing soap or detergent and a mild abrasive used externally with or without brush in the buccal cavity. Dentifrices reduce plaque formation, strengthen teeth against dental carries, remove stains and food debris, moisturize dry mouth, increase sensitivity, and prevent halitosis.

Insufflations

Insufflations are meant for being blown into various body tracts or cavities. They are medicated dusting powders meant for introduction into the body cavities such as nose, throat, ears, and vagina with the help of an apparatus known as 'insufflator'. It sprays the powder into a stream of finely divided particles all over the site of application. Insufflations are intended for local action alone. But the intranasal insufflations are designed to administer drugs into the systemic circulation through the nasal mucosa. These are used for administration of potent drugs. This method controls the dose level through metered valves. It also protects the product from external environment.

Solutions

A solution is a homogenous mixture composed of only one phase for a multidose administration. In such a mixture, a solute is dissolved in another substance known as the solvent. The concentration of a solute in a solution is a measure of the quantity of solute dissolved in the solvent. However, solutions are less stable than solid dosage forms and are bulky to carry. Moreover, accidental breakage results in complete loss of the contents.

Draughts (Haustus)

Draught is a monophasic liquid oral preparation taken as a single dose. If several doses are prescribed, each dose is dispensed in a separate container. Each dose is of the order of about 50 ml. Examples are male fern extract draught and paraldehyde draught.

Syrups

Syrup is a thick, viscous liquid consisting primarily of a solution of sugar in water. It may also contain various aromatic or pleasantly flavored substances but is nonmedicated and generally used as a vehicle, as a flavoring agent, or for preservation. Due to high osmotic pressure, simple syrup I.P. prevents the growth of bacteria, fungi, and molds that cause decomposition of solutions. Syrups are mainly of three types, namely simple, medicated, and flavored.

Spirits

Spirits are alcoholic or hydroalcoholic solutions of volatile substances and they contain 50–90% of alcohol. The high-alcoholic contents maintain water-insoluble oils in solution. If water is added to a spirit the oil gets separated. They are prepared by dissolving the volatile substances in 90% ethanol. They are mainly used as flavoring agents and some spirits are taken internally for their medicinal value.

Aromatic Waters

Aromatic waters are clear, saturated solutions of aromatic substances, which may be volatile oil dissolved in water. Due to their flavoring properties, they are used as a vehicle for oral liquid preparations.

Aromatic waters also have preservative action, due to which they are used as menstrum to extract crude drugs. Aromatic waters have mild therapeutic action such as carminative and expectorant action. They are prepared by either simple solution or diluting the concentrated preparations.

Elixirs

These are sweetened, flavored hydro-alcoholic preparations usually containing bitter or potent medicaments such as anthelmintics, antihistamines, and sedatives. The alcohol concentration of an elixir is generally between 10% and 40%. Elixirs are clear preparations and are more fluid than syrup because of the use of less-viscous ingredients. They are palatable, and hence, they are often administered to infants and children. Elixirs are classified into medicated and nonmedicated elixirs.

Linctuses

Linctuses are oral viscous liquid preparations that are generally prescribed for the relief of cough. They contain medicament that has demulcent, sedative, or expectorant action. The usual dose is 5 ml. Linctuses should be taken in small doses, sipped and swallowed slowly without diluting with water to have the maximum and prolonged effect of medicament. The viscous vehicle soothes the sore membrane of the throat. Simple syrup or sorbitol is generally used as a vehicle.

Suspensions

Suspensions are biphasic liquid dosage forms of medicament in which finely divided solid particles in the range 0.5–5.0 microns are dispersed in a liquid or semisolid vehicle. Suspensions are taken orally or by parenteral route. They are used for both internal and external applications. It is easy to dispense unstable or degradable drugs in suspension form. It is the only choice if the drug is not soluble in water and nonaqueous solvent is not acceptable, but occurrence of sedimentation of solids results in a poor form of product. It may lead to caking, which is difficult to redisperse.

Mixtures

Mixture is a liquid preparation meant for oral administration in which the medicament or medicaments are dissolved or suspended in a suitable vehicle. In general, several doses are dispensed in a bottle. A container with one dose is called “draught.” Mixtures are mainly prescribed for acute conditions such as cough, indigestion, diarrhea, and constipation. They are extemporaneously prepared for small number of doses. In case of further need, a fresh mixture is to be prepared before administration. They are classified into simple mixtures containing soluble substances, mixtures containing diffusible solids, mixtures containing indiffusible solids, mixtures containing precipitates forming liquids, and mixtures containing slightly soluble liquids.

Gels

Gels are the aqueous colloidal suspensions of the hydrated forms of insoluble drugs. A gel is a solid, jellylike material that has properties ranging from soft and weak to hard and tough. Gels are defined

as a substantially dilute cross-linked system, which exhibits no flow when in the steady state. Gels are mostly liquid, but they behave like solids due to their three-dimensional cross-linked network within the liquid, which gives them their structure and contribute to their stickiness. Examples are aluminum hydroxide gel, aluminum phosphate gel, and milk of magnesia. Gels are classified as hydrogel or aquagel, organogel, and xerogel.

Emulsions

Emulsion is a heterogeneous system consisting of one immiscible liquid dispersed in another in the form of droplets whose diameter in general exceeds 0.1 micron. Such system possesses minimal stability because the droplets quickly coalesce and the two liquids get separated. The stability of the emulsion is increased by adding another substance known as the emulsifying agent or emulsifiers. The liquid droplets are generally known as the dispersed phase or internal phase, whereas the liquid in which they are dispersed is known as the continuous phase, dispersion medium, or external phase. Emulsion increases the stability of many drugs that are unstable in an aqueous solution. It improves the taste of objectionable medicinal agents and makes them more acceptable. It also improves penetration and spreadability. Emulsions enhance the rate and extent of absorption through the alimentary canal, improve the solubility of poorly water-soluble drugs, and can prolong drug action. Examples are liquid paraffin emulsion, cod liver oil emulsion.

Collodions

Collodions are liquid preparations for external application to the skin. They are applied to cuts and abrasions. They are also used when prolonged contact between the skin and the medicament is required. Volatile vehicle is used in collodions that evaporate on application to skin, leaving a flexible, protective film covering at the site of application. Collodions are applied with a brush or rod. Collodion is a flammable, syrupy solution of pyroxylin (nitrocellulose) in ether and alcohol. It is of two types, namely flexible and nonflexible. The wound covering must be elastic to ensure that all layers constituting it are in close contact with the wound surface.

Ointments

Ointments are semisolid preparations for application to the skin or mucous membranes. They are often anhydrous and contain the medicament either dissolved or dispersed in the vehicle. The solid substances that are dispersed should be in the form of a micronized powder. Ointments are easily spreadable and their plastic viscosity may be controlled by modifications of the formulation. They are typically used as emollients, protective barriers, and vehicles to incorporate medicaments. Ointment bases are mainly of four types, namely hydrocarbon or oleaginous base, absorption base, emulsifying base, and water-soluble base. They are prepared by trituration, fusion, or chemical reaction method.

Creams

Creams are viscous emulsions or semisolid preparations consisting of solutions or dispersions of one or more medicaments in suitable base and are intended for application to the skin or mucous membrane.

Creams are applied for protective, beautifying, therapeutic, or prophylactic purposes. They contain suitable antimicrobial preservatives to have sufficient intrinsic bactericidal and fungicidal activity. Creams are mainly of two types, namely water-in-oil (w/o) and oil-in-water (o/w) types. Sometimes, dilutions of proprietary creams are required. They can also be used after dilution. For this, an appropriate diluting agent should be used and heating should be avoided. Such diluted creams should be used within two weeks of their preparation.

Pastes

Pastes are semisolid preparations intended for external application on the skin. They are generally very thick and stiff. They do not melt at ordinary temperature and thus form a protective coating over the area where they are applied. Pastes are used as antiseptic, protective, or soothing dressings, which are often spread on lint before being applied. The types of bases that are used for the preparation of pastes are hydrocarbon bases, water-miscible bases, and water-soluble bases. Pastes are prepared by trituration or fusion method. The trituration method is used when the base is liquid or semisolid and the fusion method is used when the base is semisolid or solid in nature. Paste should be stored in a well-closed container and in a cool place so as to prevent evaporation of the moisture present in the paste.

Jellies

Jellies are transparent or translucent nongreasy, semisolid preparation meant for external application to the mucus membrane. They are prepared from natural gums, such as tragacanth, pectin, sodium alginates, or from semisynthetic derivatives such as methyl cellulose and sodium carboxymethyl cellulose. There are three types of jellies, namely medicated jellies containing water soluble drugs, lubricating jellies, and miscellaneous jellies. Jellies are stored in well-filled and well-closed containers to minimize the evaporation of water and in a cool place to prevent drying out. Sterile jellies such as catheter lubricants are packed in collapsible tubes.

Suppositories

A suppository is a solid or semisolid mass meant to be inserted into any of the body orifices such as rectum, vagina, ear, nasal, and urethra to provide either local or systemic effect. They are designed to soften and melt or to dissolve or disintegrate at the body temperature. Suppositories provide systemic effect when used rectally. They are frequently used for local effects for relief of hemorrhoids or infections in the rectum, vagina, or urethra. Suppositories contain medicaments such as emollients, astringents, antiseptics, and local anesthetics, which are designed to exercise local action at the site of placement. Suppository bases are classified into oleaginous base and water-soluble and water-miscible base. Suppositories are classified into two types. The first one depends upon the route of administration—rectal suppositories, vaginal suppositories or pessaries, urethral bougies, and nasal bougies. The second one depends upon the pharmaceutical design—tablet suppositories, capsule suppositories, and coated suppositories.

Enemas

Enemas are aqueous or oily solutions or suspensions that are employed to evacuate the bowel or for cleansing, therapeutic, and diagnostic purposes. Enemas are usually warmed to body temperature and

are administered slowly. They should be stored in a cool place and in complete darkness. An expiry date of only two days after issue is advisable. Sodium chloride, sodium bicarbonate, sodium monohydrogen phosphate, and sodium dihydrogen phosphate are used in enemas.

Liniments

Liniment is a viscous, medicated topical preparation for application to the skin. It is always applied with friction on unbroken skin. A liniment is an external tincture and is to be rubbed onto sore muscles and sprains. It is usually prepared with isopropyl alcohol or ethyl alcohol. It is a solution or mixture of various substances in oil, alcoholic solution of soap, or emulsions or occasionally semisolid preparations intended for external application and should be labeled accordingly. They may contain the following substances: (a) analgesic, (b) antimicrobial, (c) rubefacient, (d) counterirritant, (e) stimulants, and (f) soothing agents.

Throat Paints

Paints are solutions or dispersions of one or more medicaments intended for application to the skin or, in some cases, to the mucous membrane. They contain a volatile solvent, which evaporates quickly to leave a dry or resinous film of drug. Throat paints are more viscous due to their high content of glycerin. They are sticky and adhere to the affected site, thereby prolonging the action of the medicaments. Paints should be kept in airtight containers. They should comply with the general requirements for labeling, in addition to the condition on the label, which states ‘For external use only.’

Mouthwashes

Mouthwash or mouth rinse is a product that is used to enhance oral hygiene. Mouth washes are aqueous solutions often in concentrated form, containing one or more active ingredients and excipients. They can be used for two purposes—therapeutic and cosmetic. Therapeutic uses include reducing plaque, gingivitis, dental caries, and stomatitis. Cosmetic uses include reducing bad breath. Flavors such as peppermint, spearmint, cinnamon, wintergreen oils, menthol, or methyl salicylate are used to overcome disagreeable tastes.

In general, mouthwashes contain antibacterial agents, alcohol, glycerin, sweetening agents, flavoring agents, and coloring agents. Mouthwashes are dispensed in white fluted bottles. The label should clearly indicate the proper directions for diluting the mouthwash before use. Moreover, the secondary label, “For external use only,” should be provided.

Gargles

Gargles are aqueous solutions containing antiseptics, antibiotics, and anesthetics. They are used for treating infections of pharynx and nasopharynx by forcing the air from lungs through the gargle that is held in the throat. Gargles must be diluted with water prior to use. They are generally dispensed in concentrated form and are pleasantly flavored and medicated. Many mouthwashes are used as gargles, either as such or diluted with purified warm water.

Lotions

Lotions are liquid dosage forms for external use. They are generally meant for application to the skin and are applied directly without friction, with the help of some absorbent material such as cotton wool, or are charged on to cotton wool or gauze and kept on the needed part of the body. Lotions may be used for local cooling, soothing, or protective purposes. They are generally applied for antiseptic action. Alcohol is sometimes included in aqueous solutions for its cooling and soothing effect. Lotions should be dispensed in colored fluted bottles to distinguish them from preparations meant for internal use. The containers should be labeled "For external use only" and "Shake well before use."

Sprays

Sprays are the liquid preparations of medicaments in aqueous, alcoholic, or glycerin-containing vehicle and are meant for application to the nose or throat by means of an atomizer or nebulizer. Coarse droplets of the medicaments will be administered to the upper respiratory tract, whereas very fine droplets penetrate into the respiratory tract. Aqueous sprays that are isotonic with nasal secretions and are of the same pH are preferred. Sprays usually contain medicaments such as antibiotics, antihistaminics, and vasoconstrictors.

Eye Drops

Eye drops are sterile, isotonic, and pyrogen-free preparations meant for instillation into the cul-de-sac of the eye for irrigatory, lubricative, diagnostic, or therapeutic activity. The container should be labeled "For external use only," and it should be used within the stipulated time after opening the seal of the container as directed on the label.

Ear Drops

These are solutions of drops that are instilled into the ear with a dropper. The solution is generally prepared in water, glycerin, propylene glycol, or diluted alcohol. Ear drops are generally used for cleaning the ear, softening the wax, and treating mild infection.

Nasal Drops

These are aqueous solutions of drops that are instilled into the nose with a dropper. Oily vehicle is not preferable because it will inhibit the movement of cilia in the nasal mucosa. Nasal drops should be isotonic, should have neutral pH and viscosity similar to nasal secretions. This can be achieved by using 0.9% sodium chloride and 0.5% methyl cellulose. Nasal drops are dispensed in colored fluted bottles fitted with a dropper or in a suitable plastic container. The label should state "For external use only."

Aerosols or Pressurized Packages

Aerosols are defined as pressurized package disperse phase systems in which solid particles or liquid droplets constitute the disperse phase and gas (propellant) the continuous phase. Compressed gases,

such as carbon dioxide and nitrogen, and liquefied gases such as halogen derivative of some saturated hydrocarbons (methane, ethane, propane, etc.) can be used as propellants. The material to be propelled may be solid or liquid. Aerosol systems are classified into two-phase systems and three-phase systems and are meant for local or systemic action.

Implants

Implants are sterile small tablets meant for insertion under the skin by making a small incision beneath the skin, which is stitched later. Implants are about 3.2 mm in diameter and 8 mm in length and prepared by compression. They are implanted subcutaneously for the purpose of providing slow and continuous release of medication over a prolonged period of time. Steroidal hormones such as testosterone and stilbestrol are formulated as implants.

Controlled Release Drug Delivery System

Controlled release refers to the release of drug into a patient's body at a predetermined rate, at specific times, or with specific release profiles. Its advantages are reduction of dosing frequency, reduction in the fluctuation in circulating drug levels, increase in patient compliance, uniform effect, and reduction in GI irritation and other dose-related side effects. However, it suffers from the drawbacks of higher cost, unpredictability, and often poor *in vitro–in vivo* correlations and dose dumping.

REVIEW QUESTIONS

Answer in Detail

1. Define a dosage form and explain the need for dosage forms.

Answer in Brief

1. Classify pharmaceutical dosage forms with examples.
2. Define solid dosage form with examples.

Answer in One or Two Sentences

1. Define drug.
2. Define dosage forms.
3. Classify dosage forms according to their physical state.
4. Define liniments.
5. Define elixirs.
6. Define emulsions.
7. What are draughts?
8. What are collodions?
9. Write the auxiliary labeling for the following:
   (a) Liniments (b) Mouthwashes (c) Collodions

10. What are the directions to be mentioned on the label for linctuses?
11. What are insufflations?

Multiple Choice Questions

1. A dose of teaspoonful is _____.
   (a) 5 ml (b) 10 ml (c) 2.5 ml (d) 7.5 ml
2. A drug is converted into a dosage form _____.
   (a) to protect the drug from contaminants
   (b) to protect the drug from the destructive effect of the gastric juice of the stomach
   (c) both
   (d) none
3. Alcohol concentration in elixir is _____.
   (a) 10–40% (b) 10–20% (c) 10–30% (d) 20–50%
4. Syrup I.P. contains _____.
   (a) 67%w/w (b) 67.5%w/w (c) 66.7%w/w (d) 66%w/w
5. Collodion is _____.
   (a) ethyl cellulose
   (b) methyl cellulose
   (c) nitrocellulose
   (d) carboxymethyl cellulose.
6. Aromatic waters are used as _____.
   (a) laxatives (b) mouthwashes (c) carminatives (d) flavoring agents
7. Ointment bases are of _____ types.
   (a) six (b) five (c) four (d) two
8. Lotions should be applied _____.
   (a) with friction (b) without friction (c) smoothly (d) by brush
9. Draught is a _____.
   (a) liquid (b) solid (c) gas (d) semisolid
10. Suppositories are administered through _____.
    (a) vagina (b) rectum (c) both (d) none

ANSWERS TO MULTIPLE CHOICE QUESTIONS

1. (a)	2. (c)	3. (a)	4. (c)	5. (c)
6. (c)	7. (c)	8. (b)	9. (a)	10. (c)

Solid Dosage Forms

5

INTRODUCTION

Solid dosage forms (SDFs) are the drug delivery devices formulated as both single and bulk dose forms suitable for oral administration. It mainly comprises of tablets, capsules, cachets, pills, powders and granules (Fig. 5.1). The oral route offers several advantages such as accurate dosing, physicochemical integrity of the active medicament, elegant appearance, flexibility in formulating the cost-effective formulations with an assured patient compliance. The two most important rate determining steps governing the overall bioavailability of drugs are disintegration and dissolution.

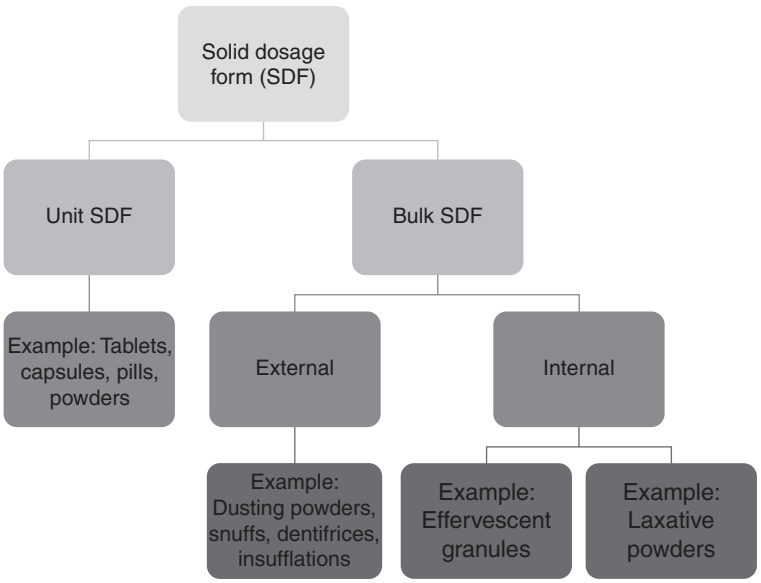

Figure 5.1 Classification of SDF

TABLETS

Learning Objective

- Definition of tablets and their types

Definition

Tablets are unit SDF each containing a single dose of one or more active medicaments with or without excipients prepared by molding or compression method.

Advantages

1. Enhanced physical and chemical stability when compared to liquid dosage forms.
2. They provide an accurately measured dose and low content variability of the unit dose.
3. Low manufacturing cost.
4. Easy for packaging and shipping.
5. Easy to identify.
6. Manufacturing processes and techniques can provide tablets with special properties. Examples are enteric coating, sustained release and fast dissolving tablets.

Disadvantages

1. Poor bioavailability of poorly soluble drugs or poorly absorbable drugs.
2. Some drugs may cause local Gastrointestinal tract (GIT) irritation effect.
3. Difficulty for swallowing in some patients such as paediatrics and geriatrics.
4. Onset of action is slow in conventional tablets when compared to other dosage forms as it has to undergo disintegration and dissolution before the drug is being released. Exceptions are soluble tablets, dispersible tablets, melt tablets and effervescent tablets.

Classification of Tablets

1. **According to drug release rate from the tablet**
   (a) **Immediate release tablet/Fast dissolving tablet:** It is the most common type and includes the following:
      (i) Disintegrating tablets
      (ii) Chewable tablets
      (iii) Sublingual tablets
      (iv) Soluble tablets
      (v) Effervescent tablets
   (b) **Modified release tablet:** They have drug release features based on time, course, or location. They must be swallowed intact. They include the following:
      (i) Extended release tablet
      (ii) Delayed release tablet
2. **According to method of manufacture**
   (a) Compressed tablet
   (b) Molded tablet

3. **According to route of administration**
   (a) **Oral tablets**
      (i) Uncoated tablets
      (ii) Sugar coated tablets
      (iii) Enteric coated tablets
      (iv) Non-enteric coated tablets
      (v) Sustained release tablets
      (vi) Controlled release tablets
      (vii) Time release tablets
   (b) **Oral cavity tablets**
      (i) Buccal tablets
      (ii) Sublingual tablets
      (iii) Lozenges
      (iv) Dental cones

Formulation of Tablets

Learning Objective

- Tablet excipients and their properties

Compressed tablets usually contain active medicament/s mixed with a number of inert substances known as excipients or additives. These additives are added to give good quality tablets. Although these additives are termed inert, they have great influence on stability, bioavailability and process by which dosage forms are prepared.

According to the activity of the additives in the preparation of tablet they may be classified as follows:

1. **Diluents:** When the dose of drug is very small, it is not practicable to compress such small amount in the form of a tablet, and then the inert substances are added to increase the bulk of the powders to be easily compressible into the tablets.
   Example: Lactose, starch, mannitol, calcium carbonate and dicalcium phosphate.

2. **Binders:** The agents used to impart cohesiveness or glue to powdered substances are known as binders. They keep tablet intact after compression. The type of binder depends upon binding force required to form granules and its compatibility with other compounds. The optimum concentration of the binder addition into the tablet formulation is very critical as it is one of the rate limiting steps for the disintegration, onset of action and bioavailability (Table 5.1).

Table 5.1 List of Binders, Their Solvents and Their Optimum Concentration

Binder	*Solvent*	*Concentration*
Acacia	Water/water-alcohol mixture	2–5%
Tragacanth	Water	1–3%

(*Continued*)

Table 5.1 Continued

Binder	*Solvent*	*Concentration*
Gelatin	Water	1–4%
Sucrose	Water	2–20%
Starch	Water	1–4%
Sodium carboxymethyl cellulose	Water	1–4%
Ethyl cellulose	Water/water-alcohol mixture	0.5–2%
Polyvinylpyrrolidone	Water/water-alcohol mixture	2–6%

3. **Disintegrating agents/Disintegrants:** These are the substances added to facilitate the disintegration or breaking apart of the tablet into small particles in GIT after administration and facilitating dissolution. Usually disintegrants are added in two steps:
   (a) **Intragranular disintegrants:** Disintegrants are added during granulation process and it enhances the disintegration of the granules.
   (b) **Intergranular disintegrants:** Disintegrants are added during the blending or lubrication stage before the compression process to facilitate bursting of the tablet into granules, when it comes in contact with the liquid.

   Disintegration mechanism is of the following two types:
   (a) Substances that swell up when they come in contact with moisture or solvent.
   (b) Substances that react with effervescence when they come in contact with moisture.

   Example: Maize starch, potato starch, Veegum, methyl cellulose, agar, bentonite, CMC, and sodium starch glycolate, citric acid, tartaric acid with sodium bicarbonate.

4. **Lubricants:** These are the substances, which are added to granules during blending process to facilitate the easy ejection of tablet from the die cavity after compression.
   Example: Magnesium stearate, Calcium stearate, Talc, etc.

5. **Glidants:** These are the substances, which are added during blending process before compression of tablet for easy flow of granules from hopper into die cavity. They act by reducing the inter particle friction between granules such that flow property is increased.
   Example: Silicates and colloidal silica.

6. **Anti-adherents:** These are the substances used to prevent sticking of tablet surface material to the punches and the tablet die wall. It avoids processing problems of sticking and picking, which occur due to the presence of excess of moisture.
   Example: Talc and corn starch. Some more examples are provided in the table below.

Ingredient	*Usual Concentration*	*Glidant Property*	*Anti-adherent*	*Lubricant*
Metallic starch	1% or <	Poor	Good	Excellent
Purified talc	1–5%	Good	Excellent	Poor
Corn starch	5–10%	Excellent	Excellent	Poor
Stearic acid	1–5%	None	Poor	Good

7. **Coloring agents:** They are used to impart elegance to the tablets. They are also used to identify the different types of tablets. Only FD&C approved color dyes are used. The colorants should be physically and chemically stable with other excipients, effective in low concentration, pharmacologically inert and should not interfere with the assay procedure of the medicament.
   Example: Frequently used colorants and their common names are mentioned in the table below.

Colorants	*Common Name*
FDC Blue #1	Brilliant blue
FDC Blue #2	Indigo tine
FDC Red #3	Erythromycin
FDC Yellow #5	Tartrazine
FDC Yellow #6	Sunset yellow

8. **Flavoring agents:** These are the substances usually used to increase the palatability of oral cavity tablets. The choice of the flavoring agent depends on the patient age and type of preparation also.
   Example: Peppermint oil, mango flavor, fruit flavor, chocolate flavor and vanilla flavor.
9. **Sweetening agents:** They are added to tablets, which are required to be dissolved in buccal cavity and to mask the unpleasant or bitter taste of the drug. The bases for the formulation are already sweet and they impart sweetness of varying degree.
   Example: Lactose, sucrose, saccharin, and cyclamates.

MANUFACTURE OF TABLETS

Learning Objective

- Different methods of tablet manufacture with their merits and demerits

Compressed tablets are manufactured by the following two methods:

1. **Dry method**
   (a) Direct compression
   (b) Slugging or double compression
2. **Wet method**

Dry Method

Direct compression: Most manufacturers agree that direct compression is superior with few steps since it does not require much equipments and handling expenses as required for wet method of tablet manufacture. The medicaments with large doses having good bulk density, flowability and compressibility can be directly compressed.

There are few crystalline substances such as inorganic salts (e.g. NaCl, KCl, and KBr), which may be compressed directly with very few additives such as lubricants and glidants. However, sometimes these compressed tablets may not disintegrate in the given time limit, and hence, substances such as disintegrating agents are added.

The different stages involved are as follows:

1. Milling or size reduction
2. Blending
3. Compression

Advantages

1. Less amount of additives are used in the formulation.
2. Number of steps involved is minimum.
3. Less equipments are used.
4. Less time consuming.

Disadvantage

1. All medicaments cannot be compressed directly.

Requirements for direct compression

1. Dose of medicament or drug should be more.
2. The medicaments should have very good mechanical strength and cohesiveness.
3. Medicament should have very good compressibility and other derived properties such as bulk density, angle of repose, etc.

Slugging or double compression: This method is used for those drugs, which are sensitive to heat, moisture, or both. This method is also called as granulation by compression or double compression method. The various process steps involved are as follows:

1. Size reduction: In this step, the size of the drug is reduced and passed through sifter to get the desired particle size of the drug.
2. **Mixing:** In this step, drug along with additives that are compressible like dicalcium phosphate granules, which are prepared previously are mixed along with glidant and lubricant and punched or compressed into compact masses called slugs by using flat punches using high compression force using multi-station tablet compression machine.
3. **Milling:** In this step, slugs are size reduced by using multi mill and passed through sifter to get the desired granules.
4. **Blending:** The obtained granules are then blended with additives such as disintegrating agents, lubricants and glidants for sufficient period of time using double cone blender.
5. **Compression:** The lubricated granules are finally compressed into tablets of desired weight, hardness, and thickness using multi station tablet compression machine.

Wet Method

The various process steps involved in wet method are as follows:

1. **Sifting/milling:** Weighed ingredients are passed through the desired sieve number such that the drug and the additives are of uniform size and shape.
2. **Dry mixing:** In this process, the drug along with additives such as diluents, disintegrating agents (half the weighed quantity as intragranular disintegrating agent), and color lakes if present in the formulae are mixed in a suitable mixer for a predetermined time.

3. **Granulation:** In this stage, the powder mixture is converted into granules by adding binder in form of solution and mixed for suitable time period to get a coherent mass or dough mass. The concentration of binder and amount of solution added should be optimized; otherwise, the granules obtained may contain large amounts of fines and may be fragile with less concentration of binder or with excess binder the granules obtained may be very hard and sometimes sticky in nature, which may impose problems during compression and disintegration.
4. **Wet sifting:** The dough mass or coherent mass obtained is then passed through a specified sieve to get the desired size wet granules. The sieve number is usually selected based on the weight of the tablet to be compressed. For example, for weights above 500 mg of the tablet weight, the sieve no. selected can be 12, for weights between 200–400 mg, the sieve no. selected can be 16.
5. **Drying:** Wet granules obtained were dried in a suitable dryer for a predetermined period of time and temperature to get the dried granules with the required moisture content.
6. **Regranulation:** Dried granules are then passed through desired sieve number to get the granules as per requirement.
7. **Blending:** In this stage, granules are transferred into a suitable blender such as double cone blender, V-cone blender, and other additives such as lubricants, glidants, anti-adherents and remaining quantity of disintegrating agents (intergranular disintegrating agent) were added and mixed for a suitable time period.
8. **Compression:** The blended granules should be carefully handled and the granules are compressed into tablets with predetermined weight, hardness and thickness using suitable punches and dies in a multi-station tablet compression machine.

Manufacturing Defects in Tablets

During production of tablets, defects arise with finished tablets, which may be due to fault in the formulation or in the tableting equipment and sometimes due to both of these reasons. Table 5.2 details few common production problems that arise during manufacturing.

Table 5.2 Production Problems with Tablet Quality

Tablet Problems	*Possible Causes*	*Corrective Action*
1. Non-uniform tablet weight	1. Feeders starved or choked	• Excessive recirculation of granulation
	2. Granulation lost or gained after proper filling of die	• Excessive vacuum pressure, or nozzle improperly located
	3. Dies not filling	• Check speed or shape of feeder paddle
	4. Lower punch pulled down before die is filled	• Inadequate recirculation of granulation
	5. Wide variation in thickness of lower punch	• Check that head thickness of lower punches is within ±0.10 inch of TSM specification

(*Continued*)

Table 5.2 Continued

Tablet Problems	*Possible Causes*	*Corrective Action*
2. Non-uniform tablet thickness	1. Non-uniform tablet weight	• Same as above
	2. Non-uniform punch lengths	• Check that working length is within ±0.001 inch of TSM specification
3. Non-uniform tablet density (friability)	1. Non-uniform tablet weight and thickness	• Same as above
	2. Low moisture content	• Add moisture to aid bonding
4. Dirt in product (black specks)	1. Dust, dirt, or press lubrication in the granulation	• Clean press more frequently • Use proper punch dust cups
5. Capping and lamination	1. Air entrapment	• Reduce press speed • Reduce quantity of fine particles in the granulation • Ensure that punch to die clearance is correct
	2. Rapid expansion of tablet upon ejection	• Taper dies
	3. Weak granulation	• Increase quantity of binder; use strong binder
	4. Excessive dry granulation	• Increase level of lubricant
	5. Punch cavity too deep	• Use punches with less concave depth
6. Picking and sticking	1. Excessive moisture	• Check moisture content of granulation • Check room humidity
	2. Poor embossing design	• Redesign embossing as per TSM guidelines
7. Mottled or marked tablets	1. Contamination of granulation usually by grease or oil or chutes or feed hoppers	• Clean and reset components correctly
	2. High moisture content of granulation	• Re-dry granulation
	3. High drying rate	• Optimize drying rate
8. Chipping or splitting	1. Poor surface finish on punch tips, worn punches, and dies	
	2. Poor tooling design(e.g.: sharp embossing or bisect line)	• Polish punch tips, replace punches and dies

(*Continued*)

Table 5.2 Continued

Tablet Problems	*Possible Causes*	*Corrective Action*
9. Splitting of layered tablets	1. Excessive pressure 2. Excessive lubrication of granules	• Decrease pressure • Reduce the amount of lubricant
10. Indistinct break line or embossing	1. Incorrect embossing design 2. Worn punch tips 3. Excessively coarse granulation 4. Inadequate binder 5. Picking	• Redesign embossing as per TSM guidelines • Replace punch • Reduce particle size • Increase binder strength • Compress granulation at lower pressure
11. Double impression of embossing	1. Rotation or jerk of the punches during compression	• Adjust anti-turning device • Use keyed punches

Some more problems that give rise to defective tablet quality are discussed below:

Binding in the die: During binding in the die, the ejection of tablet is difficult and is accompanied by a characteristic noise. The edges of the tablet become rough. This defect occurs due to poor lubrication of granules, under dried granules and worn out dies.

Capping and lamination of tablets: In capping or splitting, the upper or lower surface of the tablet is partially or completely separated out from the main body of the tablet. In lamination, the tablet separates out into two or more layers.

Causes: Capping occurs due to the following reasons:

1. Entrapment of air in the granules during compression
2. Presence of excess of fine powder in granules
3. Use of too soft granules leads to capping
4. Wear and tear of punches and dies
5. Incorrect setting of dies and punches

Picking: The surface of tablet material is removed by punches and adheres to the surface of the punches.

Causes: Picking occurs due to the following reasons:

1. Presence of scratches on punches
2. Use of wet granules

Sticking: Granules adhere to the die and lower punches cannot move freely.

Causes: Sticking occurs due to the following reasons:

1. Use of damp granules
2. Worn out dies or punches

Mottling: It occurs in colored tablets. Due to the unequal distribution of color in the tablet, different shades appear on the tablet.

Causes: Mottling occurs due to the following reasons:

1. Difference in color used, drug and the excipient
2. Migration of dyes during drying

Weight variation: This problem arises during filling of granules into die cavity.

Causes: Weight variation occurs due to the following reasons:

1. Poor flow of granules into die cavity
2. Presence of fines in granules
3. Non-uniform separation of granules
4. Improper mixing of lubricants

Hardness variation: Hardness of the tablets varies due to variation in weight of material, pressure applied on upper punches, improper space between upper and lower punches and excessive use of fatty lubricants like magnesium stearate.

Double impression: This occurs in tablets when a monogram is printed during compression.

Cause: The defect may be due to loosening of the punches in the socket grooves.

TABLET COATING

Learning Objectives

- Definition of tablet coating and their types
- Need for tablet coating and its methodology

It is a process of application of coating material onto the external surface of the core tablet. The tablets are coated for the following reasons:

1. To increase aesthetic appeal of the product
2. To mask the unpleasant taste of the drug
3. To protect the drug release in the gastric environment of the stomach with an acid resistant enteric coating material
4. To control or delay the release of the drug for a longer period of time
5. To incorporate another drug in coating
6. To avoid chemical incompatibility
7. To protect the drug from environmental decomposition

Requirements of an uncoated tablet to undergo coating procedure are as follows:

1. The tablet should possess optimum convexity to overcome the problem of edge coverage of the coat.
2. The tablet should be hard enough to withstand the rigors of coating procedure.
3. Tablets should have minimum tendency to absorb the solvent deep into the coat.
4. Friability value of the tablets should be minimum.

5. Tablets should disintegrate immediately once coating has dissolved.
6. Uncoated tablets should be in a position to subject itself to dedusting procedures. Otherwise it may impart roughness on the coated tablets.

Classification of Tablet Coating

Tablet coating is classified into the following two types:

1. Sugar coating
2. Film coating
   (a) Non-enteric coating
   (b) Enteric coating

Sugar Coating

The major ingredient used in sugar coating is sugar, which may be substituted by other materials like sorbitol.

Other additives used are as follows:

1. Fillers—calcium carbonate, talc and titanium dioxide.
2. Coloring agents—FD&C approved dyes and lakes.
3. Film formers—acacia, gelatin and cellulose derivatives.
4. Anti-adherents—talc and surfactants.
5. Flavouring agents—fruit and chocolate flavors.

Different stages of sugar coating

1. **Seal coating:** This process is carried out to encapsulate the core tablet with a layer of water resistant polymer, which would prevent the penetration of aqueous solvent into the core tablet during main coating procedure**.** The core tablets are introduced into the coating pan and subjected for dedusting followed by spraying of cellulose acetate phthalate solution and finally dried. The seal-coated tablets are treated with asbestos free talc and rotated for 3 to 5 minutes. The equipment is stopped and the tablets are dried for 1 hour with the exhaust "ON" and with the supply of cold air.
   Ingredients: Cellulose acetate phthalate, shellac, acetone and ethanol.

2. **Sub-coating:** This process is done to improve the bond between seal coat and the sugar coat by using water soluble polymer. The tablets are rotated and the solution of acacia is sprayed over the tablets after which the tablets are rotated for 15 minutes with purified talc if necessary.
   Ingredients: Acacia, gelatin, sugar cane powder and purified water.

3. **Syruping:** This is divided into the following three steps:
   (a) **Grossing:** The tablets are introduced with the exhaust "ON." Warm air is passed with a temperature of about 120 °F. The solution is sprayed containing sub-coating agents. After the coating, the tablets are rolled for 15 to 30 minutes.
   Ingredients: Sub-coating agent, coloring agent, sugarcane powder and purified water.

(b) **Heavy syrup:** The maximum weight of the tablet is gained in this step. Syrup containing coloring agent and sugar cane powder are sprayed slowly and uniformly onto the tablets at fixed temperature and relative humidity. The tablets are completely dried to ensure tackiness.
Ingredients: Sugarcane powder, coloring agent and syrup.

(c) **Regular syrup:** In this stage, the sugar cane powder and the coloring agent are dissolved in distilled water and sprayed onto the tablet at predetermined temperature. Then the entire batch is left overnight with the lid of the pan closed tightly.
Ingredients: Sugarcane powder, coloring agent and purified water.

4. **Polishing:** The coated tablets are rotated and the solution of bees wax are sprinkled slowly and uniformly, and after the process the tablets are rotated for a period of 30 minutes by passing cold air.
Ingredients: White beeswax, carnauba wax, ethanol and acetone.

Advantages

1. Sugar-coated tablets are widely accepted by the patients.
2. The raw materials used are inexpensive and easily available.

Disadvantages

1. The increase in weight and size of the finished product results (up to 40% of its core tablet weight) in increase packaging and transportation cost.
2. It is highly time consuming and laborious process.
3. Monograming and engraving of the tablet is not possible.
4. It requires services of highly skilled coating operator.

Film Coating

The composition of a coating solution is explained in Table 5.3.

Table 5.3 Composition of Film Coating Solution

Composition of Coating Solution	*Enteric Coating*	*Non-enteric Coating*
Polymer	Cellulose acetate phthalate, shellac, eudragits, hydroxypropyl methyl cellulose acetate	Ethyl cellulose, methyl cellulose, HPMC, and PVP
Solvent	Ethanol, acetone, rectified spirit, and isopropyl alcohol	
Plasticizers	PEG 200, PEG 400, and diethyl phthalate	
Coloring agents	FD&C approved colors	
Opacifying agents	Titanium dioxide, aluminum hydroxide, and purified talc	
Flavoring agents	Optional	
Surfactants	Optional	
Polishing agents	Beeswax/Carnauba wax, acetone, and alcohol	

Advantages

1. Reduction in coating time and material cost.
2. No significant increase in tablet weight.
3. No seal coating is required.
4. Number of coating steps is less.
5. It is resistant to chipping and cracking.

Disadvantages

1. It has risk of flammability hazards.
2. It is concern over environmental pollution.

Methods of Tablet Coating

Methods of tablet coating are as follows:

1. Pan coating
2. Air suspension coating
3. Dip coating
4. Compression coating

Quality Control Tests for Tablets

Tablets when formulated may undergo physical and chemical changes thereby altering the bioavailability of the dosage form. The manufactured tablet batches are to be evaluated before dispensing to ascertain stability and bioavailability throughout its shelf life.

Evaluation of tablets can be carried out by the following tests.

Unofficial Tests

Tablet appearance: The tablet appearance is considered as one of the most important factor in evaluation based on the consumer acceptance. It also ensures whether the lot of batch of tablets produced has maintained uniformity in its elegance, which includes color, taste, presence of flavor, identifying marks, surface texture, etc.

Organoleptic parameters: The organoleptic parameters, which are considered in tablets, mainly include its color, taste and odor.

1. **Color of the tablet:** The color distribution within the tablets should be uniform, and it should not vary from one lot to another. Non-uniform distribution of color within a tablet is known as mottling. Mottling should be avoided as it not only provides a poor appearance to the tablet but also does not give a satisfactory look to the consumer. Hence, color distribution in a tablet is quantitatively evaluated by the following instruments:
   (a) Tristimulus calorimetric measurements
   (b) Reflectance spectrophotometry
   (c) Micro reflectance photometer

2. **Odor of the tablet:** This helps to know whether the tablet has deteriorated thereby stability of the tablet is affected. For example, Aspirin tablet—instability indicated by a characteristic acetic acid odor.

Identification markings on tablet: These include name or symbol of the company and code of the product. These symbols are engraved and printed on the tablet surface, which helps in quick referral of the tablet when searched for identification.

Size and shape of the tablet: Tablets are designed to allow rapid production, to enable good consumer acceptance and also for identification.

Thickness of the tablet: The thickness of the tablet is influenced by the amount of fill material in the die cavity, die diameter and the compaction force applied. Thickness specification is characteristic to each tablet product, but in general the tablet thickness is required to be within ±5% of the prescribed values.

Factors affecting tablet thickness

1. The true and bulk density and also the crystalline nature of the raw material influence the tablet thickness.
2. The particle size and size distribution of the granules affect the tablet thickness.
3. The length of both upper and lower punches should be uniform, if not it affects the tablet thickness.

Thickness of the tablet is evaluated by micrometer digital readout sliding caliper scale method.

Hardness of the tablet: It is also termed as its crushing strength. It may be defined as the compressional force required to break or fracture the tablet when such force is applied diametrically. It is influenced by three variables—bonding strength, internal strain and brittleness. It is determined using the instrument Monsanto Hardness Tester or Pfizer Hardness Tester, and expressed with the units kg/cm^2.

Official Tests

Friability test Friability in addition to hardness gives the measure of tablet strength. It is defined as its resistance to shock and abrasion encountered during the process of manufacture, packing, transport and ultimately its usage.

Factors contributing to tablet friability are deep concave punches used during the compression leading to formation of whiskered tablets, high moisture content of the granules, over drying of the granules, etc. It is determined using the instrument Roche friabilator, and the value is calculated using the following equation:

$$\text{Friability\%} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

The batch tablets pass the test for friability, if the value is less than 1%.

Weight variation test: The average weight is determined by randomly selecting 20 tablets and weighing them individually. Not more than two of the individual weights deviate from the average weight by more than the percentage given in the pharmacopeia and none deviates by more than twice that percentage. IP limits for tablet weight variation are given as follows:

IP/BP	*Limit*
80 mg or less	10%
More than 80 mg and less than 250 mg	7.5%
250 mg or more	5%

Drug content: Thirty tablets are selected randomly. Ten of these tablets are assayed individually. The tablet passes the test if 9 of the 10 tablets contain not less than 85% and not more than 115% of the labeled drug content (±15%) and the 10th tablet may not contain less than 75% and more than 125% of the labeled content (±25%). If these conditions are not met, then the remaining 20 tablets are assayed individually. The batch sample complies with the test if the drug content of not more than 3 individual tablets out of the total 30 sampled tablets is outside the limits by ±15% and none may fall outside of the limits of ±25%.

Disintegration test: This method is used to evaluate the rate of disintegration of SDF of tablets. Disintegration is defined as the breakdown of SDF into small particles after it is ingested. The time of disintegration is a measure of the quality. If the disintegration time is too high, it suggests that the tablet is highly compressed. Also, if the disintegration time is not uniform in a set of samples being analyzed, it indicates batch inconsistency and lack of batch uniformity. The test is performed by randomly selecting six tablets using the instrument Disintegration Test Apparatus.

Some of the types of dosage forms and their disintegration tests are as follows:

1. **Uncoated tablets:** Tested using distilled water as medium at 37 ± 2 °C at 29–32 cycles per minute. The test is completed if all the tablets disintegrate within 15 minutes. It is acceptable when there is no palpable core at the end of the cycle and if the mass does not stick to the immersion disc.
2. **Coated tablets:** The test procedure given for uncoated tablets is adopted. For film coated tablets, the disintegration time limit is 30 minutes and for sugar coated tablets it is 60 minutes.
3. **Enteric coated/Gastric resistant tablets:** The test is carried out first in 0.1 M HCl (up to 2 hours during which all the tablets should be completely intact followed by replacement with phosphate buffer pH 6.8 for 1 hour during which the tablets should disintegrate.

Dissolution test: Dissolution is pharmaceutically defined as the rate of mass transfer from a solid surface into the dissolution medium or solvent under standardized conditions of liquid or solid interface, temperature and solvent composition. It is a dynamic property that changes with time and explains the process by which a homogenous mixture of a solid or a liquid can be obtained in a solvent.

Dissolution test can be performed in two ways—*in vitro, in vivo*.

In vivo test is performed in selected animal and human subjects (expensive and time consuming).

In vitro test is performed using dissolution test apparatus (inexpensive and less time consuming).

Factors to be considered for designing *in vitro* dissolution test are as follows:

1. Factors related to the dissolution apparatus
2. Factors related to dissolution fluid or medium
3. Factors related to the test medium

Dissolution test apparatus-1 (basket type): The sample which floats in the test media is placed in a small wire mesh basket attached to the bottom of the shaft connected to a variable speed motor. The basket is immersed in a dissolution medium (as specified in monograph) contained in a 1000 ml flask. The flask is cylindrical with a hemispherical bottom. The flask is maintained at 37±0.5 °C by a constant temperature bath. The motor is adjusted to turn at the specified speed and samples of the fluid are withdrawn at predetermined time intervals to determine the amount of drug in solutions.

Dissolution test apparatus-2 (paddle type): It is same as apparatus-1, except the basket is replaced by a paddle. The dosage form is allowed to sink to the bottom of the flask before stirring. For dissolution test USP specifies the dissolution test medium and volume, type of apparatus to be used, rpm of the shaft, time limit of the test, and assay procedure for the same. The test tolerance is expressed as a percentage of the labeled amount of drug dissolved in the time limit.

Defects of Tablet Coating

Learning Objective

- Types of coated tablet defects and its causes

Variation in formulation and processing conditions may result in unacceptable quality defects in coated tablets. Some of the defects are as follows:

1. **Picking and sticking:** Over spraying or excessive film tackiness causes the tablets to stick with each other or to the surface of the pan.
   On drying a small layer of the polymer film may remain adhered onto the pan or onto another tablet giving a picked appearance on the tablet surface.
2. **Roughness:** A rough or gritty surface on the coated tablet is a defect observed when the coating is applied by a spray gun. During the process some of the droplets may dry too rapidly before reaching the tablet bed resulting in a spray dried particles instead of finely divided droplets of coating solution.
3. **Orange peel:** Inadequate spreading of the coating solution before drying or rapid drying of the polymer solution before reaching the tablet bed due to increased temperature fluctuation causes orange peel.
4. **Bridging:** During drying, the film coat may shrink and it may pull away from the sharp corners resulting in bridging of the surface. This problem is mainly due to defects in formulation of the coating solution.

5. **Filling:** It is caused by applying or spraying more coating solution than required resulting in a thick film that fills the monogram or bisect.
6. **Blistering:** During coating when the drying temperature is increased, it leads to the change in the strength, elasticity and adhesion of film, which results in blistering.
7. **Bloom/Hazing/Dull film:** This can occur due to elevated temperature during the drying of the coated tablets and also if the coated tablets are exposed to high relative humidity.
8. **Mottling:** This can occur due to improper color selection, processing conditions, non-uniform mixing of the color with the solvent, uneven spray pattern, or over drying during coating procedures.
9. **Cracking:** It occurs if the internal stress in the film exceeds the tensile strength of the film. Tensile strength of the film can be increased by using high molecular weight polymer blends. The internal strength in the film can be increased by increasing the plasticizer concentration in the formulation.

CAPSULES

Learning Objective

- Definition of capsules, merits and demerits with its classification

Definition

Capsules are solid unit dosage form of medicament in which the drug is enclosed in a hard or soft container or shell made of suitable form of gelatin.

Advantages

1. They are attractive in appearance.
2. Drugs with unpleasant odor and taste can be enclosed in the shell.
3. The dose and combination of drug can be altered.
4. They are economical.
5. Ease of administration and portability.
6. Less formulation additives and processing steps when compared to tablets.
7. Disintegration time is lesser when compared to ordinary tablets.

Disadvantages

1. Drugs that are hygroscopic, deliquescent, effervescent or efflorescent are not suitable for filling into capsules.
2. Irritant GIT drugs cannot be formulated in capsule form.
3. They are not tamper proof resistant.

Classification of Capsules

Hard Gelatin Capsule

Manufacture of hard gelatin capsules includes the following steps:

Manufacture of capsule shells

Extraction of gelatin: Gelatin is a heterogeneous product derived by irreversible hydrolytic extraction of treated collagen obtained from animal bones and skin (Fig. 5.2). The properties of gelatin that are to be evaluated are as follows:

1. **Bloom Strength:** It is defined as assessment of cohesive strength of cross-linking taking place in between the molecules of gelatin. It is also known as gel strength of gelatin and depends on the molecular weight of gelatin. The harder the gelatin higher the bloom strength. The weight required to move a standard plunger in to standard $6\frac{2}{3}$%w/v gelatin solution determines the bloom strength of gelatin. Bloom strength must be between 150 and 250 bloom grams.
2. **Viscosity:** Viscosity of gelatin is required to control the thickness of the film, which is measured by standard $6\frac{2}{3}$%w/v gelatin solution maintained at 60 °C. The range of viscosity should be between 30 and 60 millipoise.
3. **Iron content:** Iron is present in both raw gelatin and water used for manufacturing gelatin capsule shells. Excess amount of iron can affect Food drug and cosmetics (FDC) certified dyes and may react with other organic compounds. Iron is used in a concentration not more than 15 ppm.

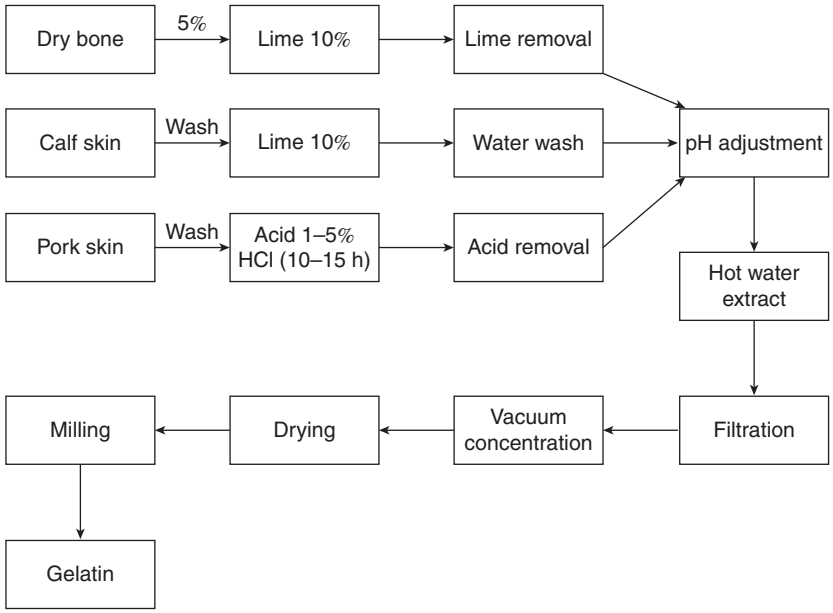

Figure 5.2 Schematic Representation for Extraction of Gelatin

Two types of gelatin used are as follows:

1. *Type A gelatin* is derived from acid treated precursor and exhibits an isoelectric point in the region of pH 9.
2. *Type B gelatin* is derived from alkali treated precursor and has an isoelectric point of pH 4.7.

Capsules can be made from either type of gelatin but usually a mixture of both is used. Bone gelatin produces a tough film but it becomes hazy and brittle. However, the pork skin gelatin contributes the plasticity, clarity and elasticity producing a transparent film. Blends of bone and pork skin gelatin of relatively high gel strength are normally used for hard capsule shell production.

Preparation of gelatin solution

1. **Gelatin**—Gelatin extracted of Type A and Type B are used.
2. **Plasticizer**— normally used are glycerin or sorbitol or in combinations. The ratio of gelatin and plasticizer is (0.4:1).
3. **Preservatives**—usually mixture of 0.2% w/v of methyl paraben and propyl paraben are used. Others like sodium sulfite or sodium metabisulpfite can also be used.
4. **Coloring agents**—Various FDC approved dyes and pigments are used.
5. **Opacifying agents**—Titanium dioxide (0.3%) is generally used to make the shell opaque, which is specially used to provide protection against light.
6. **Sugar—**included in the formulation up to 5%, which acts as a sweetening agent and also increases the viscosity of the gelatin solution.
7. **Demineralized water—**used as a vehicle for the gelatin solution preparation.

Processing of capsule shells

1. **Dipping:** The required pairs of stainless steel mould pegs or pins (long length with lesser diameter for body and short length with larger diameter for cap) are dipped in gelatin solution for a period of 12 s, which helps in achieving proper length and thickness of shells.
2. **Spinning:** After dipping, the pins are rotated for uniform distribution of gelatin solution and withdrawn with a blast of cold air.
3. **Drying:** The gelatin coated pins are introduced into the drying chamber and dried at specified temperature and humidity.
4. **Stripping:** After drying, the cap and body portions are stripped off from the pins by using jaws made of bronze.
5. **Trimming:** The body and cap portions are trimmed to required sizes. The trimmed cap and body are joined and capsule shells are sent to sorting section for inspection.

Formulation of the blend

1. **Drug:** Medicament may be single or multicomponent.
2. **Bulking agent/Diluents:** If the dose of the drug is very less and to increase the bulk volume for filling of the capsules as per the size of the capsule shell selected, bulking agent is used. For example, lactose, starch, sucrose, and mannitol.
3. **Disintegrating agent:** To enhance the rate of disintegration of capsules, especially for water insoluble drugs are used. For example, starch, sodium CMC, PVP and sodium starch glycolate.
4. **Glidant and lubricant:** For the easy flow of the powder blend from the hopper in to the body of capsule shell and also for easy ejection of the filled capsule from the capsule filling machine the above ingredients are added. For example, purified talc and magnesium stearate.

Filling, sealing and packing of capsules

Capsules are manufactured as depicted in Figure 5.3.

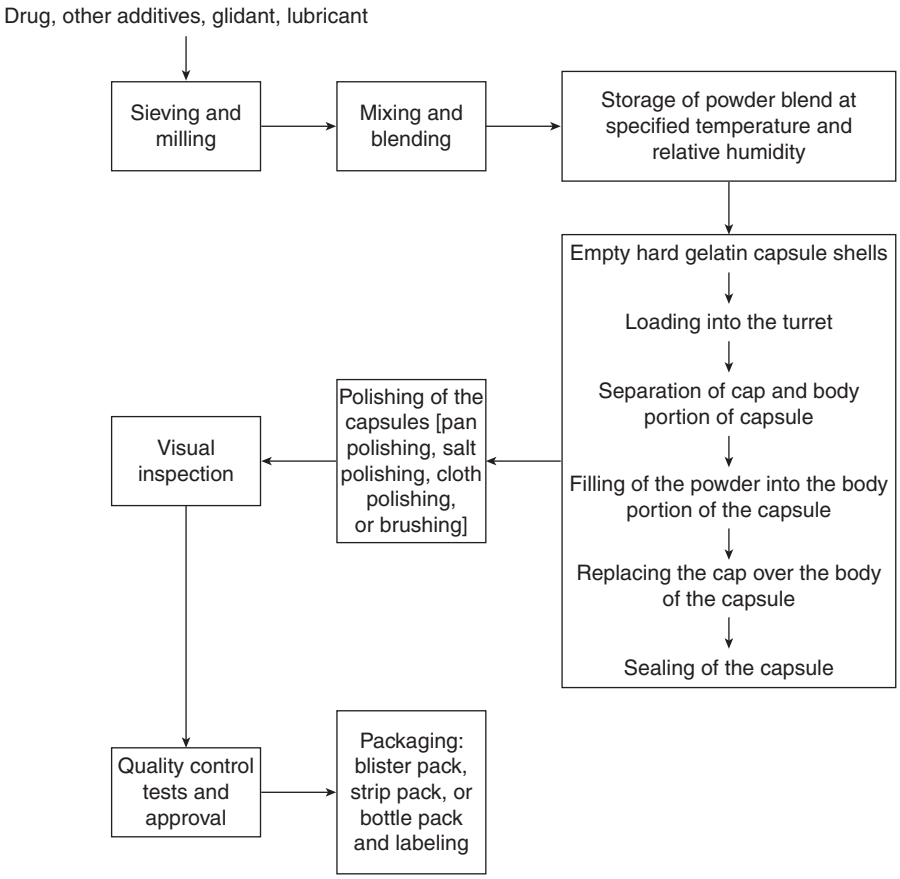

Figure 5.3 Process Layout of Capsule Manufacture

Soft Gelatin Capsules

It can be defined as the unit SDF in which the drug is enclosed in a soft shell made up of gelatin. The drug enclosed is usually in the form of solid, liquid or semi-solid.

It is a unit SDF available in various sizes and shapes such as spherical, tubular, oblongated, and ovoid.

Advantages

1. It is suitable for solids, liquids, suspension, emulsions, volatile oils, semi-solids, etc.
2. Disintegration is faster compared to hard gelatin capsules and tablets.
3. Available in various sizes and shapes.
4. It can be easily swallowed when compared to hard gelatin capsules.

Disadvantages

1. It cannot be used for drugs that are hygroscopic, effervescent and deliquescent in nature.
2. It is not suitable for acidic drugs, ketones and aqueous products.
3. The drugs that irritate the stomach extremely cannot be given in this dosage form.

Formulation of the capsule shell: The capsule shell is composed of gelatin material, water with higher concentration of plasticizer. It also contains additional ingredients such as preservatives, coloring agents, opacifying agents, flavoring agents, etc.
Some of the specifications during the manufacturing process are as follows:

1. **Gel strength or bloom strength:** It is measured by using bloom gelometer, which determines the weight in grams required to depress a standard plunger from a fixed dispenser into the surface of a $6\frac{2}{3}$%w/v of gelatin solution under standard conditions. It measures the cohesive strength of the cross link between gelatin molecules, and it is directly proportional to the molecular weight of the gelatin. The standard range for bloom strength is between 150 and 250 bloom grams.
2. **Viscosity:** 25–45 mps (millipoise).
3. **Iron content:** The iron content of the gelatin used for the manufacture of the soft gelatin capsules should not be more than 15 ppm because of its effects on the color used in the preparation and also possible chemical reaction in the product.
4. **Plasticizer:** Its concentration to that of the gelatin should be in the range of 0.8:1, which renders the shells of elasticity and increases its plasticity. For example, glycerin, sorbitol, or combination.

Formulation of the blend: During the formulation of the blend when a product is determined to be dispensed in the liquid form, then the following two parameters are to be monitored:

1. **Base absorption factor:** Formulation of suspension for gelatin encapsulation, the factor base absorption factor is considered. It can be defined as the number of grams of the liquid base required to produce an encapsulated mixture when mixed with 1 g of the solid drug.
   This can be determined by the following formula:
   Base absorption factor = Weight of the base/Weight of the solid
2. **Minim per gram factor:** It can be defined as the volume in minims occupied by 1 g of the solid drug along with the weight of the liquid base required to form an encapsulated mixture.

$$M/g = (BA + S)V/W$$

M/g = Minim per gram factor
BA = Weight of the base
S = 1 g of the solid
V = Volume occupied by encapsulated mixture
W = Weight of the encapsulated mixture
1 minim = 0.06 ml

Thus, lower the base absorption of the solids, higher will be the density of the mixture and hence smaller will be the size of the capsule shell.

Preservatives: These substances are included to prevent the microbial contamination of the shells as gelatin are obtained from animal source. Usually a combination of methyl paraben and propyl paraben are used.

Coloring agents: FD&C approved color dyes, pigments and lakes are used.

Opacifying agents: Titanium dioxide, aluminum hydroxide, etc.

Drugs: The drug, which is used for the soft gelatin capsules, may be in the form of the solid, liquid, or semi-solid. The volume of the capsule fill may range from 0.3 to 30 ml.

Manufacture of soft gelatin capsules: The manufacture of soft gelatin capsules is done by using rotary die process by form fill and seal (FFS) technique. In this method, the gelatin mass is fed by gravity on to an air cooled rotating drums. Gelatin films of controlled thickness are produced, which may vary from 0.022 to 0.045 inches and the gelatin film passes through the guider and comes in contact with two identical die-rollers, which rotate in opposite direction maintained at controlled temperature so that the gelatin film cavity is formed. The medicament to be capsulated flows by gravity into a positive displacement pump, which accurately dispenses the medicament into the gelatin wedge. After filling, by the movement of the rollers, the dies come in contact with each other such that the sealing of the capsules occur. The sealing of the capsules is achieved by mechanical pressure applied on the die rollers with the controlled temperature and relative humidity maintained. The sealed capsules are cut uniformly by the cutter and then immediately conveyed through naphtha belt to remove the excess of mineral oil lubricant. Finally, filled capsules are subjected to IR drying to remove the excess of moisture. Later the capsules are stored at specified temperature and humidity until packaged.

The soft gelatin capsules are usually blister or aluminum seal packed and the bulk package is carried out by using airtight plastic or glass container.

Differences between hard gelatin capsule and soft gelatin capsule are shown in Table 5.4.

Table 5.4 Differences between Hard Gelatin Capsule and Soft Gelatin Capsule

Sl. No	*Hard Gelatin Capsule*	*Soft Gelatin Capsule*
1.	They are made up of cap and body portions.	They are made as a single entity.
2.	Only solid medicaments can be filled.	Solid, liquid, and semi-solid medicaments can be filled.
3.	Disintegration time is low.	They undergo fast disintegration.
4.	Capsule filled can be opened and sealed.	Once opened they cannot be sealed.
5.	Capsule fill weight ranges between 100 and 950 mg.	Capsule fill volume ranges between 0.3 and 30 ml.
6.	Available in only one shape.	Available in various shapes and sizes.
7.	Concentration of plasticizer to gelatin ratio is low (0.4:1).	Concentration of plasticizer to gelatin ratio is more (0.8:1).

Quality Control Tests for Capsules

Uniformity of Weight

This test is only applicable to those capsules that need to comply with the test for uniformity of content of the main active ingredient. Weigh the capsule and open the capsule carefully without any spillage to remove the encapsulated contents completely. For soft gelatin capsules, the shell has to be washed with *ether* or any other suitable solvent and allowing the shell to stand until the odor of the solvent gets completely removed. Weigh the empty shell again and the difference between the weights is the actual weight of contents. Repeat the procedure for another 19 capsules. Record the average weight. Not more than two of the individual weights (capsules) should deviate from the average weight by more than the specified percentage deviation shown in Table 5.5 and none of the capsules to deviate by more than twice that percentage.

Table 5.5 Official Limits for Uniformity of Weight

Average Weight of Capsule Contents	*Percentage Deviation (%)*
Less than 300 mg	10
300 mg or more	7.5

Uniformity of Content

The content of active ingredient in each of 10 capsules taken at random is determined according to the method given in the monograph or by following any other relevant analytical method of high accuracy and precision. The capsules pass the test if not more than one of the individual values is outside the specified limits 85–115% percent of the average value and none should be falling outside the limits of 75–125%. If two or three individual capsule values are lying outside the limits of 85–115% of the average values, the determination has to be repeated using another 20 capsules. The capsules comply with the test if from the total sample of 30 capsules, not more than 3 individual values are outside the 85–115% and none is outside the 75–125% limits of the average value.

Diameter Check

This test is carried out using a capsule diameter sorter. The capsules are fed from the hopper into sorter and are allowed to pass into next unit maintained at 0.02 inch above the theoretical diameter of capsule. The equipment is provided with a vibrator so that capsules fit into operator.

Disintegration Test

Hard gelatin capsules: IP uses disintegration test apparatus with 250 ml or 1 L of specified disintegration medium maintained at 37 ± 2 °C and for specified time as per monograph. If 1–2 capsules fail, repeat for another 12 different units. 16 out of 18 capsules indicate that the test is affirmative.

BP uses disintegration test apparatus with water or specified liquid medium. Add a metal disc to prevent capsule from floating and operate for 30 min or as per monograph. If 1–2 fail, repeat for another 12 different units. Sixteen out of 18 indicate test is affirmative.

Soft gelatin capsules: IP uses disintegration apparatus with 250 ml or 1 L of specified medium at 37 ± 2 °C and for specified time as per monograph. To test for disintegration time, one capsule is placed in each tube and the basket rack is positioned in a 1-L beaker of water, simulated gastric fluid or simulated intestinal fluid at 37 ± 2 °C such that the sample remains 2.5 cm below the surface of liquid

on their upward movement and not closer than 2.5 cm from the bottom of the beaker in their downward movement. Move the basket containing the capsules up and down through a distance of 5–6 cm at a frequency of 28–32 cycles per minute. If 1–2 fail, repeat for 12 different units. Sixteen out of 18 capsules indicate that the test is affirmative.

United States Pharmacopoeia (USP) procedure is similar to that of uncoated tablets. Place one dosage unit in each of the tubes of the basket with water or any other specified medium (depends on individual monograph) maintained at 37 ± 2 °C. Attach a removable wire cloth with a plain square weave of 1.8–2.2 mm of mesh aperture and a wire diameter of 0.60–0.655 mm to the surface of upper rack of the basket assembly. Observe the capsules for a time limit (specified in individual monograph), at the end of prescribed time, all of the capsules must have been disintegrated excluding the fragments from the capsule shell. No palpable material to remain on the mesh. If 1 or 2 capsules fail, the test should be repeated on additional of 12 capsules. Then, not lesser than 16 of the total 18 capsules tested should disintegrate completely.

Dissolution Test

Place each of the capsules in the apparatus-1 of dissolution tester, excluding air bubbles from the surface of the capsule. Operate immediately at specified rate within specified dissolution medium at 37± 0.5 °C. Aliquots should be withdrawn at specified time points or as mentioned in individual monograph and the volume of withdrawn sample should be replaced with the fresh media to maintain the sink conditions. The withdrawn aliquots are suitably diluted and analyzed for the percentage drug release by following reported analytical procedure and instrument.

PILLS

Learning Objective

- Introduction and definition of pills

A pill is a small, round and unit solid pharmaceutical oral dosage form that was in use before the advent of tablets and capsules. They are prepared by blending or mixing the active ingredients with selected excipient glucose syrup in a mortar and pestle resulting in a paste, then rolling the resultant mass into a long cylindrical shape (pipe) and dividing it into equal portions. These portions are then rolled into balls and coated with sugar to make them more palatable. In a broad sense even tablet, capsules and caplets are still collectively referred to as "pills."

PASTILLES

Learning Objective

- Definition of pastilles and its uses

Pastilles (also known as troche) are a type of candy or medicinal pill made of a thick liquid that has been solidified and is meant to be consumed by light chewing and allowing it to dissolve in the mouth. They are made by transferring a liquid, which is viscous into a mold with added sugar or wax and then the

liquid is allowed to set and dry. The dried liquid substances when chewed slowly release the drugs and dissolve in the mouth. The released liquid is then absorbed by the mucous membrane of the oral cavity.

The base of pastilles is usually a mixture of gums such as starch and gum arabic. The gums emulsify the ingredients and fix them in a hydrocolloidal matrix. The presence of gums helps in reducing in the rate at which the pastilles dissolve and controls the concentration of active ingredient delivery at different time intervals. It also helps in making the pastilles physically stable especially during storage and transport.

VITRELLAE

Learning Objective

- Definition of vitrellae

Vitrellae are thin-walled glass capsules containing a volatile ingredient and protected by absorbent cotton wool and an outer silk bag. During its use, the capsule is crushed and the vapor is inhaled.

Liquid inhalation: Amyl nitrite 0.2 ml/dose

CACHETS

Learning Objectives

- Definition of cachets
- Classification of cachets, its merits and demerits

Cachets or wafer capsules are unit solid oral dosage forms in which drug is enclosed in a tasteless sheet formed by pouring a mixture of rice flour and water between two hot polished revolving cylinders. The water evaporates and a sheet of wafer is formed, which is termed as cachets.

Advantages

1. They are easy to manufacture. No complicated machinery is required as in case of tablets.
2. They are suitable for incorporating large doses of drugs.
3. Disagreeable drugs under investigation are dispensed extemporaneously and quickly.
4. They undergo fast disintegration in the stomach.

Disadvantages

1. They are not firm and can be easily damaged.
2. They provide poor protection to drugs from light and moisture.
3. They are to be softened before swallowing.
4. They occupy more space than the corresponding sizes of tablets and capsules.
5. They are fragile in nature and not suitable to be filled using automated machines.

Classification of Cachets

Wet Seal Cachets

They are made up of two similar convex halves having flat edges. The weighed amount of powder is placed in one half. The edges of the other are moistened with water and placed exactly over the first half containing the powder. Edges of both the halves are pressed together so as to make a perfect seal.

Dry Seal Cachets

They consist of two halves, the upper half and the lower half. The former one is little larger in diameter than the lower half. The powder is filled in lower half and upper half is fitted over it like a lid over a box. The backs of upper as well as lower halves have small projections which are used to fix the cachet in the holes of the machine. The lower halves are fitted into the lower plate of a machine and powder filled in them. The upper halves are fitted in the upper plate by means of projections, which will not allow the cachet to fall when the plate is removed. The upper plate is pressed on the lower plate forcing the upper halves or lids to fit exactly over the lower halves. The filled cachets are removed and packed in boxes.

Dispensing: The cachets are dispensed in a box if necessary empty spaces are filled by cotton wool so as to fix them properly in the boxes. The boxes are labeled with direction of use *"Immerse in water for few seconds and then swallow with little water."*

POWDERS

Learning Objectives

- Introduction to powders
- Preparation and analysis of powders

A powder is a homogenous mixture of more or less finely divided particulate material in dry form. Although the use of powders as a SDF has declined yet they are the starting material in the manufacture of many dosage forms. Powders are one of the oldest dosage forms and are used both internally and externally. They impart flexibility (with regard to a wide selection of drugs, combination and dosage ranges), stability (drugs like aspirin and penicillin are more stable in powdered form than in solution), rapid therapeutic effect (rapid attainment of therapeutic blood levels and rapid absorption from finely divided powders due to large specific surface area), and ease of administration to all categories of patients. However, the preparation of powders is not a suitable dosage form for unpleasant tasting, hygroscopic and deliquescent drugs.

Advantages

1. Powders are more physically and chemically stable when compared to liquid dosage form.
2. The drug product in the powder dosage forms is less prone to microbial contamination.
3. It is an ease mode of drug administration when the dose is very large.

4. It is well accepted by pediatric and geriatric patients.
5. The rate of dissolution and absorption is faster in powder dosage form when compared to any other SDF.

Disadvantages

1. Powders are bulky dosage form and causes difficulty in handling and transport.
2. They are not easily transferrable from a container and may spill.
3. The method of preparation and packaging are time consuming.
4. Drug substances that are having an unpleasant taste are not suitable to administer in powder form.
5. The substances that are hygroscopic, deliquescent, volatile and oxygen sensitive are not suitable to be administered in powder form.

Classification of Powders

The classification of powders is as follows:

1. **Aerosol powders:** Medicated powders that are taken or administered by inhalation with the help of a dry powder inhaler are aerosol powders. The products delivered by this route are intended for the treatment of asthma or bronchial disorders. The particle diameters, which are delivered by this route, are in the range of 1–6 μm. These products also contain inert propellants and pharmaceutical diluents to protect the powder from humidity, to aid in flow property and for the metering uniformity.
2. **Bulk powders:** Medication in bulk powder forms is limited to non-potent substances. Examples of powders taken in the bulk forms are medicated topical anti-infectives such as polymyxin B sulfate, tolnaftate, etc., douche powders for vaginal use such as Massengill powder, reconstituted antacid preparation such as sodium bicarbonate, laxative such as psyllium, etc.
3. **Divided powders:** These are properly blended by using geometric dilution method and then based on the amount to be taken at a single time are divided as single dosing units. The divided powders are packed in small piece of paper folded to enclose the medication. Examples: Powdered laxatives, douche powder and analgesic powders.
4. **Effervescent powders:** These powders when mixed with water shows effervescence with the liberation of carbon-di-oxide. The effervescence also helps in masking the bitter taste of active ingredients. The usual content of these powders are sodium bicarbonate, organic or inorganic acids such as citric acid, tartaric acid, etc.
5. **Explosive powders:** Substances such as an oxidizing agent and reducing agent when triturated in a mortar and pestle there are chances of explosion, which may occur due to the heat generation and may lead to serious consequences. To handle such type of powders each ingredient should be separately triturated and lightly mixed without applying any pressure. Alternatively the powders can be individually triturated and can be separately packed and dispensed with suitable directions to the patient regarding its use.

   Some of the oxidizing and reducing agents are listed in Table 5.6.

Table 5.6 List of Oxidizing and Reducing Agents

Oxidizing Agents	*Reducing Agents*
Potassium chlorate	Charcoal
Potassium dichromate	Sulfur
Potassium nitrate	Sulfides
Potassium permanganate	Tannic acid
Silver nitrate	

6. **Medicated powders for internal use:** These powders are available to be used both internally and externally. Internally used powders are added in water or directly taken internally. Internal medicated powders can also be inhaled for both local such as analgesics and systemic use such as laxatives. Medicated powders taken systemically will have faster rate of dissolution and absorption when compared to any other SDFs. These powders are also available in reconstituted form.
7. **Insufflations:** These powders are usually applied with an applicator known as insufflators. Insufflations are finely divided powder form introduced into different body cavities such as nose, ear, vagina, tooth sockets, etc. When the insufflator is compressed, a current of air distributes the powder particles in a stream of gas through the nozzle into the delivery site. Uniform dose delivery may not be obtained by insufflations.
8. **Dusting powders:** Dusting powders are used externally for local application, not intended for systemic action. The desirable characteristics of dusting powders are non-irritability, homogeneity, free flow, good spreadability and covering capability, fine state of subdivision, and capacity to protect the skin from chafing and irritation caused by friction, moisture, and chemical irritants. The formulation usually contains substances such as kaolin, talc, zinc oxide, starch, and boric acid. These powders are micronized by passing through sieves #85 or 120. It should be preferably dispensed in sifter-top containers. Such containers provide the protection from air, moisture, and contamination as well as convenience of application. It should contain a label as "FOR EXTERNAL USE ONLY." The categories of drugs dispensed are lubricants, protectives, adsorbents, antiseptics, antipruritics, astringents and antiperspirants. Dusting powders can be classified into the following two types:
   (a) **Medicated dusting powders:** These are the bulk SDFs, which are intended to be applied on the intact skin for local action.
   (b) **Surgical dusting powders:** These are the bulk SDF, which are intended to be applied into the deep layers of the skin. These preparations need to be sterile as it comes in contact with open wounds and deep layers of the skin.
9. **Dentifrices:** Dentifrices are bulk powders for external use to clean teeth. They mainly contain an abrasive agent such as precipitated calcium carbonate or hydrous dibasic calcium phosphate. It also contains a surfactant, mild soap or detergent and sweetening agents.
10. **Douche powders:** These powders are most commonly used for vaginal use and intended for the action of cleansing agents or used as an antiseptic. They may also be used for nasal or ophthalmic route. The main criteria for these preparations are to ensure complete mixing and to maintain the micronized particle size by passing through sieve #85.

Preparation of Powders

1. **Trituration:** In this method, particle size reduction of coarse granular substances or lumps is carried out using a mortar and pestle or mill. Sometimes even dry powder substances are mixed using this method.
2. **Pulverization:** Soft and gummy substances are difficult to powder in mortar and pestle. Such substances are powdered by adding an inert material that helps in powdering and are removed afterwards. A typical example is camphor, which is powdered by moistening in presence of alcohol and after the preparation, alcohol is allowed to evaporate.
3. **Levigation:** In this method, a solvent is added to the dry powder to form a paste. The solvent is known as the levigating agent. The powder-solvent paste is then triturated using mortar and pestle. In the preparation of semi-solid dermatological preparations, ophthalmic ointments and suspensions, this method is used, which prevent the gritty feeling in these formulations. Typical example of levigating agent is liquid Paraffin.
4. **Spatulation:** In this method, the powders are blended in small amount by movement of a spatula on an ointment tile or on a small sheet of paper. The process is only suitable for small quantities of powder. Powders having potent substances or with a large quantity are not blended by this method, because the process does not ascertain a homogenous blending. Solid substances that form eutectic mixtures are suitable for blending with spatulation because compacting of the powders results from these. Examples of substances that can be blended by this method are—camphor, menthol, phenol, thymol, aspirin, etc.
5. **Tumbling:** Special motorized powder blenders are used in this process, whereby the powder is mixed by tumbling in a rotating chamber. The process is time consuming.
6. **Sifter mixing:** Powders are mixed by passing through sifters, which results in light and fluffy products. The process is not suitable for the incorporation of potent drugs into a powder mix.

Incorporation of Ingredients into Powders

In the preparation of powders, some special modifications are followed for incorporation of some of the substances. The modified procedures are as follows:

1. **Hygroscopic and deliquescent powders:** Substances such as sodium bromide, zinc chloride, etc., have strong affinity to absorb moisture from the atmosphere. When the moisture absorption crosses the limits, these substances even liquefy. Such substances are usually used in the granular form rather than powder form to expose the lower surface area to the atmosphere. These types of powders should be double wrapped.
2. **Volatile substances:** Agents containing volatile oils undergoes volatilization in the atmosphere upon incorporation in the powder. The examples of such agents are camphor, menthol, etc. These agents should be packed by double wrapping with an inner waxed paper and outer bond paper cover by using heat sealed plastic bags.
3. **Eutectic powders:** Substances having low melting point when triturated and mixed together will form a powder blend with low melting point as compared to individual melting points and whose temperature would be less than the room temperature and hence liquify. Examples of

eutectic substances are thymol, menthol, camphor, phenol, aspirin, etc. The components of these powders should be dispensed separately with directions like powder of each kind should be taken as a dose. Another alternative method is by addition of double the proportion of an inert high melting point diluent such as magnesium carbonate, light magnesium oxide, kaolin or talc, etc., and mixing together with the eutectic substances without applying pressure.

4. **Efflorescent powders:** Crystalline substances, which liberate water of crystallization when present, cause a powder to liquefy. Examples of these substances are citric acid, ferrous sulfate, caffeine, etc. Employment of anhydrous salt of these substances is a remedy.
5. **Liquids:** Incorporation of liquids into a powder substance is done by trituration of the liquid (small concentration) with an equal volume of powder and then addition of the remaining powder in several portions with trituration.

Granules

Granules are agglomerates of powders. Depending upon the application, various granules of different size can be prepared. The usual size ranges of granules are in the range of 4–12 sieve.

Advantages of Granules

1. They flow better than powders. The easy flow characteristics are important in supplying drug materials from the hopper or feeding container into the die cavities of the tablet compression machine. For this reason, powder mixtures are usually granulated if they are intended to be compressed into tablets. Granules also eliminate or control dust.
2. They increase compressibility.
3. They have smaller surface area than a comparable volume of powders. This makes granules more stable physically and chemically than the corresponding powders.
4. They are more easily wetted by a solvent than certain powders, so that granules are also preferred in making solutions.
   Example: Ampicillin is unstable in aqueous solution, so it is usually prepared as granules and reconstituted with boiled and cooled water just prior to administration. The granules also contain colorants, flavorants and other pharmaceutical ingredients. So the resulting solution or suspension has all the desired medicinal and pharmaceutical features of a liquid pharmaceutical.
5. They produce particle-size uniformity and thus content uniformity.

Particle Size Analysis

Pharmaceutical powder particles range from about 10 mm in diameter to 1 micron or less. Particle size analysis is helpful in the determination of size, shape, distribution of drug and other components used in pharmaceutical formulations. Powder particle size influences a various physical and physiological factors. They are as follows:

1. Content uniformity or dose uniformity of drug substances in sold dosage forms.
2. Size reduction increases specific surface area of the active medicament and hence enhances the rate of dissolution and bioavailability.
3. In suspensions formulation, the particles suspendibility and uniform dispersion of solids in the liquid phase is increased.

4. In aerosol formulation, the drug particle in micronized form penetrate deep into the affected area of the body. Examples are bronchodilators, anti-inflammatory and steroidal drugs.
5. In semi-solid dosage forms such as ointments, creams and ophthalmic preparation, lack of grittiness of solid particles can be monitored.

Methods of particle size analysis

1. **Optical microscopy:** Determination of particle size by this method involves the use of microscope fitted with scaled eyepiece micrometer. Particle size ranging from 0.2 to 100 μm can be determined by this method.
2. **Sieving method:** A series of sieves are arranged in descending order of sieve number in a sieve shaker and the accurately weighed powder particles are passed through it. Then the proportion of powder passing through or being withheld on each sieve is determined. Particle size range of about 40–9500 μm can be determined accurately based on the sieve method.
3. **Sedimentation method:** In this method, Andreasen apparatus is used and the terminal settling velocity of particles through a liquid medium in a gravitational or centrifugal environment is determined. Stoke's law is used to calculate the rate of sedimentation. Particle size range of 0.8–300 μm can be determined by this method.
4. **Light scattering or light energy diffraction:** The process of light scattering involves the use of He–Ne laser, ultrasonic probe and silicon photo diode detectors for particle size determination. Range of particle size determined by this method is 0.02–2000 μm.

   Light energy diffraction involves the determination of particle size by the reduction in light reaching the sensor as particles dispersed in a liquid or gas pass through the sensing zone. Range of particle size determined is 0.2–500 μm by this method.
5. **Laser holography:** The method involves individually imaging and sizing of particles by three dimension photography with a holographic camera (in which a pulsed laser is fired through an aerosolized particle spray). The size range of particles determined by this method is 1.4–100 μm.
6. **Cascade impaction:** The principle of this method depends upon that when a particle moves through an airstream, it will hit a surface that comes across its path and the particles are rebounded and separated into different size ranges by increasing the velocity of the airstream in which the particles moves.

   For an exact determination of the size and shape parameter of the powder particles, a combination of above methods discussed is preferred. Commercially used particle size analyzers are automated and linked with computers for data processing, distribution analysis and printout.

Packaging of Powders and Granules

1. Depending upon the drug substances present in powders or/and granules the packaging is chosen. Single dose paper packets are used for powders and granules containing stable drugs.
2. A double wrapped paper packet lined with waxed paper is used for moisture sensitive drugs.
3. A wide mouth airtight glass or plastic containers are used for effervescent or granular substances. It is easy to withdraw the content from a wide mouthed container. Sometimes, a single dose or multiple dose aluminum foil is also used for packaging purposes.
4. Sifter-top packages or pressure aerosol containers are used for dusting powders.

Labeling of Powders and Granules

The following information should be there in the labels of powders and granules:

1. Name of the preparation.
2. Strength of the therapeutic agent present.
3. Directions for use like—dose frequencies for powders and granules to be taken internally, how to apply on the affected part for externally applied powders, etc.
4. It should be mentioned as "For external use only" and "Not to be applied to open wounds or to raw or weeping surfaces," in case of medicated dusting powders.
5. A warning indicating "Keep out of the reach of children."
6. Some legal requirements on the label are—batch number, license number, manufacturing date, expiry date and name of the company.

Storage Conditions

1. A cool and dry place should be chosen for the storage of powders and granules.
2. A light resistant container should be chosen for light sensitive preparation.

REVIEW QUESTIONS

Answer in Detail

1. Explain the different stages involved in sugar coating of compressed tablets.
2. Discuss in detail the steps involved in the sugar coating of tablets.
3. Give a detailed account of the different excipients used in tablet manufacture and their functions.
4. Explain in detail the different granulation techniques. Name any two equipments employed.
5. Explain in detail the evaluation tests for compressed tablets.
6. Explain the specifications and standards for empty gelatin capsules. Explain the equipment used for filling capsules.
7. What are the types of capsules? Discuss in detail about the extraction of gelatin, formulation, and filling process of hard gelatin capsules.
8. Discuss in detail the classification of powders with suitable examples.

Answer in Brief

1. Explain wet granulation method.
2. Discuss the defects in film coating.
3. Give a brief account of evaluation of tablets.
4. Write a note on slugging.
5. Explain the hardness test for tablets.
6. Explain the processes of tablet compression.
7. Discuss on the film defects of coated tablets.
8. Explain the dissolution test for tablets.

9. What are the advantages and disadvantages of dry granules?
10. Explain mottling and its prevention in tablets.
11. Discuss in handling of eutectic powders and explosive powders.
12. Explain the various methods used to determine the particle size of the powder.
13. Classify powders with suitable examples.
14. Explain the handling techniques of liquids in powder formulation.
15. Discuss on the various methods for the manufacture of powders.
16. Explain filling process of hard gelatin capsule.
17. Write a note on hard gelatin capsules.
18. Explain formulation of the capsule content in soft gelatin capsules.
19. Describe the manufacture of hard gelatin capsule shell.
20. Differentiate between hard gelatin and soft gelatin capsules.
21. Mention the importance of base absorption and minim/gram factor.
22. Give the quality control tests of hard gelatin capsules.

Answer in One or Two Sentences

1. Define enteric coating.
2. What are capping, lamination and chipping of tablets?
3. What is spray congealing?
4. Give examples of flavors.
5. What is mottling of a tablet?
6. What is meant by sugar coating?
7. What are soft gelatin capsules?
8. Which are the diluents used in chewable tablets? Why?
9. List the quality control tests performed on coated tablets with their limitations.
10. What are suppositories?
11. Define displacement value.
12. Classify tablets.
13. List the official and unofficial quality control tests for tablets.
14. How do you select the size of empty hard gelatin capsules for formulations?
15. List the enteric coating materials.
16. What are explosive powders?
17. What are pastilles?
18. What are vitrillae?
19. What are insufflations?
20. Write about eutectic powders.
21. Differentiate between hard gelatin and soft gelatin capsules.
22. Define bloom strength.
23. What is base absorption factor?
24. What is minim per gram factor?
25. What is orange peel effect?
26. What are the advantages of tablet coating?
27. Define disintegrating agents.

Multiple Choice Questions

1. The sweetening agent commonly used in chewable tablet formula is _____.
   (a) sucrose (b) mannitol
   (c) cyclamate sodium (d) saccharine sodium
2. Sub-coating is given to the tablet _____.
   (a) to increase the adhesive of syruping
   (b) to avoid deterioration due to microbial attack
   (c) to prevent the solubility in acidic medium
   (d) to avoid stickiness
3. The following ingredients are commonly used as the coating agents for film coating except _____.
   (a) cellulose acetate phthalate (b) carnauba wax
   (c) hydroxy ethyl cellulose (d) carboxy methyl cellulose
4. Sigma blade mixers are commonly used in _____.
   (a) wet granulation (b) powder mixing (c) dry granulation (d) crude fiber mixing
5. Poorly manufactured tablets may have small pin holes on the surface. This phenomenon is known as _____.
   (a) picking (b) mottling (c) leaching (d) cracking
6. Ingredients used for capsulation in soft capsules should flow by gravity at a temperature not exceeding _____.
   (a) 35°C (b) 30°C (c) 25°C (d) 20°C
7. Rotosort is an equipment used _____.
   (a) to separate unfilled capsules
   (b) to fix the cap and body of the capsules after filling
   (c) to separate the improper tablets
   (d) to adjust the required compression of the tablets
8. In capsules, rotofill is used for filling _____.
   (a) powders (b) pellets (c) liquids (d) corrosive liquids
9. The Wurster process can be used to _____.
   (a) coat tablets (b) determine the disintegration time
   (c) gas sterilized parenteral solutions (d) automatic filling of capsules
10. Shellac is used for the purpose of coating of tablets as a _____.
    (a) polishing agent (b) film coating agent
    (c) enteric coating agent (d) sub-coating agents for sugar coating
11. Of the following ingredients, _____ improves the flow property of granules.
    (a) glidant (b) emollient (c) lubricant (d) surfactant
12. Rotosort is a machine used to sort out _____.
    (a) coated tablets (b) filled capsules (c) sealed ampoules (d) sealed containers
13. In sugar coating of tablets, seal coating is done _____.
    (a) to prevent moisture absorption
    (b) to round the edges and build the tablet size
    (c) to smoothen the surface
    (d) to prevent the tablet from breaking due to vibration

14. Tablets are placed into a coating chamber and hot air is introduced through the bottom of the chamber. Coating solution is applied through an atomizing nozzle from one end of the chamber. This technique is called as _____.
    (a) sealing before sugar coating (b) coating by air suspension
    (c) spray pan coating (d) chamber coating
15. In a tablet, dissolution characteristic is tested to determine _____.
    (a) drug interaction
    (b) drug absorption and physiological availability
    (c) drug disintegration and bioavailability
    (d) drug dissociation and absorption
16. Insufflation is a medicated _____.
    (a) inhalant (b) aqueous solution for internal use
    (c) finely divided dusting powder (d) paste for external use
17. Of the following, an ingredient not used for film coating is _____.
    (a) carnauba wax (b) sucrose (c) PEG (d) povidone
18. The unofficial test for tablet is the _____.
    (a) friability test (b) hardness test (c) disintegration test (d) dissolution test
19. Shellac is useful as a _____
    (a) film-costing agent (b) enteric-coating agent
    (c) sub-coating agent (d) antioxidant
20. Lamination is a process involved in the _____.
    (a) polishing the surface of tablet (b) breaking of tablet into two or more layers
    (c) coating tablets with waxes (d) binding ingredients in tablet formation
21. The disintegration time for a sugar-coated tablet is _____.
    (a) 30 minutes (b) 45 minutes (c) 60 minutes (d) 75 minutes
22. 'Slugging' is a method involved in _____.
    (a) capsule filling (b) dry granulation technique
    (c) wet granulation technique (d) quality control test for tablets
23. The limit for friability of a tablet is _____.
    (a) not less than 1% (b) not more than 1%
    (c) in between 0.5% and 1% (d) up to 2% of the initial weight
24. The ratio of plasticizer to gelatin in hard gelatin capsules is _____.
    (a) 0.8:2 (b) 0.4:1 (c) 0.8:1 (d) 0.4:2
25. The ratio of plasticizer to gelatin in soft gelatin capsules is _____.
    (a) 0.4:1 (b) 0.8:1 (c) 0.4:2

ANSWERS TO MULTIPLE CHOICE QUESTIONS

1. (c)	2. (a)	3. (b)	4. (b)	5. (a)
6. (a)	7. (a)	8. (b)	9. (a)	10. (c)
11. (a)	12. (b)	13. (b)	14. (c)	15. (b)
16. (a)	17. (d)	18. (b)	19. (b)	20. (b)
21. (c)	22. (b)	23. (b)	24. (b)	25. (b)

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Liquid Dosage Forms

6

PART I—MONOPHASIC LIQUID DOSAGE FORMS

Learning Objectives

- Different monophasic liquid dosage forms
- Formulation consideration of monophasic liquid dosage forms
- Method of manufacturing and labeling requirements of monophasic liquid dosage forms

A solution is a homogenous mixture composed of only one phase. In such a mixture, a solute (drug substance) is dissolved in another substance, called a solvent. The concentration of a solute in a solution is a measure of the amount of solute dissolved in that solvent.

CHARACTERISTICS OF A SOLUTION

The following are the important characteristics of a solution:

1. It should be a homogenous mixture.
2. The particles of solute are not visible by naked eye.
3. It does not allow a beam of light to scatter.
4. It is stable.

Advantages

The advantages of a solution are as follows:

1. Uniformity of dosage
2. Faster absorption leading to quick onset of action
3. Pleasing appearance leading to enhanced patient compliance

Disadvantages

The disadvantages in using a solution are as follows:

1. It is less stable than solid dosage form.
2. Unpleasant flavors can be difficult to mask.
3. It is bulky to carry.
4. A dropper or measuring device is needed to administer the dose.
5. Accidental breakage leads to total loss of the contents.

CLASSIFICATION OF SOLUTIONS

Solutions are classified on the basis of the following aspects (Figure 6.1):

1. **Route of administration**
   (a) Oral solutions—through oral route
   (b) Otic solutions—instilled in the ears
   (c) Ophthalmic solutions—instilled in the eyes
   (d) Topical solutions—applied over the skin surface
2. **Composition and uses**
   (a) Syrup—aqueous solution containing high concentration of sugar
   (b) Elixir—sweetened hydroalcoholic solution

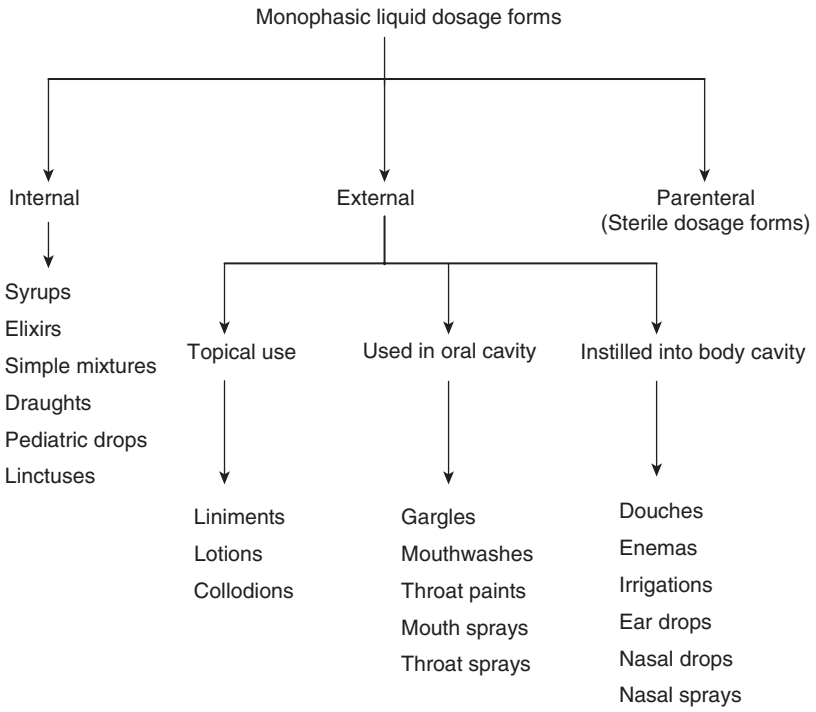


Figure 6.1 Classification of Monophasic Liquid Dosage Forms

(c) Spirit—solution of aromatic materials in alcohol
(d) Tincture/Fluid extract—solution prepared by extracting active constituents from crude drugs by use of alcohol or hydroalcohol
(e) Injection—sterile and pyrogen-free solution intended for parenteral administration

FORMULATION CONSIDERATION OF MONOPHASIC LIQUID DOSAGE FORMS

Solubility

When a solute is dissolved in a solvent, two types of interactions are possible. One is the intramolecular force of attraction between the solute molecules and the other is the intermolecular force of attraction between the solute and solvent molecules. When a solute dissolves, the intramolecular force or cohesive force must be overcome by the force of attraction between the solute and solvent molecules, that is, adhesive force. This involves breaking the solute–solute forces and the solvent–solvent forces to achieve the solute–solvent forces of attraction. The solubility of a drug in a particular solvent indicates the maximum concentration to which a solution may be prepared with that drug and that solvent. The expression of solubility according to Indian Pharmacopoeia is given in Table 6.1.

Table 6.1 Expression of Solubility According to Indian Pharmacopoeia

Descriptive Phrase	*Approximate Quantities of Solvent by Volume (ml) for 1 Part of Solute by Weight (1 g)*
Very soluble	less than 1 part
Freely soluble	from 1 to 10 parts
Soluble	from 10 to 30 parts
Sparingly soluble	from 30 to 100 parts
Slightly soluble	from 100 to 1000 parts
Very slightly soluble	from 1000 to 10,000 parts
Practically insoluble	more than 10,000 parts

Determination of Equilibrium Solubility

An excess amount of drug is placed in a vial along with a specific amount of the solvent. The tightly closed vial is then agitated at constant temperature and the amount of drug in solution is determined by a suitable analytical method. The solubility is generally expressed in mg of solute per ml of solvent at 25°C or per 100 ml. The solubility of a drug depends on the temperature, solvent, pH and chemical nature of the molecule. By modifying these parameters, the solubility of a drug can be manipulated according to the requirement of designing the dosage form.

pH

The solubility of drugs is influenced by the pH of the environment. When a weakly acidic drug is dissolved in water it remains in three states, namely undissolved, dissolved and ionized forms.

The relationship between the equilibrium solubility of a weakly acidic drug and the pH is expressed by Henderson–Hasselbalch equation:

$$pH = pK_a + \log(A^-)/\log(AH)$$

where pK_a is the dissociation constant of the acid, $[A^-]$ is the molar concentration of ionized drug and $[AH]$ is the molar concentration of unionized drug.

To maintain a drug in the soluble state, it must be dissolved in a suitable buffer solution that has adequate buffer capacity in the desired pH range, must be biologically safe for the intended use and must have minimum interference on the stability of the final product. Commonly used buffer systems are ammonium chloride, diethanolamine, carbonic acid, phosphate buffers, glutamic acid, tartaric acid, citric acid buffer and acetic acid buffer.

Cosolvency

Cosolvents are used to increase the solubility of weak electrolytes, nonpolar molecules and volatile constituents that are used to impart a desirable flavor and odor to the product. Weak electrolytes and nonpolar molecules have poor water solubility. These types of solutes are more soluble in a mixture of solvents than in one solvent alone. This phenomenon is called as cosolvency and the solvents that are used in combination to increase the solubility of the solute are called cosolvents. To increase the water solubility of a drug, another water-miscible solvent is used in which the drug has better solubility. A cosolvent works by reducing the interfacial tension between the aqueous solutions and the hydrophobic drug. Examples of commonly used cosolvents are ethanol, sorbitol, glycerin, propylene glycol and polyethylene glycol.

Dielectric Constant

The dielectric constant of a solvent is defined as the ratio of the capacitances of a capacitor filled with the solvent or air.

$$\text{Dielectric constant } (e) = C_{\text{solvent}}/C_{\text{air}}$$

where C is the capacitance of the condenser filled with respective medium (solvent or air).

Every solute shows a maximum solubility in any given solvent system at one or more specific dielectric constants. Pharmaceutical formulations of comparable dielectric constants can thus be prepared and the most appropriate solvent system can be selected on the basis of solubility, stability and organoleptic characteristic requirements.

Solubilization by Surfactants

Solubilization increases the solubility of poorly water-soluble solute molecules in an aqueous solution of surface active agents or surfactants due to which a thermodynamically stable solution is formed. When surfactants are added to water at low concentrations, they tend to orient at the air–liquid interface. As additional surfactant is added, the interface becomes fully occupied and the excess molecules moves into the bulk of the liquid. At still higher concentrations, the molecules of surfactant in the bulk of the liquid begin to form oriented aggregates or micelles. The concentration of surface active agent at which micelles occur is called "critical micelle concentration." The water solubility of the solute

increases with the concentration of the micelles. Examples of solubilizing agents are tweens, spans and sodium lauryl sulphate (SLS). Surface active agents having hydrophilic–lipophilic balance (HLB) values higher than 15 are better solubilizing agents.

Complexation

The solubility of a compound may be increased by complexing it with a complexing agent. When an insoluble compound forms a complex that is more soluble in a solvent, the total solubility is equal to the inherent solubility of the uncomplexed drug and the concentration of the drug complex in solution. When a drug is mixed with water, some amount will get dissolved while some amount will remain undissolved. If a complexing agent is added to it, some quantity of the drug will get complexed and become soluble in water and the total solubility will be increased. When the amount of complexing agent added is increased, total solubility will increase; at a certain concentration of complexing agent, the solution will become saturated with respect to the free drug and the complex. After this point, further addition of complexing agent will form complex and the excess complex will be precipitated. When no drug is left for complexation, complexes of higher order may be formed. For example, iodine is sparingly soluble in water. However in the presence of potassium iodide, it forms a poly-iodide complex, which is completely soluble in water.

Hydrotropy

The term "hydrotropy" has been used to designate the increase in solubility in water of certain substances due to the presence of large amounts of additives. This phenomenon is more closely related to complexation involving a weak interaction between the hydrotrophic agent and the solute. This phenomenon is also due to the change in the solvent character because of the large amount of additive needed to bring about the increase in solubility. Examples of hydrotropic agents are sodium benzoate, urea, sodium acetate, polyvinyl pyrrolidone and sodium salicylate.

Chemical Modification

This enhances the solubility of poorly water-soluble drugs by modifying them into their water-soluble derivatives. For example, the solubility of disodium phosphate ester of betamethasone in water is 1000 times greater than its parent compound.

Solvents Used for Oral Preparations

The solvents usually used in the oral liquid preparations are purified water, alcohol, glycerin and propylene glycol.

Purified water: Naturally occurring water exerts its solvent effect on most of the drug substances. In oral preparations, demineralized water or purified water is used.

Alcohol: This is the most useful primary solvent for many organic compounds. It acts as a cosolvent and increases the solubility of drugs. Alcohol is preferred because of its miscibility with water and its ability to dissolve many water-insoluble ingredients. It is also used in liquid products either as an antimicrobial preservative alone or as a co-preservative with parabens, benzoates, sorbates and other agents.

Glycerin: It is a clear syrupy liquid with a sweet taste. It is miscible with water and alcohol. It has preservative qualities. However, because of its viscosity, solutes are slowly soluble in it unless it is rendered less viscous by heating.

Propylene glycol: It is a viscous liquid and is miscible with water and alcohol. It is a useful solvent with a wide range of applications and is frequently substituted for glycerin in pharmaceutical formulation.

Buffers

These are compounds or mixtures of compounds that resist changes in the final pH upon addition of small quantities of acid or base. Hence, buffering agents are used in the liquid preparation to prevent changes in the pH upon dilution or addition of an acid or alkali. They dissolve weakly acidic or basic drug in solution and increase the stability of the drug. The usual buffering agents used in oral liquid preparations are acetate buffer and phosphate buffer.

Sweeteners

Solutions come into immediate contact with the taste buds on the tongue. Drugs and other adjuvants are generally not palatable. To enhance the palatability and to mask the undesired taste of the drugs, sweeteners are used. Examples of sweeteners are sucrose, saccharin, aspartame, sucralose and liquid glucose.

Coloring Agents

To enhance the appeal and for easy identification of different products, a coloring agent is used. The coloring agent should match well with the flavor in the preparation, for example, green with mint and brown with chocolate flavor. The colorant used should be generally water soluble, nonreactive with other components, stable at the pH range and under the intensity of light that the liquid preparation is likely to be exposed during its shelf life, non-toxic and not have any physiological activity, noninterfering with other adjuvants and analytical procedures, free from objectionable odor and taste and inexpensive. Some of the food, drug and cosmetics colorants that are used in pharmaceuticals are brilliant blue, tartrazine, erythrosine and indigotine.

Preservatives

The sources of contamination in pharmaceuticals arises from raw materials, processing containers, equipment, manufacturing environment, working personnel and packaging materials. These contaminants allow the growth of various microorganisms such as *Salmonella* species, *Escherichia coli*, *Enterobacter* species, *Pseudomonas aeruginosa*, *Clostridium* and *Candida albicans* which are undesirable in oral liquid preparations. The presence of a preservative will hinder the growth of microbes, thereby extending the shelf life of the product (Table 6.2). An ideal preservative should possess the following characteristics:

1. It must be effective against a broad spectrum of microorganisms.
2. It must be physically, chemically and microbiologically stable during the shelf life of the product.
3. It must be nontoxic, nonsensitizing, adequately soluble, compatible with other formulation components and acceptable with respect to taste and odor at the concentrations used.

Table 6.2 Pharmaceutically Useful Preservatives and Their Concentration

Preservative	*Concentration (%)*
Phenol	0.2–0.5
Chlorocresol	0.05–0.1
O-Phenyl phenol	0.005–0.01
Alkyl esters of para-hydroxy benzoic acid (e.g., methyl and propyl paraben)	0.001–0.2
Benzoic acid and its salts	0.1–0.3
Boric acid and its salts	0.5–1.0
Sorbic acid and its salts	0.05–0.2
Chlorobutanol	0.5
Benzyl alcohol	1.0
b-Phenylethyl alcohol	0.2–1.0
Thiomersal	0.001–0.1
Phenyl mercuric acetate and nitrate	0.002–0.005
Nitromersol	0.001–0.1
Benzalkonium chloride	0.004–0.02
Cetylpyridinium chloride	0.01–0.02

Syrups

Syrups usually contain 85%–86% w/v of sucrose. They resist bacterial growth by virtue of their exosmotic effect on microorganisms. For syrups containing less than 85% w/v sucrose, sufficient concentration of polyols such as sorbitol, glycerin, propylene glycol or polyethylene glycol should be added to have the required osmotic pressure.

Flavoring Agents

Objectionable taste in the formulation may lead to nausea, vomiting and patient non-compliance. An attractive flavor will encourage palatability and easy administration. The four basic taste sensations are salty, bitter, sweet and sour. A combination of flavoring agents is usually selected based on the nature of formulation and age group of the patients to whom it is administered. Table 6.3 provides a list of flavors recommended based on the taste sensation.

Table 6.3 Taste Sensation and the Recommended Flavors

Taste Sensation	*Recommended Flavor*
Salty	Butterscotch, maple, apricot, peach, vanilla, mint
Bitter	Wild cherry, walnut, chocolate, mint combinations, anise
Sweet	Fruit and berry, vanilla
Sour	Citrus flavors, liquorice, root beer, raspberry

Manufacturing Consideration of Monophasic Liquid Dosage Forms

The following need to be considered in the manufacture of monophasic liquid dosage forms:

1. **Raw materials:** Raw materials should be tested against specifications such as identity, purity, uniformity and freedom from microbial contamination before the start of manufacturing process. Additional processing such as size reduction, milling or sterilization is required before manufacturing. In preparation of oral liquids, the water used should meet the pharmacopoeial requirements. It should be obtained by distillation or ion exchange treatment.
2. **Equipment:** The following types of equipment should be used in the manufacture of oral liquid solutions:
   (a) Stainless steel mixing tanks and storage tanks equipped with an agitator
   (b) Measuring devices for large and small amounts of solids and liquids
   (c) A filtration system
   Tanks are usually constructed of stainless steel and are jacketed to allow for heating or cooling of the contents. They are covered and equipped with transparent charging ports and illumination for easy observation of the contents. If the tanks are used for the compounding of bulk liquid, they have a built-in agitation system. The compounded liquid may then be transported to the filling line, either by manually filling into portable transport tanks or by pumping through a liquid delivery unit. All the equipment and pipelines should be easy to disassemble, clean and sanitize. All equipment must be thoroughly cleaned and sanitized before use. The commonly used disinfectants for cleaning of equipments are dilute solutions of hydrogen peroxide, phenol derivatives and paracetic acid. The equipment is sterilized by use of alcohol, boiling water, autoclaving, steam or dry heat.
3. **Method of manufacture:** Purified water is heated to approximately 50°C–60°C to facilitate the dissolution of the solid solutes, which are added to warm water and stirred to dissolve the drug. Additives should be dissolved separately and then mixed with the bulk mixture. Large volume liquids such as glycerol and sorbitol solution are added and mixed until homogeneous. Coloring agents should be dissolved in a small amount of water and then transferred to the bulk mixture. Flavoring agents should be added at low temperature especially at the end since most of the flavors are volatile. The flavor should be dissolved in a small amount of alcohol, propylene glycol or glycerin and mixed with the bulk mixture. The final volume is made up to the mark with purified water. The mixture is agitated thoroughly until homogeneity is obtained. Finally, the product should be filtered to get a clear solution.

Oral Solutions

Solutions intended to be taken orally are called oral solutions. Their advantages include faster absorption from the gastrointestinal tract, uniformity of dosage, safe means of administering substances such as potassium iodide, which cause gastric pain and attractive appearance of the product. For drugs that are slowly soluble, the rate of dissolution may be enhanced by application of heat. However, this approach is suitable only for thermostable drugs. There may be a possibility of chemical interactions between the various components of a solution leading to alteration in the preparation's stability and potency. Liquid pharmaceuticals for oral administration are usually formulated and administered in a convenient volume, such as 5 ml, 10 ml or 15 ml. Solutions for pediatric use are given by drops, with the help of a calibrated dropper supplied within the product package. The strengths of pharmaceutical preparations are usually expressed in terms of % w/w, % w/v and % v/v.

Syrups

Syrups are concentrated, aqueous preparations of a sugar or sugar substitutes with or without flavoring agents and medicinal substances.

Syrups containing flavoring agents but not medicinal substances are called flavored vehicles/syrups, for example, cherry syrup, cocoa syrup. Syrups containing medicinal agents are called medicated syrups, for example, chlorpheniramine maleate syrup. Most syrups contain the following components in addition to purified water and any medicinal agents:

1. Sugar, usually sucrose or sugar substitutes that are used to provide sweetness and viscosity
2. Antimicrobial preservatives
3. Flavors
4. Colorants

Sucrose is most frequently employed in syrups, but sometimes it may be replaced by other sugars such as dextrose or nonsugars such as sorbitol, glycerin and propylene glycol. Syrup imparts a characteristic viscosity; along with the sweetness and flavors, it results in a type of pharmaceutical preparation that is effective in masking the taste of the added medicinal agents. When the syrup is swallowed, only a portion of the dissolved drug actually makes contact with the taste buds, the remainder of the drug being carried down the throat in the containment of the viscous syrup. The thick sweet syrup has a soothing effect on the irritated tissues of the throat as it passes over them. Simple syrup I.P. contains 66.7% w/w sucrose. At this concentration, the syrup is resistant to microbial growth, due to the unavailability of the water required for the growth of microorganisms. Under cool storage conditions, some sucrose might crystallize from the solution when the syrup is completely saturated with sucrose. This can be prevented by the addition of sorbitol in the preparation, which would prevent recrystallization of the excess sugar from the supersaturated sugar solution during normal storage conditions.

Preparation of Syrups

Syrups are prepared by any of the following four general methods, depending upon the physical and chemical characteristics of the ingredients:

1. Solution of the ingredients with the aid of heat
2. Solution of the ingredients by agitation without the use of heat
3. Addition of sucrose to a prepared medicated liquid or to a flavored liquid
4. Percolation of either the source of the medicating substance or the sucrose

Solution with the aid of heat: Sugar is added to the purified water and heated until it dissolves. Then, the other required heat-stable components are added to the hot syrup, the mixture is cooled and its volume is adjusted by the addition of purified water. The use of heat facilitates the rapid solubility of the sugar and other components of syrups. If excessive heating occurs, then sucrose may be hydrolyzed into dextrose and fructose. This hydrolytic reaction is called "inversion," and the combination of the two monosaccharides is known as "invert sugar." When heat is applied in the preparation of sucrose syrup, some inversion of the sucrose is certain and the speed of inversion is greatly influenced by the presence of acids. Invert sugar is colorless and sweeter than sucrose. Syrup darkens due to the effect of overheat of fructose. When the syrup is overheated, it becomes amber colored due to the caramelization of the sucrose.

Solution by agitation without heat: Sucrose and other ingredients are dissolved in purified water by placing the ingredients in a vessel of greater capacity than the volume of syrup to be prepared, thus permitting thorough agitation of the mixture.

Addition of sucrose to a medicated liquid or to a flavored liquid: Medicated liquid such as tincture or fluid extract is employed as the active ingredient in the preparation of syrup. If the extract contains alcohol-soluble ingredients and the amount of alcohol is high, then sucrose is added directly and stirred. If the alcohol content is low and all the ingredients are water soluble, then the liquid extract is directly mixed with the prepared syrup.

Preparation of syrup by percolation: Purified water or an aqueous solution is added slowly to a bed of crystalline sucrose, thereby dissolving it and forming the syrup. If needed, a portion of the percolate is recycled.

Simple Mixtures Containing Soluble Solids

A mixture is a liquid preparation intended for oral administration, in which the drug is dissolved, suspended or dispersed in a suitable vehicle. In general, several doses are contained in a bottle. A simple mixture contains only soluble ingredients. Advantages of a simple mixture are as follows:

1. It can be given to children and geriatric patients having difficulty in swallowing tablets and capsules.
2. It has a faster onset of action.
3. The uniformity of dose is maintained.
4. It provides pleasant appeal to the patients.

However, a simple mixture suffers from the following drawbacks:

1. It has lesser stability than solid dosage forms.
2. It is difficult to mask the unpleasant taste of some drugs.
3. It is difficult to carry due to the bulk and weight.
4. Accidental breakage leads to complete loss.

Example

Weak iodine solution or tincture of iodine I.P.

Iodine	2.0 g
Potassium iodide	2.5 g
Alcohol (50% v/v in water) (q.s.)	100 ml

Potassium iodide and iodine react together to form polyiodides, which enhance the solubility and provide a more stable solution. Potassium iodide and iodine are triturated in a pestle and mortar with sufficient quantity of 50% alcohol. After complete solubilization of iodine, more vehicle is added to make up the volume to the required level.

Aromatic Waters

Aromatic waters are clear, saturated solutions of aromatic substances, which may be volatile oils or volatile solids in water. They are mainly used as the vehicle for oral liquid preparations due to their

flavoring properties, for example, peppermint water. Some aromatic waters have preservative action and hence they are used as menstrum to extract crude drugs, for example, chloroform water. Few aromatic waters have mild therapeutic action. Camphor water has carminative action and anise water has carminative and mild expectorant action. Aromatic waters are classified into two types, namely simple and concentrated aromatic waters.

Methods of Preparation

The following are the various methods of preparation of aromatic waters:

1. **Simple solution method:** The volatile oil is shaken with 500 times its volume of purified water for a period of 30 minutes and set aside for 12 hours or overnight. The resulting mixture is filtered and suitably packed.
2. **Using distributing agents:** Volatile oil is triturated with a sufficient quantity of powdered talc or kieselghur in a mortar. To this, purified water 100 times the volume of oil is added and mixed well. The resultant mixture is filtered and suitably packed.
3. **Dilution from concentrated preparations:** Concentrated aromatic water is prepared as per the formula given in the pharmacopoeia or formulary. In general, 1 ml of the prepared concentrated aromatic water is diluted with the required volume of purified water and mixed. The resulting solution is suitably packed.

Example

Chloroform water

Chloroform	2.5 ml
Purified water (q.s.)	1000 ml

This is a saturated solution of chloroform in purified water. The solubility of chloroform is 1 in 800 parts of water. The required quantity of chloroform is added to purified water and mixed well so that chloroform gets uniformly mixed. The usual dose is 15 ml to 30 ml. It is used as a pharmaceutical aid and should be stored in an airtight container in a cool place away from light.

Spirits

Spirits are alcoholic or hydroalcoholic solutions of volatile substances and contain 50% to 90% of alcohol. Water-insoluble oils are presented as solutions due to the high alcoholic content of spirit. Spirits are prepared by dissolving the volatile substances in ethanol 90% with the exception of aromatic ammonia spirit, which is prepared by distillation method. They are used as flavoring agents. Examples are lemon spirit, peppermint spirit and compound orange spirit. Some spirits are taken internally for their medicinal value, for example, aromatic spirit of ammonia I.P., which is a respiratory stimulant.

Methods of Preparation

Spirits can be prepared by the following methods:

1. Simple solution method, for example, chloroform spirit I.P., spirit of ether I.P.
2. Solution with maceration, for example, compound orange spirit I.P.
3. Distillation, for example, aromatic spirit of ammonia I.P.

Example

Aromatic spirit of ammonia

Ammonium bicarbonate	2.5 g
Ammonia solution strong	7 ml
Lemon oil	0.5 ml
Nutmeg oil	0.3 ml
Alcohol (90% v/v)	75 ml
Purified water (q.s.)	100 ml

Lemon oil, nutmeg oil, alcohol 90% and half the quantity of purified water are taken in a still and distilled. The first and second portions of the distillate are collected separately. The second distillate is taken in a bottle, to this ammonium bicarbonate and strong ammonia solution are added. The bottle is closed and warmed gently at 60°C on a water bath. The bottle is shaken continuously to dissolve the salt completely. The solution is cooled and filtered through cotton wool. This solution is then mixed gradually with the first distillate. To this, sufficient purified water is added and the volume is made up. Nutmeg oil contains both volatile oil and nonvolatile resinous substances. So, by distillation method only the volatile part is separated out. The first distillate mainly contains alcohol and the aromatic part of the volatile oils. The second distillate mainly contains water. Ammonium bicarbonate is not soluble in alcohol, so it is dissolved in the second distillate, which is aqueous. Ammonium carbonate decomposes in water to produce ammonia, carbon dioxide and water. To reduce this decomposition, strong ammonia solution is added. The preparation should be stored in a tightly closed container in a cool place.

Elixirs

These are hydroalcoholic preparations containing more potent substances such as antibiotics, antihistamines and sedatives. Alcohol concentration is usually 10%–40%. Elixirs are clear preparations and colored medications. They are more fluid than syrup because of the use of less-viscous ingredients. The characteristics of an elixir include the following:

1. It solubilizes the active ingredients and some excipients.
2. It retards the crystallization of sugar.
3. It preserves the finished product.
4. It provides sharpness to the taste.
5. It aids in masking the unpleasant taste of the active ingredients.
6. It enhances the flavor.

Elixirs are of two types as follows:

1. **Non-medicated elixir:** These are used as diluting agents or solvents for drugs containing approximately 25% alcohol.
2. **Medicated elixirs:** Elixirs containing therapeutically active compounds are known as medicated elixirs, for example, phenobarbital elixir USP, dexamethasone elixir USP.

Example

Piperazine citrate elixir I.P.

Piperazine citrate	18 g
Chloroform spirit	0.5 ml
Glycerin	10 ml
Orange oil	0.025 ml
Syrup	50 ml
Purified water (q.s.)	100 ml

Piperazine citrate is dissolved in a part of purified water. Orange oil, glycerin, syrup, chloroform spirit and sufficient quantity of water are added to produce the required volume. The resulting solution is mixed well and filtered if needed.

Linctuses

Linctuses are viscous liquid oral preparations that are prescribed for relief of cough. They contain medicaments that have demulcent or expectorant action. Linctuses should be taken in small doses, sipped and swallowed slowly without diluting with water to have the maximum and prolonged effect of medicament. Linctuses normally do not have any major side effects. In case of overdose, they may cause headache, stomach upset and diarrhea.

Formulation of linctuses requires the following:

1. **Vehicles:** Simple syrup is commonly used as the vehicle. Syrup tolu is preferred in certain cases because of its aromatic odor and flavor. Moreover, it is believed to have a mild expectorant action.
2. **Adjuvants:** Commonly used adjuvants in linctuses are as follows:
   (a) *Chemical stabilizers:* The stability of linctuses is due to the presence of the simple syrup as vehicle.
   (b) *Coloring agents:* Coal tar dyes
   (c) *Flavoring agents:* Lemon syrup, black current syrup, oxymel
   (d) *Preservatives:* Syrup has high osmotic pressure, which eliminates additional use of other preservatives.

Example

Codeine linctus BPC

Codeine phosphate	0.3 g
Lemon syrup	20 ml
Benzoic acid solution	2 ml
Chloroform spirit	2 ml
Compound tartrazine solution	1 ml
Purified water	2 ml
Syrup (q.s.)	100 ml

Codeine phosphate is dissolved in water. To this, benzoic acid solution, chloroform spirit and compound tartrazine solution are added and mixed well. Then, lemon syrup is added and the volume is made up with syrup.

Mouthwashes

Mouthwashes are aqueous solutions, often in concentrated form, containing one or more active ingredients and excipients. Mouthwash is used to enhance oral hygiene. It can be used therapeutically for reducing plaque, gingivitis, dental caries and stomatitis or cosmetically for reducing bad breath through the use of antimicrobial and flavoring agents. Flavors are used in conjunction with alcohol and humectants to overcome obnoxious odor and taste. Commonly employed flavoring agents are peppermint oil, spearmint oil, cinnamon oil, wintergreen oil, menthol and methyl salicylate. Mouthwashes have a pleasant taste and odor. In general, they are dispensed in white fluted bottles. The label should clearly indicate the proper directions for diluting the mouthwash before use, along with the auxiliary labeling, "For external use only" and "Not to be swallowed in large quantities."

Example

Compound sodium chloride mouthwash BPC

Sodium chloride	15 g
Sodium bicarbonate	10 g
Peppermint water (q.s.)	1000 ml

Sodium bicarbonate and sodium chloride are dissolved in sufficient quantity of peppermint water. The volume is made up with the remaining peppermint water.

Other examples of mouthwashes are as follows:

1. Phenol and alkaline mouthwash
2. Potassium chlorate and phenol mouthwash
3. Thymol glycerin mouthwash
4. Hydrogen peroxide mouthwash
5. Buffered sodium perborate mouthwash

Throat Paints

Throat paints are viscous liquid preparations containing one or more medicaments and are used for throat and mouth infections. They are highly viscous due to their high content of glycerin. They are made viscous so that the drug would remain in contact with the mucus membrane for a longer time period. Throat paints are applied as such without dilution on the affected area with the help of a brush or cotton plug. They should be stored in colored fluted airtight containers. The general requirements for labeling should be complied with. In addition, the containers should state "For external use only" and "Apply with brush." Throat paints are useful in the treatment of pharyngitis, laryngitis and follicular tonsillitis. However, they suffer from the drawback of increased salivary secretion due to which the patient may spit out the preparation. The formulation of throat paint requires viscous vehicles, flavoring agents, coloring agents and sweetening agents. Medicaments such as antiseptics, astringents and anti-infectives are commonly incorporated in throat paints.

Example

Mandl's paint

Iodine	1.25 g
Potassium iodide	2.5 g
Purified water	2.5 ml
Peppermint oil	0.42 ml
Alcohol (95%)	3.75 ml
Glycerin (q.s.)	100 ml

In this preparation, iodine acts as an antiseptic and potassium iodide dissolves the iodine. Peppermint oil acts as the flavoring agent and produces a cooling effect. Alcohol is used as a solubilizing agent for the peppermint oil. As the preparation contains iodine, it should be prepared in a glass apparatus. Potassium iodide and iodine are dissolved in purified water using a glass mortar and pestle with a small portion of glycerin. To this, peppermint oil dissolved in alcohol is added and mixed and then sufficient glycerin is added to produce the required volume.

Other examples of paints are brilliant green and crystal violet paint, coal tar paint and tannic acid glycerin paint.

Enemas

Enemas are solutions intended for introduction into the rectum or colon to cause evacuation of bowel or to bring about local or systemic effects. They are used for diagnostic purpose, especially for X-ray examination of bowel. Enemas are classified into the following five types:

1. Cleansing or evacuating enema, for example, saline solution
2. Carminative enema, for example, milk, olive oil
3. Retention enema, for example, paraldehyde, starch and water
4. Lubricating enema, for example, vegetable and mineral oil
5. Medicated enema, for example, sodium phosphate, decussate sodium

Administration of enemas requires the help of trained personnel, a pharmacist or a nurse. Enemas are introduced after warming the solution to body temperature. The volume of enema administered is based on the age and condition of the patient.

Enemas are dispensed usually in volume of 1000 ml in colored fluted glass bottles, which should bear the labels "For external use only," "Lubricate the nozzle before administration," and "Warm the solution to body temperature," "For external use". They are suitable for drugs that cannot be given through oral or parenteral route. However, enemas may cause discomfort to the patients. Moreover, the liquid pressure should be controlled, as high pressure may cause pain and rupture the intestinal wall. Formulation of enema requires suitable soluble drugs in the selected solvent and stabilizers. Since the drugs used are mostly water soluble, simple solution method is usually employed for manufacture. Commonly used medicaments include laxatives, sedatives and anthelmintics.

Example

Glycerin enema

Glycerin	50 ml
Purified water	100 ml

As glycerin is miscible with water, it gets mixed well and forms a homogeneous solution. Glycerin stimulates the rectal mucosa, promotes defecation and lubricates and softens fecal material.

Douches

A douche is an aqueous solution that is administered against a part or into a cavity of the body. It acts as a cleansing agent or antiseptic. Douches are directed to the appropriate body parts by using bulb syringe. They are more frequently dispensed in the form of powder with directions for dissolving in a specified quantity of warm water. Compound sodium borate solution National formulary is used as nasal or pharyngeal douch. Douches can be used to clean the body cavities and to promote healing of wounds.

Medicaments commonly employed as douches include:

1. Cleansing agents, for example, sodium chloride and sodium bicarbonate;
2. Antiseptics, for example, chlorhexidine and lactic acid; and
3. Astringents, for example, tannic acid and zinc sulfate.

Douches are classified into the following four types:

1. Eye douche—used to remove foreign particles and discharges from the eyes, is applied gently at an oblique angle and is allowed to run from the inner to outer corner of the eye
2. Pharyngeal douche—used to prepare the interior of the throat for an operation and to cleanse it in conditions of formation of discharge of pus
3. Nasal douche—used to cleanse nasal passage
4. Vaginal douche—used for irrigative cleansing of the vagina and should be sterile in nature

Example

Potassium permanganate vaginal douche

Potassium permanganate	1.0 g
Purified water (q.s.)	1000 ml

Potassium permanganate is soluble in water. Potassium permanganate is triturated with appreciable amount of purified water in a pestle and mortar. Trituration is continued until potassium permanganate gets dissolved completely in water. The solution is filtered through sintered glass filter. To this, purified water is added to make up the volume and is packed in a suitable container.

Eye Drops

Eye drops are sterile aqueous or oily solutions or suspensions that are used for instillation into the eye. They are applied into the cul-de-sac, the space between the eyeball and eyelid. Eye drops solution should have the following essential characteristics:

1. It should be sterile.
2. It should be iso-osmotic with lachrymal secretions.

3. It should have neutral pH.
4. It should be free from foreign particles.
5. It should remain stable during its storage.

Preparation of eye drops consists of the following four stages:

1. Preparation of bactericidal and fungicidal vehicles
2. Solution of the medicaments or active ingredients and if needed the appropriate adjuvants
3. Clarification
4. Sterilization

The preservative is dissolved in purified water in the prescribed concentration. All the medicaments and adjuvants are dissolved in the antimicrobial solutions to form a stable mixture. The solution is clarified by passing through a membrane filter having pore size of 0.2 mm to remove any particulate matter. The clarified solution is immediately transferred into final containers and sealed. Eye drops are sterilized by any one of the sterilization methods such as autoclaving, heating at 98°C–100°C for 30 minutes or filtration through 0.22 mm membrane filter. Eye drops are dispensed in neutral glass containers. Either a glass dropper or plastic cap-nozzle is used for administration. Eye drops should be labeled "For external use only" along with the storage conditions to maintain its activity during storage.

Example

Sodium chloride eye lotion BPC

Sodium chloride	9 g
Purified water (q.s.)	1000 ml

This is a simple solution prepared by dissolving sodium chloride in purified water filtered and sterilized. This is also called as normal saline solution.

Ear Drops

These are solutions that are instilled into the ear with a dropper. The solution is generally prepared in water, glycerin or propylene glycol. Ear drops are generally used for cleaning the ear, softening the wax and treating mild infections. However, this may cause inconvenience to patients because they have to lie down or tilt their head at angle of 45° when ear drops are administered. The important consideration in the formulation of ear drops is the selection of vehicle. The vehicle should mix easily with ear wax and should make maximum contact between the drug and the tissues of the ear. Anhydrous glycerin and propylene glycols are the commonly used vehicles. These vehicles remove the moisture from the tissue, thereby reducing the growth of microorganisms and inflammation. For the purpose of preservation, preservatives such as chlorobutanol and thiomersal are employed in the formulation. The commonly used medicaments in ear drops include anti-infectives, wax softener, antiseptics, astringents and anti-inflammatory agents.

Example

Sodium bicarbonate ear drops BP

Sodium bicarbonate	5 g
Glycerin	30 ml
Purified water (q.s.)	100 ml

Sodium bicarbonate is dissolved in water. To this, glycerin is added and mixed well. Glycerin provides the softening capacity to the solution and it reduces itching due to its emollient property. To this solution, the remaining quantity of water is added and the required volume is made up.

Nasal Drops

These are aqueous solutions that are instilled into the nose with a dropper. Nasal drops should be isotonic, having neutral pH and viscosity similar to nasal secretions. Use of oily vehicle is restricted, because it inhibits the movement of cilia in the nasal mucosa and if used for long periods, it reaches the lungs and causes lipoidal pneumonia. Nasal drops are dispensed in colored fluted bottles fitted with a dropper or in a suitable plastic container. The label should bear the indication "For external use only." The drops are used to reduce the swelling of nasal mucosa and the underlying tissues. They reduce nasal congestion by retaining the solution within the nasal cavity. A nasal drop should have pH between 5.5 and 7.5, with mild buffer capacity, should be isotonic, should not modify the viscosity of mucus, should be compatible with ciliary movement and with medicament, should be inert, nontoxic and stable. Formulation of nasal drops requires vehicles such as purified water and liquid paraffin, tonicity-adjusting materials such as sodium chloride and dextrose, preservatives such as chlorobutanol and benzalkonium chloride and buffers such as phosphate buffer. Commonly incorporated medicaments in nasal drops include sympathomimetics, anti-inflammatory agents, adrenergic agents and decongestants

Example

Ephedrine nasal drops BPC

Ephedrine hydrochloride	9.14 g
Chlorobutanol	4.5 g
Sodium chloride	4.5 g
Purified water (q.s.)	1000 ml

Chlorobutanol is dissolved in sufficient quantity of purified water. Ephedrine hydrochloride and sodium chloride are dissolved in purified water in a separate container. These two solutions are mixed together and the final volume is adjusted with purified water to make up the required volume.

Collodions

Collodions are the liquid preparations meant for external application to the skin. They are easy to apply on small cuts and abrasions. They are used when prolonged contact between the skin and the medicament is required. The vehicle used is volatile and it evaporates on application to skin, leaving a flexible, protective film covering at the site of application. Collodions are applied with a brush or rod. Collodion is a flammable, solution of pyroxylin, that is nitrocellulose in ether and alcohol. Collodions are of two types, namely flexible and non-flexible collodions. Flexible collodions are often used as a surgical dressing or to hold dressings in place. When painted on the skin, collodion dries to form a flexible cellulose film. While it is initially colorless, it discolors over time. Non-flexible collodion is used in theatrical makeup.

Properties of Collodions

The following are some important properties of collodions:

1. They should not irritate the tissue of the wound and must be free of antigens.
2. The wound covering must be elastic to ensure that all layers constituting it are in close contact with the wound surface.
3. The collodion must be flexible.

Example

Simple collodion

Nitrocellulose—Film former
Castor oil—Plasticizer
Alcohol—Vehicle
Solvent ether—Vehicle

The following are some examples of official collodion:

1. Collodion USP is a clear or slightly opalescent viscous liquid prepared by dissolving 4% w/v pyroxillin in 3:1 mixture of ether and alcohol.
2. Flexible collodion USP is prepared by adding 2% of camphor and 3% castor oil to the collodion.
3. Salicylic acid collodion USP is 10% solution of salicylic acid in flexible collodion. It is used for its keratolytic effect especially in the removal of corns from the toes. It is also called as "corn solvent."

Lotions

Lotions are liquid dosage forms for external use. They are generally meant for application to the skin and are applied directly without friction, with the help of some absorbent material such as cotton wool or are charged on to cotton wool or gauze and kept on the needed part of the body. Lotions may be used for local effects such as cooling, soothing or protective purposes. They are generally applied for antiseptic action. Alcohol is sometimes included in aqueous solutions for its cooling and soothing effect, for example, salicylic acid lotion. Lotions should be dispensed in colored fluted bottles in order to distinguish them from preparations meant for internal use. The containers should be labeled "For external use only." Lotions have a tendency to separate out on long-tem storage. Therefore, the container must be labeled "Shake well before use." Lotions should be stored in a well-fitted, well-closed airtight container in a cool place.

Liniments

Liniment is a solution or mixture of various substances in oil, alcoholic solution of soap or emulsion intended for external application. They should comply with the labeling requirements of liquid dosage forms. They are applied to the unbroken skin with rubbing or massaged directly on the affected area as counterirritating or stimulating agents. Liniments have substances such as analgesics, antimicrobials, rubefacients, counterirritants, stimulants and soothing agents. Alcohol is primarily used as the solvent in liniments. It enhances the penetration of the medicaments into the skin and has counterirritant or

rubefacient action. Counterirritants are used to mask pain from fibrositis, neuralgia and similar complaints by producing warmth, tingling and numbness. When rubbed onto the skin, they cause redness and hence are called as rubefacients. Cottonseed oil and arachis oil are less irritating to the skin than alcohol and spread more easily on the skin.

Example

Camphor liniment

Camphor	20 g
Arachis oil	80 g

Camphor is freely soluble in arachis oil. Camphor is dissolved in arachis oil in a closed vessel and mixed well. The resulting solution is packed in a suitable container.

Table 6.4 Examples of Marketed Products

S. No.	*Brand Name*	*Type*	*Composition*	*Manufacturer*
1.	Rotate	Solution	Potassium citrate, citric acid	Peerage Pharma
2.	Alex-P	Syrup	Paracetamol, phenylephrine, guaiphenesin	Glenmark Pharmaceuticals
3.	Grilinctus	Linctus	Dextromethorphan HBr, chlorpheniramine maleate, ammonium chloride, guaiphenesin	Franco-Indian Pharma
4.	Otrivin-C	Nasal spray	Fluticasone	Novartis
5.	Naselin	Nasal drops	Oxymetazoline	Cipla
6.	Genticyn	Ear drops	Gentamycin	Allergan
7.	Hiora	Mouthwash	Pilu, Bibhitaka, Nagavalli, Gandhapura taila Ela, Peppermint satva, Yavani, satva	Himalaya
8.	Colocort	Enema	Hydrocotisone	Ani Pharmaceuticals
9.	Salactol	Collodion	Salicylic acid, lactic acid	Dermal Laboratories

REVIEW QUESTIONS

Answer in Detail

1. Classify monophasic liquid dosage forms.
2. Explain the formulation considerations in development of monophasic liquid dosage forms.

Answer in Brief

1. How do you classify solutions?
2. Explain the method of preparation of syrups.
3. Write the differences between syrups and elixirs.
4. Write the differences between gargles and mouthwashes.
5. Write the differences between liniments and lotions.
6. What are collodions?
7. Define syrups.
8. Define elixirs.
9. What is the concentration of sugar to be used in simple syrup I.P and why?
10. A preservative is not used in simple syrup. Justify.
11. What are the directions to be mentioned on the label of linctuses?
12. Write the principle involved in the preparation of cresol with soap solution I.P.
13. Name the organoleptic additives used in the preparation of monophasic liquid dosage forms.
14. Give examples of coloring and flavoring agents used in liquid oral preparations.
15. Give examples of four solvents used in pharmaceutical preparations.
16. Give any four examples for antioxidants.
17. Give examples of preservatives and antioxidants used in liquid oral preparations
18. Write the auxiliary labels for liniments.
19. What are the directions to be mentioned on the label of liniments?
20. What are throat paints? How do they differ from mouthwashes?

Answer in One or Two Sentences

1. Define syrups.
2. Define elixirs.
3. What is the concentration of sugar to be used in simple syrup and why?
4. A preservative is not used in simple syrup. Justify.
5. What are the directions to be mentioned on the label of linctuses?
6. Write the principle involved in the preparation of cresol with soap solution I.P.
7. Differentiate between strong iodine and weak iodine solutions.
8. Write the principle involved in the preparation of strong ammonium acetate solution.
9. Name the organoleptic additives used in the preparation of monophasic liquid dosage forms.

Multiple Choice Questions

1. Freely soluble is _____.
   (a) < 1 part (b) < 5 part (c) < 10 part (d) < 15 part
2. _____ is a cosolvent.
   (a) Acetone (b) Ethanol (c) Chloroform (d) Benzene
3. An example of solubilizing agent is _____.
   (a) acacia (b) xanthan gum (c) tweens (d) methyl cellulose
4. _____ is a hydrotropic agent.
   (a) Urea (b) SLS
   (c) Sodium hydroxide (d) Sodium chloride

5. The concentration of chlorobutanol as preservative in monophasic liquids is _____.
   (a) 0.3% (b) 0.8% (c) 0.6% (d) 0.5%
6. Tincture of iodine is a _____.
   (a) strong iodine solution
   (b) weak iodine solution
   (c) potassium iodide solution
   (d) complex iodine solution
7. Preparation of eye drops has _____ stages.
   (a) two (b) three (c) four (d) five
8. Elixirs are of _____ types.
   (a) two (b) three (c) four (d) five
9. Which of the following should be applied with a brush?
   (a) Ointment (b) Throat paint (c) Face cream (d) Insufflations
10. Enemas are classified into _____ types.
    (a) two (b) three (c) four (d) five

ANSWERS TO MULTIPLE CHOICE QUESTIONS

1. (a)	2. (b)	3. (c)	4. (a)	5. (d)
6. (b)	7. (c)	8. (a)	9. (b)	10. (d)

PART II—BIPHASIC LIQUID DOSAGE FORMS

Learning Objective

- Differences between monophasic and biphasic liquid dosage forms

Biphasic dosage forms can be classified as follows:

1. Suspensions
2. Emulsions

Biphasic dosage forms contain the following two phases:

1. Disperse or internal phase
2. Dispersion medium or continuous or external phase

SUSPENSIONS

Learning Objective

- Disperse systems and their types

Disperse systems consist of particulate matter known as the dispersed phase, distributed throughout a continuous or dispersion medium. Based on the size of the dispersed phase, these are classified into following three types:

1. Molecular dispersion: less than 1 nm
2. Colloidal dispersion: From 1 nm to 0.5 μm
3. Coarse dispersion: Greater than 0.5 μm

Learning Objective

- Basic principle of suspensions

Suspensions are biphasic, heterogenous systems in which finely divided insoluble solid particles (disperse phase) are dispersed or suspended in a vehicle (dispersion medium). The diameter of the disperse phase may range from 0.5 μm to 100 μm. Systems in which the particle size diameter falls below this range are termed colloidal (1 nm–0.5 μm).

A suspension would be considered stable if after agitation (shaking), the drug particles are homogeneously dispersed for a sufficient time to ensure that an accurate dose is removed for administration to the patient.

Suspensions can be used as oral dosage forms, applied topically to the skin or given parenterally by injection.

Properties of a Good Suspension

1. The dispersed particles should settle slowly and should redisperse immediately on shaking.
2. The product should remain sufficiently homogenous for at least the period between shaking the container and removing the required dose.

3. The viscosity of the suspension should be such that it can be easily removed from the container and transferred to the site of application without any difficulty.
4. The sediment produced on standing should not form a hard cake.
5. Any suspended particles should be small and uniformly sized in order to give a smooth, elegant product free from grittiness.
6. The suspension should be physically and chemically stable during handling and storage conditions.
7. It should have good syringibility in case of parenteral suspensions.
8. It should produce thixotropic property (gel to sol upon shaking and sol to gel during storage).

Advantages of Suspensions

1. Insoluble drugs may be made more palatable.
2. Insoluble drugs may be prepared in a more stable manner.
3. Suspended insoluble powders are easy to swallow.
4. Suspensions enable easy administration of bulk insoluble powders.
5. When compared to solid dosage forms, absorption is faster.
6. Lotions will leave a cooling layer of medicament on the skin.
7. It can be formulated for both immediate and sustained drug release preparations.

Disadvantages of Suspensions

1. Suspensions require shaking before use, to ensure uniformity of dose.
2. If the preparation is not shaken well, the accuracy of dose is likely to be less when compared to solutions.
3. Improper storage conditions can affect the disperse system.
4. Since suspensions are stored in glass or plastic containers, they are bulky, difficult to transport and prone to container breakages.

Classification of Suspensions

Based on Type of Solids

Learning Objective

- Differences between diffusible and indiffusible suspensions

1. **Diffusible suspensions:** These are suspensions containing diffusible solids. These are light powders, which are insoluble or only very slightly soluble in the vehicle but readily mix with water and remain suspended throughout the liquid for a sufficient time after shaking, allowing an accurate dose to be withdrawn. On standing, the insoluble solids settle at the bottom of the bottle, which requires the shaking of the bottle every time a dose is to be withdrawn.

   Examples of diffusible solids are calcium carbonate, light magnesium carbonate, magnesium trisilicate, rhubarb powder and light kaolin.

2. **Indiffusible suspensions:** These are suspensions containing indiffusible solids. These are heavy powders, which are insoluble in the vehicle and on shaking do not remain uniformly distributed in the vehicle for a long time to allow an accurate dose to be withdrawn. Indiffusible suspensions contain a suspending agent or a thickening agent to delay the sedimentation rate and prevent the formation of aggregates.

   Examples of indiffusible solids are calamine, hydrocortisone, precipitated sulfur, zinc oxide, aspirin, chalk powder, zinc oxide and phenobarbitone.

Based on Flocculated and Deflocculated Systems

Learning Objective

- Differences between flocculated and deflocculated suspensions

The suspensions are said to be flocculated when the individual particles are in contact with each other to form loose aggregates or a network-like structure. They are easily redispersible, but the rate of sedimentation is fast, the product will look inelegant and there is also a danger of an inaccurate dose being administered.

Nonflocculated or deflocculated suspensions are those in which the dispersed particles exist as separate entities. They have a slow rate of sedimentation, thereby enabling a uniform dose to be taken from the container. However, when settling occurs, the sediment forms a highly compacted cake, which is difficult to redisperse (Table 6.5).

Controlled flocculation: Correct degree of flocculation must be induced. Underflocculation will result in all the undesirable properties associated with deflocculated suspensions. An overflocculated product will look inelegant, and to minimize settling, the viscosity should be high.

Controlled flocculation can be achieved by the combination of particle size control, addition of polymers to enable cross-linking between particles and the use of electrolytes to control zeta potential.

Table 6.5 Differences between Flocculated and Deflocculated Suspensions

Sl. No.	*Flocculated Suspension*	*Deflocculated Suspension*
1.	Particles form loose aggregates or network-like structure called floccules.	Particles exist as separate entities.
2.	Rate of sedimentation is high.	Rate of sedimentation is less.
3.	Sediment is rapidly formed.	Sediment is slowly formed.
4.	Sediment is loosely packed and does not form a hard cake.	Sediment is closely packed and forms a hard cake.
5.	Sediment is easy to redisperse.	Sediment is difficult to redisperse.
6.	The supernatant liquid becomes clear very quickly.	Supernatant liquid will remain cloudy for a long time due to slow settling of particles.
7.	The floccules stick to the sides of the bottle.	The particles do not stick to the sides of the bottle.
8.	Product will be unpleasant in appearance.	Product will be pleasant in appearance.

(***Note:*** Zeta potential [ζ]: is defined as the difference in the potential between the surface of a tightly bound layer (shear plane) and the electro neutral region of the solution. The potential located at the shear plane is known as the electrokinetic or zeta potential. It has practical application in the stability of disperse systems since this potential governs the degree of repulsion between adjacent, similarly charged, dispersed particles. If the ζ is reduced below a certain value, the attractive forces exceed the repulsive forces and the particles come together, leading to flocculation. If the ζ value is increased, repulsion occurs.

Electrolytes act as flocculating agents by decreasing the electric barrier between the particles due to decrease in the ζ and the formation of a bridge between adjacent particles so as to link them together in a loosely arranged structure.)

Based on Use or Application

Learning Objective

- Formulations that are available in suspension form

1. **Oral suspensions:** Examples of oral suspensions include
   (a) antacid suspensions—magnesium hydroxide mixture, such as Gelusil and Digene (both contain a combination of magnesium hydroxide and aluminum hydroxide)
   (b) pediatric paracetemol oral suspension
   (c) chloramphenicol (antibiotic suspension)
   (d) amoxicillin and potassium clavulanate suspension (reconstituted)
   (e) magnesium hydroxide mixture—laxative.
2. **Suspensions for topical administration:** An example of this type of suspension is calamine lotion.
3. **Suspensions for parenteral use and inhalation therapy:** Examples include
   (a) cholera vaccine—dispersions of killed microorganisms
   (b) adsorbed diphtheria and tetanus vaccine—constituent toxoids are adsorbed to a substrate of aluminum hydroxide or phosphate. Thus, a prolonged antigenic stimulus is provided, resulting in a high antibody titer.

Formulation of Suspensions

Learning Objective

- Principles involved in the formulation of suspensions

The formulation of a suspension involves the following:

1. **Medicament:** This is the drug with non-aqueous solubility.
2. **Flocculating agents:** The particles in a suspension should be well dispersed in the vehicle. Dispersion can be improved by adding a surfactant, electrolyte or polymer, which acts

as the flocculating agent. The nonionic surfactants act by reducing the surface tension or by forming bridges between the particles. The use of an ionic surfactant to wet the solid could produce either a flocculated or a deflocculated suspension depending on the charge already present on the particle. If the particles have a charge opposite to that of the surfactant, then neutralization occurs and the electrical barrier between the particles is reduced, resulting in flocculation.

(a) **Electrolytes:** These act as flocculating agents by decreasing the electric barrier between the particles due to a decrease in zeta potential. This results in the formation of a bridge between adjacent particles so as to link them together in a loosely arranged structure. The addition of an inorganic electrolyte to an aqueous suspension will alter the zeta potential of the dispersed particles and if this value is decreased flocculation will occur.

Examples are sodium salts of acetates, phosphates and citrates.

(b) **Surfactants:** Ionic surface active agents may also cause flocculation by the neutralization of charge on each particle, thus resulting in a flocculated system. Nonionic surfactants adsorb onto more than one particle, thereby forming a loose flocculated structure.

(c) **Polymers:** The linear-branched chain molecules of polymers form a gel-like network within the system, which become adsorbed onto the surfaces of the dispersed particles, thus holding them in a flocculated state.

Examples are starch, alginates, cellulose derivatives, tragacanth, carbomers and silicates.

3. **Deflocculating agents:** When the particles have the same charge as that of the surfactant, they repel each other. The particles remain separate, resulting in deflocculation.

4. **Suspending agents:** These act mainly by increasing the viscosity of the external phase and thus reducing the rate of sedimentation of the dispersed particles. These substances are added to a suspension to increase the viscosity of the continuous phase, so that the particles remain suspended for a sufficiently long time, making it easier to withdraw a uniform dose. The viscosity of the preparation should be such that it can be easily poured from the container and transferred to the site of application. They are also known as thickening agents.

The amount of suspending agent used in any given formulation depends on the volume of vehicle being thickened. A suspending agent is intended to increase the viscosity of the vehicle and therefore slow down sedimentation rates. This can also be achieved by decreasing the particle size of the powder in suspension.

The following are the most common suspending agents used in extemporaneous dispensing:

(a) Tragacanth BP: Used in internal or external suspensions at a concentration of 0.2%
(b) Compound tragacanth powder BP (containing 15% tragacanth, 20% acacia, 20% starch and 45% sucrose): Used in internal suspensions at a concentration of 2.0%
(c) Bentonite BP: Used in external suspensions at concentrations of 2%–3% (e.g., calamine lotion)

5. Examples of agents that can be used as suspending agents or thickening agents are given below:

(a) **Natural polysaccharides**

(i) Acacia: This acts as a protective colloid and suspending agent and is used in the preparations containing resinous tinctures that precipitate on addition of water. Acacia mucilage becomes acidic on storage as a result of enzyme activity. It also

contains an oxidase enzyme, which may cause deterioration of active agents that are susceptible to oxidation.

(ii) Tragacanth: This is a better thickening agent than acacia. It is used as compound tragacanth powder or tragacanth mucilage.

(iii) Alginates: These are viscous in nature immediately after preparation, but the viscosity decreases within 24 hours. Alginate mucilages must not be heated above 60°C.

(b) **Semisynthetic (cellulose derivatives)**

(i) Methyl cellulose: Used in a concentration of 0.5%–2% as a suspending agent

(ii) SCMC (Sodium Carboxymethyl Cellulose): Used in a concentration of 0.25%–1% in products for oral, external and parenteral use

(c) **Inorganic agents**

(i) Bentonite: Used in a concentration of up to 3% in preparations for external use such as calamine lotion

(ii) Magnesium aluminum silicate (Veegum): Used in a concentration of up to 5%

(d) **Synthetic compounds**

(i) Carbomers: Used in a concentration of up to 0.5% for external use

(ii) Colloidal silicon dioxide (Aerosil): Used in a concentration of up to 4% for external use

6. **Wetting agents:** These substances reduce the interfacial tension between the solid particles and the liquid medium, thus producing a suspension of required quality. This is achieved by the addition of a suitable wetting agent that is adsorbed at the solid–liquid interface in such a way that the affinity of the particles towards the surrounding medium is increased, thereby helping in the penetration of liquid into the particles, thus producing good suspension. Examples are spans and tweens.

7. **Preservatives:** These substances are used to protect the suspension against bacterial growth. The preservatives should be effective against a wide range of microorganisms. They should be chemically and physically compatible with the other ingredients in the formulation. Examples are benzoic acid and methyl and propyl paraben.

8. **Organoleptic additives:** The following are the various organoleptic additives used in the formulation of a suspension:

(a) Flavoring agents are added to oral preparations. Examples are vanilla, banana, strawberry and pineapple flavors.

(b) Sweetening agents are added to oral preparations. Examples are sucrose, saccharin sodium and aspartame.

(c) Coloring agents are added to preparations for oral and external use. Examples are sunset yellow, erythrosine and tartrazine.

(d) Perfumes are used in preparations meant for external use. Examples are rose water and lavender oil.

Methods of Dispensing Suspensions

Learning Objective

- Preparation of different types of suspensions

Suspensions Containing Diffusible Solids

The method of preparation of suspensions containing diffusible solids is as follows:

1. The drug is finely powdered with the other solid ingredients.
2. Three-fourths of the vehicle is added to the powder mixture and triturated to form a smooth cream.
3. More vehicle is added.
4. Any other liquid ingredients, if present, are added and the suspension is made up to volume.
5. The suspension is transferred to a bottle, corked and labeled.

Example: R_x Light kaolin
Light magnesium carbonate
Sodium bicarbonate
Peppermint water

Labeling: SHAKE WELL BEFORE USE

Suspensions Containing Indiffusible Solids

The thickening agents used in indiffusible suspensions are given below:

1. **Compound tragacanth powder:** This is a mixture of powdered tragacanth (15%), acacia (20%), starch (20%) and sucrose. This powder is preferred when a vehicle other than water or chloroform water is used.
2. **Tragacanth mucilage:** This is a mixture of tragacanth powder, 90% ethanol and chloroform water. It is used only when the vehicle is water or chloroform water (because if it is added to preparations containing a medicinally active vehicle, the mucilage may replace the medicinally active vehicle, thereby decreasing its activity).
   The methods of preparing suspensions containing indiffussible solids are described below:
   (a) **Preparation using compound tragacanth powder**
      (i) The indiffusible solids are finely powdered and mixed with 2% w/w compound tragacanth powder.
      (ii) Three-fourths of the vehicle is added to the powder mixture and triturated to form a smooth cream.
      (iii) Any soluble ingredient is dissolved in the remaining vehicle and added slowly with trituration to the cream.
      (iv) Any other liquid ingredients, if present, are added and the suspension is made up to volume.
      (v) The suspension is transferred to a bottle, corked and labeled.

      Example: R_x Bismuth carbonate
      Prepared chalk
      Kaolin
      Tincture catechu
      Water

   (b) **Preparation using tragacanth mucilage**
      (i) The indiffusible solids are finely powdered and mixed with soluble solids.
      (ii) The powder is then triturated with one-fourth the volume of tragacanth mucilage to form a smooth cream.

3. One-half of the vehicle is then added.
4. Any other liquid ingredients, if present, are added and the suspension is made up to volume.
5. The suspension is transferred to a bottle, corked and labeled.

Example: R_x Aspirin
Oxyphenbutazone
Simple syrup
Water
Labeling: SHAKE WELL BEFORE USE

Suspensions Containing Precipitate-forming Liquids

Liquid preparations containing resinous matter when mixed with water show precipitation of resin, which sticks to the sides of the bottle and will not diffuse on shaking. Examples are compound benzoin tincture and tolu tincture. To prevent this, suspending agent such as compound tragacanth powder or tragacanth mucilage is added.

Preparation Using Compound Tragacanth Powder

1. The diffusible and indiffusible solids are finely powdered and mixed with compound tragacanth powder.
2. Three-fourths of the vehicle is added to the powder mixture and triturated to form a smooth cream.
3. The precipitate-forming liquid is added in a slow stream into the center of the cream with rapid stirring.
4. Any soluble ingredient is dissolved in the vehicle and added slowly with trituration to the cream.
5. Any other liquid ingredients, if present, are added and the suspension is made up to volume.
6. The suspension is transferred to a bottle, corked and labeled.

Preparation Using Tragacanth Mucilage

1. Tragacanth mucilage is mixed with an equal volume of vehicle.
2. The precipitate-forming liquid is added in a slow stream into the center of mucilage with constant stirring.
3. Solid substances are dissolved in one-fourth of the vehicle and mixed with the above.
4. Any other liquid ingredients, if present, are added and the suspension is made up to volume.
5. The suspension is transferred to a bottle, corked and labeled.

Labeling: SHAKE WELL BEFORE USE

Suspensions Containing Poorly Wettable Solids

Some substances such as sulfur and hydrocortisone are both insoluble in water and poorly wetted by it. When preparing simple aqueous dispersions, it is difficult to disperse clumps and the foam produced on shaking is slow to subside because it is stabilized by the film of unwettable solid at the liquid–air interface. To ensure satisfactory wetting, the interfacial energy between the solid and liquid must be reduced. This may be achieved by adding a suitable wetting agent, which is adsorbed at the solid–liquid interface in such a way that the affinity of the particles for the surrounding medium is increased while the interparticular forces are decreased.

For example, sulfur lotion–quillaia tincture is used as a wetting agent. The saponins in quillaia extract have been used to suspend sulfur in lotion.

Suspensions Produced by Chemical Reaction

Very occasionally, the insoluble active constituent of a lotion is produced by a chemical reaction. A finer precipitate is obtained if dilute solutions of the reactants are mixed. Hence, the reacting substance should be dissolved separately in approximately half volumes of the vehicle and the two parts mixed. When prepared in this manner, the precipitate is diffusible and no suspending agent is required. An example is magnesium hydroxide mixture.

Example: Zinc Sulfide lotion BPC (used to treat acne and scabies)

R_x Sulfurated potash
Zinc sulfate
Concentrated camphor water
Water

Sulfurated potash is a mixture of potassium polysulfides and other sulfur-containing compounds. It should be freshly prepared, as its solubility decreases on storage. It reacts with zinc sulfate and produces a precipitate of zinc sulfide, which is diffusible, provided sulfurated potash is added to zinc sulfate and not vice versa.

The precipitate of zinc sulfide agglomerates quickly and clays badly. Hence, the suspension should be freshly prepared and quickly used. Protection from light is necessary to reduce the oxidation of the sulfide to sulfite or sulfate.

(***Note:*** If sulfurated potash is added to zinc sulfate, the precipitate obtained is diffusible,
If zinc sulfate is added to sulfurated potash, the precipitate obtained is indiffusible.)

Evaluation of Suspensions

Learning Objective

- Tests used to determine the stability of suspensions

The following are the tests to determine the stability of suspensions:

1. **Determination of rate of sedimentation:** Redispersibility is one of the major considerations in assessing the acceptability of the suspension. Since the sediment formed should be easily dispersed by moderate shaking, measurement of the sedimentation volume and its ease of redispersion form two of the most common evaluative procedures for suspensions.

   Measurement of sedimentation volume is carried out in a measuring cylinder under standard conditions.

$$\text{Sedimentation volume} = \frac{\text{Ultimate height of sediment } (H_u)}{\text{Initial height of sediment } (H_o)}$$

   The larger this fraction, the better is the suspendability.

Evaluation of redispersibility is carried out using a mechanical shaking device, which simulates the human arm motion during the shaking process.

2. **Determination of viscosity (Rheological method):** The viscosity and the type of flow of the preparation are determined using a Brookefield's viscometer at specified temperatures.
3. **Determination of zeta potential:** Zeta potential controls flocculation of the dispersed phase. It can be determined by an instrument called *Zetameter*, which measures the electrophoretic mobility of particles in suspension.
4. **Determination of particle size change:** There are chances that the particle size of the dispersed phase undergoes changes after storage of suspensions for a long time due to the effect of temperature on the suspensions. This results in the change in particle size distribution and crystal growth. This can be studied by Coulter counter or by microscopic method.

Marketed Formulations

Lacto Calamine (Nicholas Piramal)
Caladryl (Pfizer)
Calak Lotion (SPPL)
Dey's Milk of Magnesia (Dey's)
Digene Gel (Abbott)
Gelupin-MPS (Lupin)
GelusiL-MPS (Pfizer)
Advent Forte (Dry powder suspension for reconstitution—amoxycillin and clavulanate potassium)

EMULSIONS

Learning Objective

- Basic principle and different types of emulsions

Emulsions are biphasic heterogeneous systems consisting of two immiscible phases, one of which (the dispersed phase) is finely subdivided and uniformly distributed as droplets throughout the other (the dispersion medium). An emulsion is rendered homogeneous by the addition of an emulsifying agent. The emulsifying agent ensures that the droplets (dispersed phase) is finely dispersed throughout the dispersion medium as minute globules.

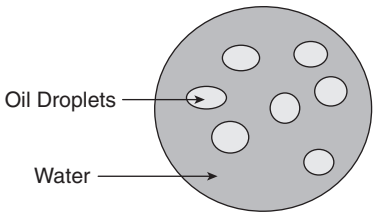
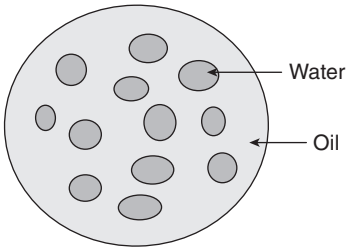
There are two types of emulsion:

1. **Oil in water (O/W) emulsions:** The oil (internal or dispersed) phase is dispersed as droplets throughout the aqueous phase (external or continuous phase or dispersion medium). Oil is the dispersed phase and water is the dispersion medium.
2. **Water in oil (W/O) emulsions:** The internal phase is composed of water droplets and the external phase is nonaqueous. Water is the dispersed phase and oil is the dispersion medium.

In general, all oral emulsions tend to be oil-in-water as the oily phase is usually less pleasant to take and more difficult to flavor. The differences between O/W and W/O emulsions are provided in Table 6.6.

The major use of emulsions is as cream formulations (for external application). However, they may also be administered intravenously, rectally or orally. Emulsions are physically unstable and the various excipients in the formulation are present primarily to stabilize the physical properties of the system.

Table 6.6 Differences between O/W and W/O Emulsions

Si.No.	*Oil in Water Emulsion (O/W)*	*Water in Oil Emulsion (W/O)*
1.	Oil is the dispersed phase and water is the dispersion medium.	Water is the dispersed phase and oil is the dispersion medium.
2.	They are nongreasy and easily washed from the skin surface.	They are greasy and not easily washed by water.
3.	They are used externally to provide a cooling effect, for example, vanishing cream.	They are used externally to prevent evaporation of moisture from the surface of skin, for example, cold cream.
4.	Water-soluble drugs are more quickly released from O/W emulsions.	Oil-soluble drugs are more quickly released from W/O emulsions.
5.	They are preferred for oral formulations as the taste of oils can be masked.	They are preferred for topical preparations such as creams.
6.	O/W emulsions give a positive conductivity test since the external phase is water, which is a good conductor of electricity.	W/O emulsions do not give a positive conductivity test since the external phase is oil, which is a poor conductor of electricity.
7.		

Microemulsions

Clear dispersions of oil in water or water in oil are called microemulsions. The disperse phase globules are very small, ranging in diameter from 100A° to 600A°. These emulsions appear as transparent solutions and are more acceptable physically as compared to conventional emulsions.

Self-emulsifying Systems

These are anhydrous products that when added to excess of water form emulsions spontaneously without requiring too much agitation. These systems are known as self-emulsifying drug delivery systems (SEDDS) and can be formulated by the use of a combination of hydrophilic and lipophilic surfactants.

Complex Emulsions (Multiple Emulsions)

1. **W/O/W emulsions:** An oil droplet enclosing a water globule may be dispersed in water to give W/O/W emulsions; see Fig. 6.2(a).
2. **O/W/O emulsions:** A water droplet enclosing an oil globule may be dispersed in oil to give O/W/O emulsions; see Fig. 6.2(b).

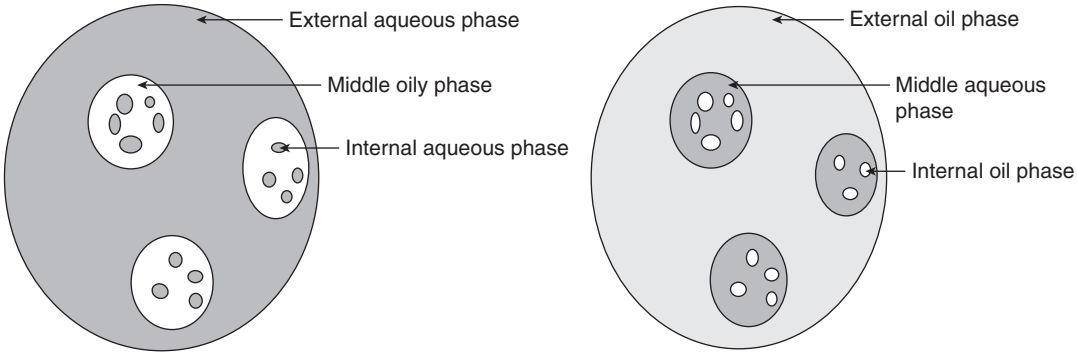


Figure 6.2 Complex Emulsions (a) W/O/W Emulsion (b) O/W/O Emulsion

Advantages and Disadvantages of Emulsions as Dosage Forms

The following are the advantages of using emulsions as dosage forms:

1. Unpalatable oils can be administered in a palatable form.
2. The aqueous phase is easily flavored.
3. The taste of oils can be masked.
4. Absorption is faster when compared to solid dosage forms.
5. It is possible to include two incompatible ingredients, one in each phase of the emulsion.
6. Emulsions of the O/W type are administered orally for the following purposes:
   (a) Disguise the taste or oiliness of medicinal oils such as liquid paraffin and cod liver oil. The aqueous continuous phase, which will be pleasantly flavored, isolates the unpleasant disperse phase from the tongue and, if the patient wishes, allows the residue of the dose to be rinsed easily from the mouth with water.
   (b) To improve the absorption of oils
   (c) Sometimes O/W emulsions of nutritive oils and fats are administered intravenously to patients who are unable to ingest food in the normal way.
7. Semisolid emulsions are O/W (vanishing creams) or W/O (cold creams). O/W emulsions are preferred over W/O emulsions. They can be easily rubbed into the skin and can be easily removed by washing.

The following are the disadvantages of using emulsions as dosage forms:

1. Calculation of primary emulsion formulae and technical expertise are needed for the manufacture of stable emulsions.
2. A measuring device is needed for administration.
3. Emulsions require shaking before use to ensure uniformity of dose.
4. If the preparation is not shaken well, the accuracy of dose is likely to be less when compared to solutions.
5. Improper storage conditions can affect the disperse system.
6. Since emulsions are stored in glass or plastic containers, they are bulky, difficult to transport and prone to container breakages.
7. Microbial contamination of emulsions can lead to cracking.

Tests for Identification of Emulsion Type

Learning Objective

- Tests that can be carried out to identify emulsion type

The tests that can be performed to distinguish between O/W and W/O emulsions are given below (Table 6.7):

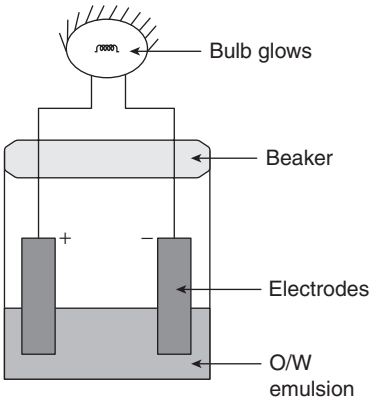
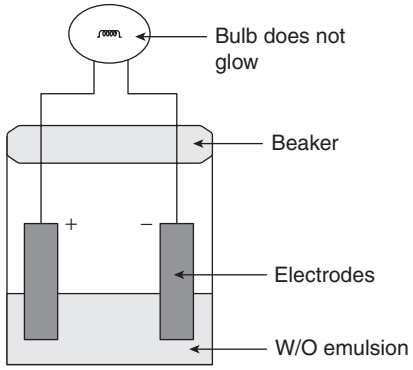
1. Dilution test
2. Dye solubility test
3. Conductivity test
4. Cobalt chloride test
5. Fluorescence test

Table 6.7 Tests to distinguish between O/W and W/O Emulsions

Sl. No.	*O/W Emulsion*	*W/O Emulsion*
1.	**Dilution Test or Miscibility Test**	
	Dilute the emulsion with water or oil	
	When diluted with water, emulsion is stable When diluted with oil, cracking occurs	When diluted with oil, emulsion is stable When diluted with water, cracking occurs
2.	**Dye Solubility Test or Staining Test**	
	An oil-soluble or water-soluble dye is added to the emulsion and observed under a microscope.	
	Water-soluble dye (amaranth): Continuous phase is colored and disperse phase is colorless. Oil-soluble dye (scarlet red): Disperse phase is colored and continuous phase is colorless.	Water-soluble dye (amaranth): Disperse phase is colored and continuous phase is colorless. Oil-soluble dye (scarlet red): Continuous phase is colored and disperse phase is colorless.

(*Continued*)

Table 6.7 Continued

Sl. No.	O/W Emulsion	W/O Emulsion
3.	**Conductivity Test**	
	Immerse a pair of electrodes in the emulsion and connect them to a bulb.	
	When current is applied, if the bulb glows it indicates water is the continuous phase. This is because water is a good conductor of electricity.	When current is applied, if the bulb does not glow it indicates oil is the continuous phase. This is because oil is a bad conductor of electricity
		
4.	**Cobalt Chloride Test**	
	Anhydrous cobalt is blue and hydrated cobalt is red. Treat a filter paper with cobalt chloride solution and dry it. Dip the dry-treated paper in the emulsion.	
	The change in color from blue to pink red indicates an O/W emulsion.	If there is no change in color, it indicates W/O emulsion.
5.	**Fluorescence Test**	
	Many oils show fluorescence when exposed to UV light. The emulsion is observed against UV light under microscope.	
	Spotty fluorescence is observed against a colorless background.	Colorless droplets are observed against a fluorescent background.

Routes of Administration of Emulsions

The following are the various routes of administration of emulsions:

1. **Oral emulsions:** In general, O/W emulsions are preferred for internal use, as the oil is more readily absorbed in a fine state of subdivision through the gastrointestinal tract and the preparation becomes more palatable when water forms the continuous phase. Oral emulsions are also used to improve the absorption of the oil-soluble drugs such as vitamins A, D, E and K.

   Example 1: Liquid paraffin oral emulsion

Liquid paraffin	500 ml
Methyl cellulose	20 g
Vanillin	0.5 g

Chloroform	2.5 ml
Benzoic acid solution	20 ml
Saccharin sodium	0.05 g
Purified water (q.s.)	1000 ml

Uses: Laxative—It acts as an emollient purgative in chronic constipation, especially during pregnancy and in geriatrics.

Example 2: Castor oil emulsion

Castor oil	16 ml
Gum acacia	q.s.
Water	80 ml

Uses: Purgative

2. **Rectal emulsions:** Enemas can be formulated as O/W emulsions.
3. **Topical emulsions:** For external use, emulsions may be either O/W or W/O type. O/W emulsions have been used for formulation of moisturizing lotions, hand lotions and makeup foundation lotions. W/O emulsions are preferred when oily layers are desired to prevent moisture loss from the surface of skin or for barrier action and for cleansing action.

Example 1: Cold cream

Liquid paraffin	20 g
Hard paraffin	4.5 g
Lanette wax	3.5 g
Glycerin	4.5 g
Water	17.5 g
Propyl paraben	0.1 g

Uses: Emollient

Formulation of Emulsions

Learning Objective

- Principles involved in the preparation of emulsions

Choice of Emulsion Type

Fats or oils for oral administration are formulated as O/W emulsions. In this form, they are pleasant to take and the inclusion of a suitable flavor in the aqueous phase will mask any unpleasant taste. Emulsions for intravenous administration must also be of O/W type, although intramuscular injections can be formulated as W/O products if a water-soluble drug is required for depot therapy.

Semisolid emulsions for external application can be of O/W or W/O type. O/W type is used for topical application of water-soluble drugs. It is not greasy, is pleasant to use and can be easily washed from skin surfaces. W/O type will act as an occlusive barrier and is useful for cleansing the skin of oil-soluble dirt, but its greasy texture is not acceptable.

Choice of Oil Phase

In many instances, the oil phase of an emulsion is the active agent and its concentration in the product is predetermined. For example, liquid paraffin, castor oil, cod liver oil and arachis oil are medicaments formulated as emulsions for oral administration. Cottonseed oil, soya bean oil and sunflower oil are used in parenteral emulsions for their high calorific value. Turpentine oils and benzyl benzoate are externally applied oils. Many emulsions for external use contain oils that are present as carriers for the active agent.

The type of oil used may also have an effect on the viscosity of the product and the penetration of drug into the skin. For example, in liquid paraffin, hard or soft paraffin can be used individually or in combination with each other to control emulsion consistency. This will ensure that the product spreads easily and forms a thin film over the skin.

Choice of Emulsifying Agent (Emulgent)

Emulsifying agents are the substances added to an emulsion to prevent the coalescence of the globules of the dispersed phase. They are also known as emulgents or emulsifiers. These agents have both a hydrophilic and a lipophilic part in their chemical structure. Emulsifying agents are adsorbed onto the oil–water interface to provide a protective barrier around the dispersed droplets. In addition to this protective barrier, emulsifiers stabilize the emulsion by reducing the interfacial tension of the system. Some emulgents enhance stability by imparting a charge on the droplet surface, thereby reducing the physical contact between the droplets and decreasing the potential for coalescence. Thus, these act in three ways:

1. Formation of a protective barrier
2. Reduction of interfacial tension
3. Decreasing the potential for coalescence by forming an electrical double layer

Emulsifying agents reduce the interfacial tension between the two phases—oil phase and aqueous phase—and thus make them miscible with each other to form a stable emulsion. The choice of the emulgent to be used depends not only on its emulsifying ability but also on its route of administration and its toxicity.

HLB system (Hydrophile–Lipophile balance): Hydrophile–lipophile balance (HLB) method has been devised by Griffin to calculate the relative quantities of the emulgents necessary to produce the most physically stable emulsion or a particular oil–water combination. Each emulsifying agent has a hydrophilic or polar portion and a lipophilic or a nonpolar portion (Fig. 6.3).

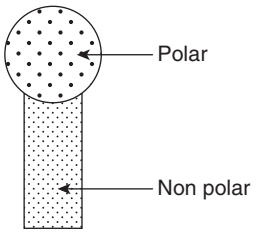


Figure 6.3 Emulsifying Agent

Each portion may be more or less predominant, that is, some agents may have more hydrophilic portion and some may have more lipophilic portion. The HLB system is based on the balance between the hydrophilic and lipophilic portions of the surfactant.

Each surfactant is allocated a HLB number, which represents the relative proportions of its lipophilic and hydrophilic portions. The values are assigned from 1 to 40 and are an indication of the polarity of the substances, but the usual range is between 1 and 20. Emulgents with higher numbers (8–18) indicate hydrophilic properties and produce O/W emulsions, whereas those with lower numbers (3–6) indicate lipophilic properties and produce W/O emulsions.

Table 6.8 shows the classification of agents according to their HLB values and Table 6.9 shows the HLB values of various emulgents.

Table 6.8 Classification of Agents According to Their HLB Values

Category	*HLB Values*
Antifoaming agents	1–3
W/O emulsifying agents	4–6
Wetting agents	7–9
O/W emulsifying agents	8–18
Solubilizers	15–20
Detergents	13–15

Table 6.9 HLB Values of Various Emulgents

Emulgents	*HLB Values*
Oleic acid	4.3
Sorbitan monolaurate (Span 20)	8.6
Sorbitan monostearate (Span 60)	4.7
Sorbitan monooleate (Span 80)	4.3
Sorbitan trioleate (Span 85)	1.8
Polysorbate 20 (Tween 20)	16.7
Polysorbate 60 (Tween 60)	14.9
Polysorbate 80 (Tween 80)	15.0
Potassium oleate	20.0
SLS	40.0
Acacia	8.0
Tragacanth	13.2

Classification of Emulsifying Agents or Emulgents

Learning Objective

- Different classes of emulsifying agents used to stabilize an emulsion

There are two types of emulsifying agents (Figure 6.4):

1. Primary (true) emulsifying agents, which produce emulsions with good stability
2. Secondary emulsifying agents or emulsion stabilizers, which are used in combination with primary emulsifying agents to improve the stability of the emulsion

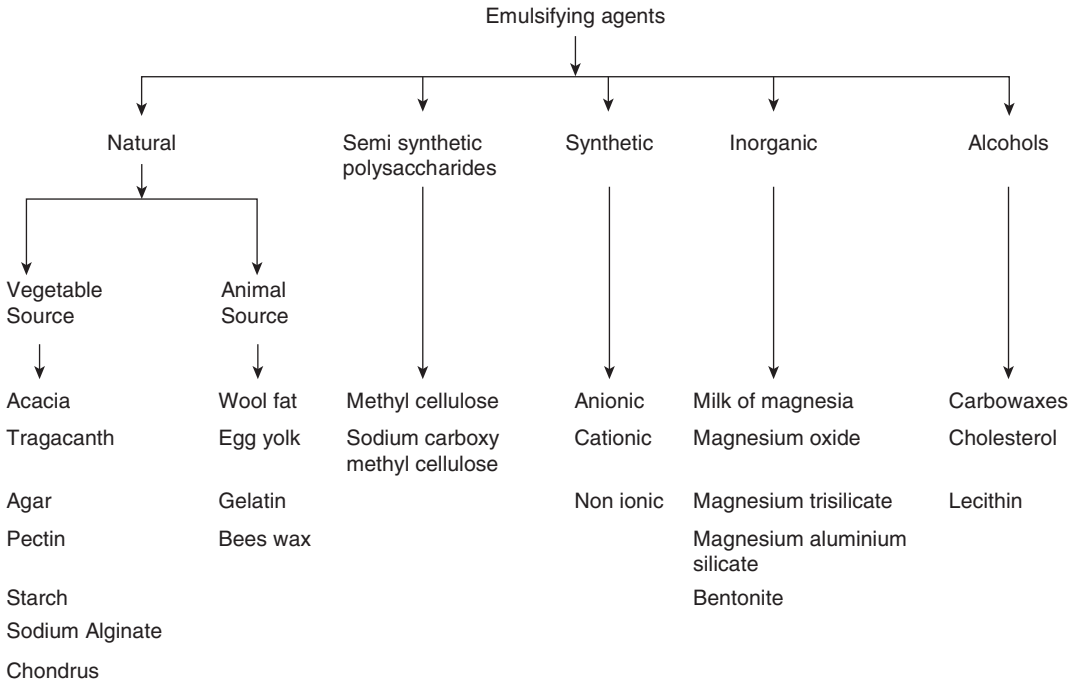


Figure 6.4 Classification of Emulsifying Agents

The emulsifying agents are classified into the following categories:

1. **Natural products:** The following are the different natural emulsifying agents:
   (a) Acacia is the best emulsifying agent for the extemporaneous preparation of emulsions. Preparations of good quality, stability and appearance can be made only with a mortar and pestle. This is because the concentrated emulsion produced in the initial stage of preparation is very viscous and sticky. Therefore, the oil cannot escape the vigorous shearing action of the pestle and is easily reduced to fine globules.

   Acacia emulsions are of low viscosity. Therefore, thickening agents such as tragacanth and sodium alginate are added. These emulsions are palatable and are stable over a wide pH range (2–10).

(b) Tragacanth is rarely used alone because of its high viscosity. The emulsions are coarse and are used as a stabilizer in acacia emulsions in the proportion 1:10 (acacia).
(c) Sodium alginate has high viscosity and is used as an emulsion stabilizer along with acacia.
(d) Agar is the dried extract obtained from certain seaweeds. It is used as an emulsion stabilizer in liquid paraffin emulsions prepared with acacia. It is soluble in boiling water, producing solutions of high viscosity.
(e) Starch is a poor emulsifying agent and is used for the preparation of enemas containing oils.
(f) Pectin is obtained from the inner rind of citrus fruits or from the apple pulp that remains after the making of cider. In acid media, it is a good O/W emulgent but degrades in alkaline pH. It is employed in the preparation or stabilizing of cosmetic creams and lotions.
(g) Chondrus is dried seaweed. It is not suitable for small-scale emulsification because preparation of the mucilage is time consuming and its emulsions must be homogenized. It is used in the emulsification of cod liver oil emulsions to mask the unpleasant odor and taste of the oil; 2.5% mucilage will emulsify an equal volume of fixed oil.
(h) Wool fat is a type of wax that consists chiefly of fatty acid esters of cholesterol and other sterols together with normal fatty alcohols. It can absorb 50% of water, but when mixed with other fatty substances it can emulsify several times its own weight of aqueous or hydroalcoholic liquids. The emulsions made are of W/O type.
(i) Gelatin is used for the emulsification of liquid paraffin emulsions at a concentration of 1%. Gelatin emulsions are prone to bacterial growth, and therefore, a suitable preservative should be added.
(j) Egg yolk is an emulsifying agent because of the presence of lecithin and cholesterol. It is rarely used in industrial preparations as they are spoiled during transportation or if not preserved properly. It is used for the emulsification of fish liver oils.

2. **Semisynthetic polysaccharides:** The following are the different semisynthetic polysaccharides:
   (a) Methyl cellulose is of low viscosity and is suitable as emulgents and emulsion stabilizers. It is suitable for emulsifying mineral and vegetable oils and is used at a concentration of 2%.
   (b) SCMC is of medium viscosity grade and is used at a concentration of 0.5% to 1% as emulsion stabilizer.

3. **Synthetic polysaccharides:** These are further classified into the following types:
   (a) **Anionic:** In aqueous solution, these substances ionize into a large anion, which is responsible for their emulsifying ability, and a small cation. These are of five types and bear a negative charge on them.
      (i) Alkali metal and ammonium soaps
      (ii) Soaps of divalent and trivalent metals
      (iii) Amine soaps
      (iv) Alkyl sulfates
      (v) Alkyl phosphates

      (i) Alkali soap emulsions (monovalent soaps) are stable above pH 10 but are sensitive to acids. High concentration of electrolytes can salt out the soap. They are incompatible with polyvalent cations (Mg^{2+}, Al^{3+}, Zn^{2+}), as they can cause phase reversal. Their physiological action and unpleasant taste make them unsuitable for internal

emulsions. Moreover, because of their alkaline pH, they should not be used in preparations for application to broken skin. They can be used as emulgents only in O/W emulsions.

(***Note:*** Alkali metal and ammonium soaps are the sodium, potassium or ammonium salts of long chain fatty acids such as oleic, stearic and ricinoleic acids. They produce O/W emulsions that can be prepared with either of the following:

- A preformed soap such as soft soap (turpentine liniment)
- A soap formed during the preparation of emulsion such as ammonium soap made from oleic acid and ammonia (white liniment)

(ii) Among the soaps of divalent and trivalent metals, usually only the calcium soaps are used as W/O emulsifying agents. They cannot be used internally, but they are less alkaline and less sensitive to acid.

(***Note:*** Ca^{2+}, Mg^{2+}, Al^{3+} and Zn^{2+} salts of fatty acids are also W/O emulsifying agents, but only calcium soaps are commonly used.)

(iii) Triethanolamine (amine) soaps produce fine-grained, almost neutral (pH 7.5 to 8) O/W emulsions. They can be applied to broken skin but are unsuitable for internal use.

(iv) Alkyl sulfates are esters of fatty alcohols and sulfuric acid. Among alkyl sulfates, SLS is used alone to produce O/W emulsions of low stability. However, when it is used in conjunction with fatty alcohols, products of excellent stability and quality are obtained.

(v) Alkyl phosphates are also used in combination with fatty alcohols. They are similar to alkyl sulfate but the alcohols are phosphated instead of sulfated.

(b) **Cationic:** In aqueous solution, these substances ionize into a large cation, which is responsible for their emulsifying ability, and a small anion. They bear a positive charge on them, for example, quaternary ammonium compounds. They have emulgent properties apart from their disinfectant and preservative properties. If used alone, their emulsifying power is poor, but they produce emulsions of great stability when combined with fatty alcohols. Examples are benzalkonium chloride, benzethonium chloride and cetrimide (cetyl trimethyl ammonium bromide).

(c) **Nonionic:** They do not ionize in aqueous solutions. The emulsion prepared is stable over a wide range of pH and is not affected by the addition of acids and electrolytes. Examples are glycol and glycerol esters (glyceryl monostearate), sorbitan esters (spans), polysorbates (tweens), macrogols (polyethylene glycol) and polyvinyl alcohol.

4. **Inorganic agents:** Finely divided solids with suitable balanced hydrophobic and hydrophilic properties are adsorbed at an oil–water interface, forming a coherent film that prevents coalescence of the dispersed globules. If the solid particles are preferentially wetted by the oil, then W/O emulsions are formed, whereas wetting by water results in O/W products. Examples are milk of magnesia (10%–20%), magnesium oxide (5–10%) and magnesium aluminum silicate (1%).

5. **Alcohols:** These are further classified into the following types:
   (a) Carbowaxes are used in the preparation of ointments and creams. The substances with a molecular weight of 200–700 are viscous, light-colored, hygroscopic liquids, whereas those with a molecular weight above 1000 are wax-like solids.

(b) Cholesterol is used only in combination with other emulsifying agents to produce a stable emulsion.
(c) Lecithin

Formulation of Emulsions

The formulation of emulsions involves the following:

1. **Oil phase:** The oil (medicament or vehicle) used for the preparation of emulsion may be of fixed oil, mineral oil, volatile oil or oleo resin type. Depending upon the origin, suitable ratio of oil, water and emulgent must be used for the preparation of primary emulsion.

2. **Aqueous phase:** Freshly boiled and cooled purified water is normally used because of the increased risk of microbial contamination.

3. **Preservative:** The desirable features of a preservative suitable for use in an emulsion include the following:
   (a) Wide spectrum of activity against all bacteria, yeast and molds
   (b) Bactericidal rather than bacteriostatic activity
   (c) Freedom from toxic, irritant and sensitizing activity
   (d) High-water solubility. Because the growth of microorganisms occurs in the aqueous phase, it is important that the preservative has a low O/W partition coefficient. The more polar the oil phase, the more difficult it is to preserve the product adequately, owing to the solubility of the preservative in both the phases.
   (e) Compatibility with the other ingredients in the preparation and with the container
   (f) Stability and effectiveness over a wide range of pH and temperature
   (g) Freedom from color and odor
   (h) Retention of activity in the presence of large number of microorganisms

   Examples are benzoic acid (0.1%–0.2%), methyl and propyl paraben (0.1%–0.2%), chloroform (0.25%), chlorocresol (0.1%) and phenyl mercuric nitrate (0.004%–0.01%).

4. **Emulsifying agent (emulgent):** The quantity of emulsifying agent added is determined by the type of oil to be emulsified and the quantity of emulsion to be prepared.

5. **Antioxidant:** This is used to increase the stability of the oil phase in the emulsion by preventing the oxidation of the oil during its shelf life. Examples are butylated hydroxy anisole (BHA), butylated hydroxy toluene (BHT) and tocopherol.

6. **Flavoring agent:** This is used to increase the palatability of the final preparation. Examples are pineapple, orange, chocolate and mint flavors.

7. **Coloring agent:** This is used to identify the preparation and to increase the aesthetic appeal of the preparation. Examples are Food, Drug and Cosmetic Act-approved colors such as erythrosine and tartrazine.

8. **Perfume:** This is used only for external preparations such as creams.

Preparation of Emulsions

Learning Objective

- Methods involved in the preparation of emulsions

The preparation of an emulsion involves two stages:

1. Preparation of the primary emulsion
2. Dilution of the primary emulsion

Calculation of Primary Emulsion Formula

The amount of emulsifying agent used is dependent on the amount and type of oil to be emulsified. Oils can be divided into three categories: fixed oils, mineral oils and volatile oils.

1. **Fixed oils**
   Oil: 4 parts by volume
   Aqueous phase: 2 parts by volume
   Gum: 1 part by weight
2. **Mineral oils**
   Oil: 3 parts by volume
   Aqueous phase: 2 parts by volume
   Gum: 1 part by weight
3. **Volatile (aromatic) oils**
   Oil: 2 parts by volume
   Aqueous phase: 2 parts by volume
   Gum: 1 part by weight.

(***Note:*** Gum is the emulsifying agent or emulgent.)

These proportions are important when making the primary emulsion to prevent the breaking down of emulsion on dilution or storage.

The ratio of oil to water to gum for a primary emulsion can be calculated using the formulae shown in Table 6.10. (The quantities for primary emulsion have been obtained by experience.)

Table 6.10 Primary Emulsion Formulae

Type of Oil	*Examples*	*Oil*	*Water*	*Gum (Emulgent)*
Fixed oil	Arachis oil, castor oil, cod liver oil, almond oil	4	2	1
Mineral oil	Liquid paraffin	3	2	1
Volatile (aromatic) oil	Cinnamon oil, turpentine oil, peppermint oil	2	2	1
Oleo resin	Male fern extract	1	2	1

There are two methods used in the preparation of emulsions:

1. **Trituration method:** This includes the dry gum and wet gum methods.
   (a) **Dry gum or Continental method:** In this method the emulsifying agent (usually acacia) is mixed with the oil before the addition of water.

   Acacia is triturated with the oil in a perfectly dry porcelain mortar until thoroughly mixed. A mortar with a rough surface must be used to ensure proper grinding action and reduction of globule size. After the oil and gum have been mixed, the amount of water required for the primary emulsion is added in small portions with continuous trituration. Trituration is continued in one direction until the primary emulsion is creamy white and a cracking sound is produced by the movement of the pestle. Other soluble liquid ingredients are then mixed into the primary emulsion. Solid substances such as preservatives, stabilizers, colorants and any flavoring agents are usually dissolved in a suitable volume of vehicle and added to the primary emulsion. The emulsion is then made up to volume with the remaining vehicle.

   (b) **Wet gum or English method:** In this method, the emulsifying agent is added to water to form the mucilage and then the oil is slowly added to form the emulsion.

   In the wet gum method, the same proportions of oil, water and gum as given in Table 6.10 are used, but the order of mixing is different. Mucilage of the gum is prepared by triturating with water. The oil is then added in small portions with trituration. After the addition of the entire oil, the mixture is thoroughly triturated in one direction to form the primary emulsion. Other soluble liquid ingredients are then mixed into the primary emulsion. Solid substances such as preservatives, stabilizers, colorants and any flavoring agents are usually dissolved in a suitable volume of vehicle and added to the primary emulsion. The emulsion is then made up to volume with the remaining vehicle.

2. **Bottle or Forbes method:** This method is employed for preparing emulsions containing volatile and nonviscous oils. Both dry gum and wet gum methods can be employed for the preparation.

   Since volatile oils have a low viscosity as compared to fixed oils, they require comparatively large quantities of gum for emulsification. In this method, the oil or water is first shaken vigorously with the calculated amount of gum. Once this has emulsified completely, the second liquid (water or oil) is then added all at once and the corked bottle is again shaken vigorously to form the primary emulsion. More water is added in small portions, with constant shaking after each addition, to produce the final volume.

   This method is not suitable for viscous oils as they cannot be thoroughly agitated in the bottle when mixed with the emulgent. When the intended dispersed phase is a mixture of fixed oil and volatile oil, the dry gum method is generally employed.

Instabilities in Emulsions

Learning Objective

- Stability problems encountered during the preparation of emulsions

An emulsion is a thermodynamically unstable preparation. So, care has to be taken to maintain the physical and chemical stability of the preparation throughout its shelf life. There should be no appreciable change in the mean particle size or the size distribution of the droplets of the dispersed phase. The droplets of the dispersed phase should remain uniformly distributed throughout the system.

Instabilities in emulsion can be grouped as follows:

1. Cracking
2. Creaming
3. Phase inversion

Cracking

The globules of the disperse phase coalesce together and form a separate layer. Redispersion cannot be achieved by shaking and the preparation is no longer an emulsion. Cracking may be caused by the following:

1. Addition of emulsifying agents of the opposite type. Soaps of monovalent metals produce O/W emulsions whereas soaps of divalent metals produce W/O emulsions. Addition of a monovalent soap to a divalent soap emulsion or vice versa leads to cracking. Anionic and cationic emulsifying agents are mutually incompatible. Gums, proteins, gelatin and casein are insoluble in alcohol and if alcohol is added to emulsions prepared with these materials, the emulgent is precipitated and cracking occurs.
2. Decomposition of the emulsifying agent due to microbial action. Emulsions not intended for immediate use should contain a preservative to prevent growth of molds and bacteria, which might over a period of time destroy the emulsifying agent and cause cracking.
3. Addition of common solvent. The addition of a liquid in which both the disperse and continuous phases are soluble forms a one-phase system and destroys the emulsion.
4. Oil turning rancid during storage. The acid formed denatures the emulsifying agent, causing the two phases to separate.
5. Change of storage temperature. The change of extreme storage conditions during the shelf life may lead to the cracking of the emulsion.

Creaming

Creaming is the separation of an emulsion into two regions, one of which is richer in the disperse phase than the other. It is not a serious instability problem as a uniform dispersion can be reobtained by shaking the emulsion. However, there may be coalescence of droplets as they are present close to each other. Larger droplets may cream more rapidly and coalesce more readily in the cream layer; therefore, the emulsion may eventually crack. It is a temporary or reversible process.

If the disperse phase is less dense than the continuous phase, as in O/W emulsions, the velocity of sedimentation becomes negative and *upward creaming* results.

If the internal or disperse phase is heavier than the external phase, the globules settle, as in W/O emulsions, where the internal aqueous phase is denser than the continuous oil phase. This effect is known as *downward creaming*.

Stoke's law is used to express the velocity of sedimentation.

According to Stoke's law $V = \dfrac{2r^2(\sigma_s - \sigma_o)g}{9\eta}$ or $V = \dfrac{d^2(\sigma_s - \sigma_o)g}{18\eta}$

where V = velocity in cm/s (rate of creaming)
r = radius of the globules
d = diameter of the globules in cm
σ_s = density of dispersed phase

σ_o = density of dispersion medium
g = gravitational constant
η = viscosity of the dispersion medium

The factors in Stoke's equation can be altered to reduce the rate of creaming in an emulsion.

1. By decreasing the diameter of the oil globules, the rate of creaming decreases. This is because small globules cream less rapidly than large ones. This can be achieved by the use of a homogenizer.
2. The viscosity of the external or continuous phase can be increased by adding a thickening agent. Increased viscosity will retard the movement of globules. The inclusion of methyl cellulose will reduce the mobility of the dispersed droplets in an O/W emulsion. The addition of soft paraffin will have the same effect on water droplets in a W/O emulsion.
3. The possibility of creaming is decreased by the reduction in density differences between the two phases. Creaming can be prevented if the densities of the two phases are identical.
4. Storage in a cool place can decrease creaming. Temperature rise decreases the viscosity of the continuous phase and increases the number of collisions between the globules. Freezing of the aqueous phase must be avoided since ice may separate and cause cracking by exerting pressure on the globules.

Phase Inversion

This is the process when an O/W emulsion changes to a W/O emulsion or vice versa.

As already mentioned, soaps of monovalent metals produce O/W emulsions, whereas soaps of divalent metals produce W/O emulsions. The emulsion type is determined by the solubility of the emulsifying agent. If it is more soluble in water than in oil, the water will be the continuous phase and vice versa. The addition of a substance that alters the solubility of the emulsifying agent may cause reversal of the phases. For example, if calcium chloride is added to an O/W emulsion stabilized by sodium soap, phase reversal may occur resulting in a W/O emulsion.

For stability of an emulsion, the optimum range of concentration of the dispersed phase is 30%–60% of the total volume. If the concentration of disperse phase exceeds this concentration, phase inversion occurs.

Phase inversion can be minimized by using the proper emulsifying agent in adequate concentration, keeping the concentration of dispersed phase between 30% and 60% and storing the emulsion in a cool place.

Packaging, Labeling and Storage of Emulsions

Depending on the use, emulsions should be packed in suitable containers. Emulsions meant for oral use are usually packed in well-filled airtight bottles. Light-sensitive products are packed in amber-colored bottles. Viscous emulsions should be dispensed in wide-mouthed bottles.

The label on the emulsion should mention that these products have to be shaken thoroughly before use. Topical products should clearly mention on their label that they are meant for external use only. Emulsions should be stored in a cool place but refrigeration should be avoided to maintain the stability of the preparation.

Labeling for Emulsions: SHAKE WELL BEFORE USE

Preservation of Emulsions

1. **Preservation from microorganisms:** Contamination due to microorganisms can result in problems such as color and odor change, gas production, hydrolysis, pH change and eventually breaking down of emulsion. Therefore, it is necessary that emulsions are adequately preserved.

   An ideal preservative should be nonirritant, nonsensitizing and nontoxic in the concentration used. It should be physically as well as chemically compatible with the other ingredients of the emulsions and with the container of the product. It should not impart any taste, color or odor to the product. The preservative should be stable and effective over a wide range of pH and temperature. It should have a wide spectrum of activity against a range of bacteria, yeasts and molds. The selective preservative should have high water solubility and a low oil–water partition coefficient. It should have bactericidal rather than bacteriostatic activity.

   Examples of antimicrobial preservatives used to preserve emulsified systems include p-hydroxybenzoate esters such as methyl, propyl and butyl parabens, organic acids such as ascorbic acid and benzoic acid, organic mercurials such as phenylmercuric acetate and phenylmercuric nitrate, quaternary ammonium compounds such as cetrimide, cresol derivatives such as chlorocresol and miscellaneous agents such as sodium benzoate, chloroform and phenoxyethanol.

2. **Preservation from oxidation:** Oxidative changes such as rancidity and spoilage due to atmospheric oxygen and the effects of enzymes produced by microorganisms are seen in many emulsions containing vegetable and mineral oils and animal fats. Antioxidants can be used to prevent the changes occurring due to atmospheric oxygen.

   The ideal antioxidant should be soluble in the vehicle, nontoxic, nonirritant and effective at low concentration under the expected conditions of storage and use. Antioxidants for use in oral preparation should also be odorless and tasteless.

   Some of the commonly used antioxidants for emulsified systems are ethyl gallate, propyl gallate, dodecyl gallate, butylated hydroxyanisole (BHT) and butylated hydroxytoluene (BHT)

Evaluation of Emulsions

Learning Objective

- Tests that can be carried out to ensure the stability of an emulsion

The physical stability of emulsions can be tested by performing some simple tests such as the following:

1. **Macroscopic examination:** The physical stability of an emulsion can be tested by examination of the degree of creaming occurring over a period of time. This is carried out by calculating the volume of the creamed or separated part of the emulsion to the total volume.
2. **Globule size analysis:** Globule size can be determined by microscopic examination, electronic particle counting devices such as Coulter counter or Laser diffraction.
3. **Viscosity changes:** The changes in viscosity can be determined using a viscometer.

Marketed Formulations

Agarol (Pfizer)
Cremaffin (Liquid paraffin in combination with milk of magnesia) (Abbott)
Duolaxin (Glenmark)

REVIEW QUESTIONS

Answer in Detail

1. Discuss the various instabilities in emulsions.
2. Compare between O/W and W/O emulsions. Give the tests used for the identification of emulsions.
3. Define and classify emulsions. Describe the methods of preparation.
4. What are suspensions? Discuss the factors affecting the stability of suspensions.
5. Mention the applications of suspensions. Describe the various types of suspensions with examples.

Answer in Brief

1. Write the principle involved in the preparation of magnesium hydroxide mixture.
2. Enlist the ingredients in calamine lotion with their objective.
3. Write the primary emulsion formula for different types of oils with examples.
4. What are the differences between flocculated and deflocculated suspensions?
5. What will be the amount of emulsifying agent to prepare 30 ml of liquid paraffin emulsion containing 20% of liquid paraffin?
6. What are the instabilities in an emulsion?
7. State the additives used in liquid dosage forms.
8. Describe the different tests used to identify the types of an emulsion.
9. Classify liquid dosage forms with examples.
10. Give the tests used for the identification of emulsions.
11. Describe the various organoleptic additives used in pharmaceutical formulations.
12. Write the formula of liquid paraffin emulsion I.P.
13. Give two examples each of diffusible and indiffusible solids.
14. Give examples for antioxidant and sweetening agents.
15. Name four tests used for identification of emulsions.
16. Name four flocculating agents.
17. Give two examples for stabilizers and colorants
18. What are deflocculated suspensions? Give examples.
19. Describe emulsifying agents with examples.
20. What are the differences between emulsion and suspension?
21. Give two examples each of coloring and flavoring agents.
22. Write the primary emulsion formulae for mineral oils and volatile oils.

Answer in One or Two Sentences

1. Write the formula of liquid paraffin emulsion I.P.
2. Give two examples each of diffusible and indiffusible solids.
3. Give examples for antioxidants and sweetening agents.
4. Name four tests used for identification of emulsions.
5. Name four flocculating agents.
6. Give two examples for stabilizers and colorants.
7. What are deflocculated suspensions? Give examples.
8. Describe emulsifying agents with examples.
9. Differentiate between emulsions and suspensions.
10. Give two examples each of coloring and flavoring agents.
11. Give the primary emulsion formulas for mineral oils and volatile oils.

Multiple Choice Questions

1. Which of the following is a mineral oil?
   (a) Peppermint oil BP (b) Sunflower oil
   (c) Arachis oil BP (d) Liquid paraffin BP
2. Which of the following is a volatile oil?
   (a) Almond oil (b) Liquid paraffin
   (c) Peppermint oil (d) Sesame oil
3. Which of the following cannot be used as an emulgent or emulsifying agent?
   (a) Acacia (b) Chlorocresol
   (c) Tragacanth (d) Methylcellulose
4. What would the proportions of oil: water: emulgent for a primary emulsion containing a fixed oil?
   (a) 4:2:1 (b) 3:2:1 (c) 2:2:1 (d) 1:2:1
5. Which of the following statements is correct?
   (a) A creamed emulsion will reform on shaking.
   (b) A creamed emulsion will not reform on shaking.
   (c) A cracked emulsion will reform on shaking.
   (d) A phase-inverted emulsion will revert to its original form on shaking.
6. You are asked to prepare 100 ml of an emulsion containing 40% of peppermint oil BP, 0.5% of amaranth and 10% of syrup. How much acacia BP would be needed to prepare the primary emulsion?
   (a) 9 g (b) 10 g (c) 20 g (d) 18 g
7. What specific instruction should be included on the label of all emulsions?
   (a) For external use only (b) Not to be taken
   (c) Shake the bottle (d) Store in a cool place
8. Which of the following is an example of an indiffusible powder?
   (a) Chalk BP (b) Light kaolin BP
   (c) Sodium bicarbonate BP (d) Light magnesium carbonate BP

9. Which of the following is an example of a diffusible powder?
   (a) Calamine BP (b) Lactose BP
   (c) Sodium bicarbonate BP (d) Magnesium trisilicate BP
10. Which of the following suspending agents would be unsuitable for use for a suspension intended for the oral route of administration?
   (a) Tragacanth BP (b) Bentonite BP
   (c) Methylcellulose BP (d) Compound tragacanth Powder BP
11. Which of the following is not a suspension?
   (a) Pediatric kaolin mixture (b) Zinc sulfate lotion BP
   (c) Sulfur lotion compound BPC (d) Calpol

ANSWERS TO MULTIPLE CHOICE QUESTIONS

1. (d) 2. (c) 3. (b) 4. (a) 5. (a)
6. (c) 7. (c) 8. (a) 9. (d) 10. (b)
11. (b)

Exercises

1. Calculate the formula for preparing 200 ml of 30% cod liver oil emulsion.

Sl. No.	*Ingredients*	*Official Formula*	*Working Formula*
1.	Cod Liver Oil	30 ml	60 ml
2.	Acacia BP	q.s.	q.s.
3.	Double strength chloroform water BP	50 ml	100 ml
4.	Purified water (q.s)	100 ml	200 ml

Formula for Primary Emulsion: Cod liver oil BP is a fixed oil. Therefore, the primary emulsion ratio is as follows:

Oil	:	Water	:	Gum
4	:	2	:	1

60 ml of cod liver oil BP is required. 4 parts = 60 ml. 1 part will therefore be 60 ÷ 4 = 15.
The amount of freshly boiled and cooled purified water needed is 30 ml.
The amount of acacia BP required = 15 g.
Therefore the product formula for 200 ml of cod liver oil 30% emulsion is as follows:
Cod liver oil BP 60 ml
Acacia BP 15 g
Double strength chloroform water BP 100 ml
Purified water (q.s.) 200 ml

2. Calculate the formula for preparing 200 ml of 15% liquid paraffin BP emulsion.

Sl.No.	*Ingredients*	*Official Formula*	*Working Formula*
1.	Liquid paraffin	15 ml	30 ml
2.	Acacia BP	q.s.	q.s.
3.	Double strength chloroform water BP	50 ml	100 ml
4.	Purified water (q.s.)	100 ml	200 ml

The quantity of emulsifying agent (acacia BP) required to produce 200 ml of the emulsion must be calculated.

Formula for Primary Emulsion: Liquid paraffin BP is a mineral oil. Therefore, the primary emulsion ratio is as follows:

Oil	:	Water	:	Gum
3	:	2	:	1

30 ml of liquid paraffin BP is required. 3 parts = 30 ml. 1 part will therefore be 30 ÷ 3 = 10.
Therefore, the amount of freshly boiled and cooled purified water needed = 2 × 10 = 20 ml.
The amount of acacia BP required = 10 g.
Therefore, the product formula for 200 ml of liquid paraffin BP 30% emulsion is as follows:
Liquid paraffin BP 30 ml
Acacia BP 10 g
Double strength chloroform water BP 100 ml
Purified water (q.s.) 200 ml

3. Fill out the proportions of primary emulsion formulae in the following table:

Type of oil	*Oil*	*Water*	*Gum*
Fixed oil			
Mineral oil			
Volatile oil			
Oleo resins			

Semisolid Dosage Forms

7

INTRODUCTION

Learning Objectives

- Introduction to semisolids
- Mechanism of drug absorption
- Permeation enhancers and kinetics of drug absorption

Semisolid dosage forms are mainly meant for external application on the skin or mucous membrane. They are traditionally used for treating topical ailments. They are also used for treating ophthalmic, nasal, buccal, rectal and vaginal ailments. Semisolid dosage forms may be used for therapeutic, cosmetic or protective properties. Examples are ointments, pastes, creams, gels and jellies. Suppositories are also included in this category, although they come under solid unit dosage forms.

MECHANISM OF PERCUTANEOUS DRUG ABSORPTION

On topical application of a semisolid drug, the drug diffuses passively out of its vehicle and partitions into either the stratum corneum or the sebum-filled ducts of the pilosebaceous glands. Inward diffusive movements continue from these locations to the viable epidermal and dermal points of entry. Thus, a concentration gradient develops across the skin up to the outer reaches of the skin's microcirculation, where the drug is swept away by the capillary flow and rapidly distributed throughout the body.

The following are the two principle absorption routes:

1. Transepidermal route involving diffusion of drug directly across the stratum corneum
2. Transfollicular route involving diffusion through the follicular pore

1. **Transepidermal route:** It is generally believed that the transepidermal pathway is responsible for diffusion across the skin. It involves direct partitioning into the stratum corneum. Majority

of the drugs diffuse across the stratum corneum through the intercellular lipoidal route. There appears to be another microscopic path through the stratum corneum for extremely polar compounds and ions. During permeation through stratum corneum, the drug enters the epidermis. As the epidermis has no direct blood supply, the drug is forced to diffuse across to reach the underlying vasculature. The epidermal cell membranes are tightly joined, and there is little to no intercellular space for ions and polar nonelectrolyte molecules to diffuse through the membrane.

2. **Transfollicular route:** The skin appendages such as sebaceous glands and eccrine glands distributed over the entire body offer secondary avenues for drug permeation and are regarded as shunt pathways. The orifice of eccrine glands are tiny and up to a miniscule fraction of the body's surface. They are either evacuated or so profusely active that the molecule cannot diffuse inwardly against the gland's output. Hence, they are not considered as a significant route of percutaneous absorption. Follicular route still remains an important route for percutaneous absorption, since the opening of the follicular pore is relatively large and sebum assists in diffusion of penetrants.

KINETICS OF DRUG PERMEATION

Skin can act as a barrier and prevent deep penetration of drug molecules. Percutaneous absorption of most drugs is a passive diffusion process that can be described by Fick's first law of diffusion. In the initial diffusion stage, drug molecules may penetrate the skin along the hair follicles or sweat ducts and then be absorbed through the hair follicular epithelium and sebaceous glands. When a steady state has been reached, diffusion through stratum corneum becomes the dominant pathway.

The membrane-limited flux under steady condition is described by the expression

$$J = \frac{DA\,K_{o/w}C}{h}$$

where

J = Amount of drug passing through the membrane per unit area, unit time
D = Diffusion coefficient of the skin
A = Area of the membrane
$K_{o/w}$ = Membrane or vehicle partition coefficient
C = Drug concentration in the vehicle or delivery system
h = Thickness of the membrane

Permeation Enhancers or Penetration Promoters

The permeation of the drug involves the following steps:

1. Sorption by stratum corneum
2. Penetration of drug through viable epidermis
3. Uptake of the drug by the capillary network in the dermal papillary layer

The rate of permeation across the skin (dQ/dt) is given by the expression

$$dQ/dt = Ps(Cd - Cr)$$

where

Cd = Concentration of the skin penetrant in the donor compartment (on the surface of the stratum corneum)
Cr = Concentration of the skin penetrants in the receptor compartment (body)
Ps = Overall permeability coefficient of the skin tissues to the penetrants

The permeability coefficient is given by the relationship

$$Ps = KsDss/Hs$$

where

Ks = Partition coefficient for the interfacial partitioning of the penetrant molecule from a solution medium on to the stratum corneum
Dss = Apparent diffusivity for the steady state diffusion of the penetrant molecule through a thickness of the skin tissues
Hs = Overall thickness of skin tissues

As *Ps*, *Ks*, *Dss*, and *Hs* are constant under given conditions, the permeability coefficient (*Ps*) for skin penetrants can be considered to be a constant.

With the introduction of various penetration enhancers, drug delivery through the transdermal route has been enhanced severalfold by altering the structure of the skin (by modifying the diffusion coefficient) or by increasing the solubility of the drug in the skin. Table 7.1 provides a list of permeation enhancers and the drugs using those enhancers.

Table 7.1 Permeation Enhancers Used with Drugs

Sl. No.	*Permeation Enhancer*	*Drug Used*
1.	Menthol, carvacrol, linalool	Propranolol hydrochloride
2.	Limonene	Indomethacin, ketoprofen
3.	Geraniol, nerolidol	Diclofenac sodium
4.	Oleic acid	Piroxicam
5.	Lecithin	Hydrocortisone acetate, heparin
6.	Propylene-glycol-dipelargonate	Heparin
7.	Cyclodextrins	Hydrocortisone

The mechanism of permeation enhancers involves the following steps:

1. Reversibly disordering the lamellar packing of stratum corneum
2. Increasing the thermodynamic activity of the drug
3. Increasing the amount of drug in solubilized form at the skin surface

Along with penetration enhancers, inclusion of cosolvents that deliver a drug in solubilized form has resulted in higher drug permeability. Table 7.2 provides a list of drugs that use a combination of permeation enhancers and cosolvents.

Table 7.2 Drugs Using Combination of Permeation Enhancers and Cosolvents

Sl. No.	*Permeation Enhancer*	*Cosolvent*	*Drug Used*
1.	Isopropyl myristate	Propylene glycol	Diclofenac sodium
2.	Cineole	Ethanol	TRH analogue *p*-Glu-3-methyl-His-Pro amide
3.	Ethanol	Propylene glycol	Aspirin

PHYSICAL METHODS OF TOPICAL DRUG DELIVERY

Iontophoresis

This is a process or technique involving the transport of ionic or charged molecules into a tissue by the passage of direct or periodic electric current through an electrolyte solution containing the ionic molecules to be delivered using an appropriate electrode polarity.

Electroporation

This process involves the application of transient high voltage electrical pulse to cause rapid reversible dissociation of the stratum corneum through which large and small peptides, oligonucleotides and other drugs can pass in significant amounts. It involves temporary changes in membrane cells due to the application of large transmembrane voltage.

Sonophoresis

This involves the use of low-frequency ultrasound waves. The ultrasound application results in the permeation of low-frequency ultrasound, which in turn, increases severalfold the permeability of the skin to many drugs including high molecular weight protein.

Phonophoresis

The movement of drugs through living intact skin and into the soft tissues under the ultrasound perturbation is called phonophoresis. The technique involves placing an ultrasound coupling agent on the skin over the area to be treated and massaging the area with an ultrasound source.

Vesicular Concept

In this process, drug-enclosed vehicle made from phospholipids and nonionic surfactants is used for transport of drug into and across the skin.

Microfabricated Microneedles Technology

This technology employs silicon-based micron-sized needles. These microneedles after insertion into the skin create a pathway for the transfer of drug through the stratum corneum.

OINTMENTS

Learning Objectives

- Definition of ointment and its classification with examples
- Ointment bases and their classification with merits and demerits
- Different methods of manufacture of ointments

Ointments (unguents) are soft semisolid preparations meant for external application to the skin or mucous membrane. They usually contain medicament that is dissolved, suspended or emulsified in an ointment base. They may contain suitable antimicrobial preservatives. Ointments have emollient and protective action on the skin. They are also used to deliver drugs into eye, nose, vagina, and rectum. Ointments intended for ophthalmic purposes are required to be sterile.

Characteristics of an Ideal Ointment

1. It should have high physicochemical stability.
2. It should be smooth and not gritty.
3. It should melt or soften at body temperature.
4. It should be easy to apply.
5. Base(s) should be nonirritant and should have no therapeutic action.
6. It should be thixotropic in nature.

Advantages of Ointments

1. Handling is comparatively easier than bulky liquid dosage forms.
2. Chemical stability is more than liquid dosage forms.
3. They promote direct application to the affected body part and avoids unnecessary exposure of other parts to the medication.
4. They are suitable for patients sensitive to parenteral and oral routes.
5. They prolong the contact time between the medicament and affected region.
6. Drugs with extensive first-pass metabolism by oral route can be formulated as topical dosage forms.

Disadvantages of Ointments

1. They are bulkier compared to solid dosage forms.
2. They have less stability than solid dosage forms.

Classification of Ointments

Ointments are classified on the basis of several factors:

1. According to their therapeutic properties with penetration of skin
2. According to their therapeutic uses

Based on Therapeutic Properties with Penetration

1. Epidermic ointments
2. Endodermic ointments
3. Diadermic ointments

1. **Epidermic Ointments:** These ointments are intended to produce localized effect on the skin surface. They are not absorbed completely. They are used as protectives, antiseptics, and parasiticides.
2. **Endodermic Ointments:** These ointments are intended to release the medicaments that penetrate into the layers of the skin to produce local action. They act as emollients, stimulants, local irritants and are anti-inflammatory in nature.
3. **Diadermic Ointments:** These ointments when applied to the skin penetrate deeply through the layers of the skin and mix with the blood circulation to produce systemic effect. The ointments used in the treatment of hemorrhoids are diadermic ointments.

Based on Therapeutic Uses

1. Acne treatment—resorcinol, sulfur
2. Antibiotic—bacitracin, neomycin
3. Anti-eczematous—hydrocortisone, ichthamol, salicylic acid
4. Antifungal—benzoic acid, nystatin, clotrimazole
5. Anti-inflammatory—betamethasone valerate, hydrocortisone
6. Antipruritic—benzocaine, coal tar
7. Antiseptic—ammoniated mercury, zinc oxide
8. Astringent—calamine, zinc oxide, tannic acid
9. Counterirritant—capsicium oleoresin, methyl salicylate
10. Dandruff treatment—salicylic acid, cetrimide
11. Emollient—soft paraffin
12. Keratolytic—resorcinol, salicylic acid, sulfur
13. Keratoplastic—coal tar
14. Parasiticide—benzyl benzoate, gamma-benzene hexachloride (GBH), sulfur
15. Protective—silicones, titanium dioxide, calamine, zinc oxide, petrolatum

Ointment Base

The ointment base is an integral part of an ointment preparation and serves as a carrier or vehicle for the medicament.

Ideal Properties of a Base

1. Physically, chemically, and pharmacologically inert
2. Nonirritating and nonsensitizing
3. Compatible with skin pH and drug
4. Good solvent and/or emulsifying property
5. Emollient, protective, nongreasy, easily spreadable and removable
6. Able to release medicament readily at the site of action

7. Pharmaceutically elegant and should possess good stability
8. Easily available and economical

Classification of Ointment Bases

Ointment bases are classified into the following categories:

1. Oleaginous (hydrocarbon) bases
2. Absorption bases
3. Water-miscible bases
4. Water-soluble bases

Oleaginous (Hydrocarbon) bases: These bases consist of oils and fats and, hence, are hydrophobic in nature, with the least water absorption capacity. Oleaginous bases provide emollient and protective properties by restricting the loss of moisture from the skin and remaining on the skin for prolonged periods. They are occlusive in nature. Removal of hydrocarbon bases from the skin is difficult. They undergo no action with the skin and are economical. The following are the different types of oleaginous bases:

1. **Petrolatum (Soft paraffin):** It is a purified mixture of semisolid hydrocarbons obtained from petroleum or heavy lubricating oil. It is available in the form of white soft paraffin and yellow soft paraffin.
2. **Hard paraffin (Paraffin):** It is a chemical mixture of solid hydrocarbons obtained from petroleum. It is a colorless or white, odorless, translucent and waxlike substance, which solidifies between 50°C and 57°C. It can be used to stiffen ointment bases.
3. **Liquid paraffin (Liquid petrolatum or white mineral oil):** It comprises liquid hydrocarbons obtained from petroleum. It is a transparent, colorless, odorless and viscous liquid. Practically, it is used along with hard paraffin and soft paraffin to get desired consistency of ointment for easy extrudability from the collapsible tubes and spreadability on the affected part.

The advantages of hydrocarbons bases are as follows:

1. They maintain the skin soft by remaining on the surface as an occlusive layer and preventing the loss of moisture.
2. They ensure prolonged contact between skin and medicament due to their stickiness.
3. They are almost physicochemically inert, with little tendency of rancidity.
4. They can withstand heat sterilization. Hence, they can be employed in the formulation of sterile ophthalmic ointments.
5. They are easily available and very cheap.

The following are the disadvantages of hydrocarbon bases:

1. Prolonged use may result in water logging with maceration of the skin.
2. They retain body heat, thereby producing an uncomfortable feeling of warmth.
3. They are immiscible with water. Both application and removal after treatment are difficult.
4. They are sticky, making the application unpleasant, and might cause staining of clothes.
5. They are poor in absorbing exudate from moist lesions as their water absorption capacity is very low.

Absorption (Emulsifiable) ointment bases: The term "absorption base" signifies the water-absorbing or emulsifying property of these bases and does not describe their action on the skin. They contain relatively less emollient properties than hydrocarbon bases. They are hydrophilic in nature and have a tendency to absorb large quantities of water and aqueous solutions. Such preparations normally do not contain water as a component of their basic formula, but if water is incorporated, it results in a water-in-oil (w/o) emulsion.

1. **Wool fat (Anhydrous lanolin):** This is obtained from the wool of sheep as a purified anhydrous fat. It is practically insoluble in water but can absorb water up to 50% of its own weight. It is used along with other bases in the preparation of a number of ointments. For example, simple ointment I.P. contains 5% and eye ointment base B.P. contains 10% of wool fat.
2. **Hydrous wool fat (Lanolin):** This is a mixture of 70% w/w of wool fat and 30% w/w of purified water. It is a w/o type of emulsion. Hence, aqueous liquids can be emulsified with it. Examples are hydrous wool fat ointment B.P.C. and calamine coal tar ointment.
3. **Wool alcohol:** This is an emulsifying fraction of wool fat. Wool alcohol is obtained by treating wool fat with alkali, with the separation of the fraction containing cholesterol and other alcohols. Normally, it contains not less than 30% of cholesterol. It is pharmaceutically employed as an emulsifying agent and to improve texture, stability and emollient properties in the preparation of w/o emulsions and absorb water in ointment bases. For example, wool alcohol ointment B.P. contains 6% wool alcohol.
4. **Beeswax:** This is obtained from the honey comb of bees as a purified wax, which is available as yellow beeswax and white beeswax. It is used in ointment preparations as a stiffening agent. For example, paraffin ointment B.P.C. contains beeswax.
5. **Cholesterol:** Animals are the main source for cholesterol as it is extensively distributed in them. Wool fat is also used as an alternative source of cholesterol. It is mainly used to increase the water-absorbing capacity of an ointment base. For example, hydrophilic petroleum U.S.P. contains 3% cholesterol, 3% stearyl alcohol, 8% white beeswax and 86% white soft paraffin.

The following are the advantages of absorption bases:

1. The base is easily spreadable and less occlusive in nature
2. They assist in permeation of oil-soluble medicaments into the skin.
3. They possess good emollient property.
4. They are compatible with most of the medicaments.
5. They are relatively thermostable or heat stable.
6. They may be used in their anhydrous form or in an emulsified form.
7. They absorb a large quantity of water or aqueous substances.

Water-miscible bases: These bases are miscible with large amounts of water. Ointments made from such bases are easily removable after use. The three anhydrous water-miscible ointment bases are as follows:

1. Emulsifying ointment B.P. (contains anionic emulsifier).
2. Cetrimide emulsifying ointment B.P. (contains cationic emulsifier)
3. Cetomacrogol emulsifying ointment B.P. (contains nonionic emulsifier)

An example of an ointment containing water-miscible base is compound benzoic acid ointment (Whitfield's ointment), which is an antifungal ointment.

The following are the advantages of water-miscible bases:

1. Ready miscibility with the exudates from lesions
2. Reduced interference with normal skin function
3. Good adherence to the skin because of their surfactant content
4. Easy removal from the skin and hair
5. High cosmetic acceptability

Water-soluble bases: These bases primarily consist of water-soluble ingredients such as polyethylene glycol (PEG), which are popularly known as "carbowaxes" and commercially known as "macrogols." Solids can be easily incorporated into these bases without much difficulty. Their water solubility promotes complete removal from the skin. Water-soluble bases are a range of compounds with the general formula $CH_2OH(CH_2OCH_2)_nCH_2OH$. The PEGs are mixtures of polycondensation products of ethylene oxide and water and are exemplified by numbers representing their average molecular weights. They vary in consistency from viscous liquids to waxy solids. For example, macrogols 200, 300, and 400 are viscous liquids, macrogols 1500 are greasy semisolids and macrogols 3000, 4000, and 6000 are waxy solids. Different grades of PEGs are mixed to get an ointment of desired consistency.

The advantages of PEGs as ointment bases are as follows:

1. They are readily water soluble and, hence, are freely miscible with tissue exudates; they can be easily removed from the skin.
2. They promote good percutaneous absorption.
3. They possess good solvent properties. Some water-soluble dermatological drugs such as salicylic acid, sulfonamides and sulfur are easily soluble in this base.
4. They are nongreasy with good aging property.
5. They neither hydrolyze nor undergo rancidity and hardly support microbial growth.
6. They are compatible with many dermatological medicaments.
7. They can be sterilized by heat and, hence, are preferred for ophthalmic ointments.

The following are their disadvantages:

1. Packaging in plastic containers is difficult due to its remarkable solvent property.
2. There is a reduction in the potency of activity of certain antibacterial agents, such as phenols, hydroxybenzoates and quaternary compounds, when used in PEGs bases.

Methods of Manufacture of Ointments

The following are the various methods of manufacturing ointments:

1. Fusion method
2. Trituration method
3. Chemical reaction method
4. Emulsification method

Fusion Method

This method is applicable to melt multiple ingredients, especially when an ointment base contains a number of solid ingredients such as white beeswax, cetyl alcohol, stearyl alcohol, stearic acid, and hard paraffin. The components of the formula are melted in the decreasing order of their melting point in the grated form. That is, the substance with the highest melting point should be melted first followed by the substance with the next-highest melting point and so on. The medicament is added slowly into the melted base with intense stirring until the mass cools down and a homogeneous product is formed at the room temperature.

Example:

Simple ointment I.P.

Wool fat	50 g
Hard paraffin	50 g
Cetostearyl alcohol	50 g
White soft paraffin	850 g

Type of preparation: Absorption ointment base

Hard paraffin and cetostearyl alcohol in grated form are introduced into the preheated china dish placed over a water bath. Wool fat and white soft paraffin are mixed and stirred until all the ingredients are melted completely. If necessary, they are decanted or strained and stirred until cold and packed in a suitable container.

Trituration Method

This method is applicable for the preparation of most of the medicated ointments containing insoluble drug substances. Finely powdered solids are passed through sieve #85. The medicament is taken on an ointment slab and triturated lightly with a small amount of the base. A steel spatula with long, broad blade is used for this purpose. To this, additional quantities of the base are incorporated and triturated until the medicament is fully mixed with the base. Finally, liquid ingredients are incorporated to this semisolid mass.

Example:

Whitfield's ointment (Compound benzoic acid ointment B.P.C.)

Benzoic acid	6 g
Salicylic acid	3 g
Emulsifying ointment	91 g

Benzoic acid and salicylic acid are sieved through #85 sieve. They are mixed on the tile with small amount of base and levigated until smooth and diluted gradually.

Chemical Reaction Method

Several famous ointments of the past were prepared by chemical reactions. An example is the strong iodine ointment B. Vet. C. (British Veterinary Pharmacopoeia), which is used to treat ringworm in cattle. It contains free iodine. Earlier, these types of ointments were used as counterirritants in the treatment of human rheumatic diseases. A limitation is that these ointments stain the skin with a deep red color. The water dries up due to improper storage and the iodine crystals irritate the skin. Hence, instead of water, glycerol is sometimes added to dissolve the iodine–potassium iodide complex.

Example:

Strong iodine ointment B. Vet. C.

Iodine

Wool fat

Yellow soft paraffin

Potassium iodide

Water

Dissolve iodine in aqueous potassium iodide solution. Melt the wool fat and yellow soft paraffin together and maintain the temperature to about 40°C. Slowly add iodine solution with stirring and continue until room temperature attained. The product is stored in a wide-mouthed amber-colored glass jar. It is used to treat ringworm in cattle.

Alternative method of preparation: Iodine is effectively reacted with unsaturated jelly acids of the fixed oils. The free iodine gets complexed with the double bonds of the unsaturated constituents.

$$\underset{\text{Oleic acid (unsaturated fatty acid)}}{CH_3 \cdot (CH_2)_7 \cdot CH = CH \cdot (CH_2)_7 \cdot COOH} + I_2 \longrightarrow \underset{\text{Diiodostearic acid (saturated fatty acid)}}{CH_3 \cdot (CH_2)_7 \cdot CHI\ CHI \cdot (CH_2)_7 \cdot COOH}$$

Example:

Nonstaining iodine ointment B.P.C. 1968

Iodine

Arachis oil

Yellow soft paraffin

Iodine is finely powdered in a glass mortar and the required amount is added to a glass-stoppered conical flask containing arachis oil and stirred well. The mixture is cautiously heated at 50°C in a water bath in a closed condition, preventing the sublimation of iodine. Heating is continued until the initial brown color is changed to greenish-black, which concludes the chemical reaction process. From this preparation, 0.1 g of the substance is weighed and the amount of iodine is determined by B.P.C. method. The amount of soft paraffin base is calculated suitably to give the product the required strength. Soft paraffin is warmed to 40°C. The iodized oil is added and mixed well. The final preparation is packed in a warm, wide-mouthed, and amber-colored glass bottle. It should be allowed to cool without further stirring.

Emulsification

An emulsion system contains an oily phase, an aqueous phase, and an emulsifying agent, complying with the basic requirements for the formation of a stable emulsion. For oil-in-water (o/w) emulsion systems, the following emulsifying agents are used:

1. Water-soluble soap
2. Cetyl alcohol
3. Glyceryl monostearate
4. Combination of emulsifiers, for example: triethanolamine stearate and cetyl alcohol
5. Nonionic emulsifiers, for example: glyceryl monostearate, glyceryl monooelate, propylene glycol stearate

For w/o emulsion system, the following emulsifiers are used:

1. Polyvalent ions, for example: magnesium, calcium, and aluminum
2. Combination of emulsifiers, for example: beeswax and divalent calcium ion

Evaluation Tests for Ointments

The formulated ointments should be subjected to the following evaluation tests before being considered for the batch process.

1. **Penetration test:** This test is carried out by the following methods:
   (a) A weighed quantity of ointment under test is rubbed on a particular area of skin. After a particulate time period, the ointment is scrapped and weighed. The difference between the initial and final weights will give the rate of penetration of ointment. However, this is a crude method and the results obtained may not be reproducible.
   (b) It can be tested by using a semipermeable cellulose membrane as diffusion membrane.
   (c) The Keshery–Chien cell or Franz diffusion cell method is a widely used *in vitro* instrument for the study of drug penetration. The diffusion membrane used can be a synthetic semipermeable membrane, animal skin membrane or cadaver skin. The study simulates the physiological conditions of human and the results obtained are reproducible.
   (d) The cup plate method is also used. If the ointment contains any antimicrobial substance, then 2% w/v agar culture media with susceptible microorganism is taken in a petri dish. Bores are made and a preweighed sample of the ointment is introduced aseptically and incubated at 37°C. At frequent intervals of time, the petri dish is taken out and the zone of inhibition is measured, using which the rate of penetration can be calculated.
2. **Absorption of a drug:** This test is performed for diadermic ointments (systemic circulation). A weighed quantity of ointment is applied to the skin (or mucous membrane). At frequent intervals of times, either the blood or the urine samples are collected and analyzed for drug content, from which the rate of absorption of drug is estimated.
3. **Test for sensitivity or irritability:** A known amount of ointment is applied to the skin of a rabbit or human and checked for any lesions, patches, redness or any other allergic manifestations for a period of 2–3 weeks. The ointment passes the test if it does not produce any allergy or sensitivity.

Quality Control Tests for Ointments

1. **Leak test:** Randomly 10 sealed ointment tubes are selected and cleaned with an absorbent cloth. The samples are placed in a horizontal position on a sheet of absorbent blotting paper. This is placed in an oven and maintained at a temperature 60°C for eight hours. All the ointment tubes should pass the test without any leakage.
2. **Spreadability test to check for particles:** Randomly 10 ointment tubes are selected and each ointment tubes is extruded into a flat-bottomed petri dish, melted and allowed to solidify, which is then scanned under a low power microscope. The requirements are met if the total number of particles in all the petri dishes does not exceed fifty and not more than one petri dish contains more than eight particles.
3. **Drug content:** From the weighed quantity of the test ointment, the drug is extracted by suitable method and assayed by suitable analytical techniques to determine the percentage of medicament present in the sample ointment. This is compared with the amount claimed in the label claim.
4. **Viscosity test:** Depending upon the internal standards of the formulator, the viscosity of the formulation is set. The viscosity of the preparation is determined by using "Brookfield viscometer."
5. **Microbial limit test:** This test is conducted for both raw materials and finished products. The formulation should be free from viable microorganisms. The total aerobic count must not be more than 5000 microorganisms per gram of the ointment. It should not contain more than 100 moulds per gram of ointment. It should also not contain more than 100 yeast per gram and 90 coliforms per gram of ointment.

PASTES

Learning Objectives

- Introduction to pastes
- Differences between ointments and pastes

Pastes can be defined as the semisolid dosage forms mainly meant only for external application to the skin. They are usually stiffer in nature but are less greasy than ointments. They do not melt at ordinary temperature and hence acts as a protective layer over the skin surface.

Bases Used for Paste Preparation

Hydrocarbon or oleoginous bases, water-miscible bases and water-soluble bases are used for the preparation of pastes.

Method of Preparation

Pastes are prepared either by trituration or by fusion method.

Differences between Ointments and Pastes

Table 7.3 provides the differences between ointments and pastes.

Table 7.3 Differences between Ointments and Pastes

Ointment	*Paste*
1. It contains less concentration of solids.	It is more concentrated than ointments.
2. It is less viscous in nature.	It is more viscous in nature.
3. It is less stiff in nature.	It is more stiff in nature.
4. It is more greasy in nature.	It is less greasy in nature.
5. It can be applied to both skin and mucous membrane.	It can be applied only to the skin surface.
6. Oleoginous, water-soluble, water-miscible, and absorption bases can be used for preparation.	Except absorption bases, all other bases can be used.
7. It can be prepared by fusion, trituration, spatulation, and chemical reaction methods.	It can be prepared by fusion and trituration methods.

JELLIES

Learning Objectives

- Introduction to jellies and their classification, with examples
- Types of gelling agents

Jellies are transparent or translucent, nongreasy semisolid preparations generally applied externally to the skin or mucous membrane. They resemble mucilages but are with higher jellylike consistency. They are mainly applied for medication, lubrication and some miscellaneous uses.

Types of Jellies

Medicated Jellies

The water-soluble drugs such as local anesthetics, spermicides and antiseptics are suitable for incorporation in the jellies as these preparations contain large amounts of water. They are easy to apply and produce a pleasant cooling effect on evaporation of the water content. Usually, the medicinal film firmly adheres to the skin and gives protection, but it is readily removed by washing after the treatment is complete. Examples are ephedrine sulfate jelly, which is used to arrest bleeding from nose; pramoxine HCl, a local anesthetic that relieves discomfort of pruritis and hemorrhoids and phenylmercuric nitrate, which is used as a spermicidal contraceptive.

Lubricant Jellies

These find application in proper and easy handling of surgical aids such as catheters, items of electrodiagnostic equipment such as cystoscopies and rubber gloves or finger stalls used for rectal and other examinations. The lubricants must be sterile if used in the inner regions of the body.

Miscellaneous Jellies

The following are more specialized uses of jellies:

1. **Patch testing:** In this case, jelly is the vehicle for the allergens applied to the skin to detect sensitivity. Several allergens may be applied on one person at a time for diagnostic purposes.
2. **Electrocardiography:** In order to reduce the electrical resistance between the patient's skin and the electrodes of the cardiograph, a jelly containing sodium chloride and pumice powder is applied. Sodium chloride provides good conductivity. Pumice powder, when applied to the skin, removes a part of the horny layer of epidermis, which is the main barrier of electrical resistance.

Formulation

Pharmaceutical jellies are usually prepared by adding a thickening agent such as tragacanth or carboxy methylcellulose (CMC) to an aqueous solution in which the drug has been dissolved. The mass is then triturated in a mortar until a uniform product is obtained.

The following gelling agents are used for the preparation of jellies.

1. **Tragacanth:** Bassorin is the main hydrophilic component of tragacanth, which gels in water; hence, tragacanth jellies are sometimes called bassorin paste. The amount of gum required for the preparation varies with its use. For example, for lubricating jelly, 2–3% and for dermatological vehicles about 5% is used.
2. **Sodium alginate:** It is available in several grades as compared to tragacanth. Traces of calcium chloride are added to increase the viscosity of the final formulation. It is used as a lubricant jelly in the concentration of 1.5–2% and as a dermatological vehicle with 5–10% concentration.
3. **Pectin:** Pectin is a very good gelling agent and is an important component of many types of jellies including edible jellies. Glycerin is used as a dispersing agent and humectant in dermatological jellies. It must be packed in well-closed containers because it loses water rapidly by evaporation.
4. **Starch:** Starch alone is not used, but it is commonly used in combination with gelatin and glycerin for preparations of jellies. Glycerin in the concentration of 50% may act as a preservative and the medicaments are incorporated in the cold jelly by trituration.
5. **Gelatin:** It is insoluble in cold water but swells and softens in it. It is soluble in hot water. Hot solution containing 2% w/v gelatin forms a jelly on cooling. Very stiff (15%) jellies are melted before use and, after cooling to desired temperature, are applied with a brush on the affected area. The area is covered with bandage and the dressing may be left in place for several weeks. An example is the zinc–gelatin jelly (Unna's paste).
6. **Cellulose derivative:** Methyl cellulose and sodium carboxymethyl cellulose produce neutral jellies of stable viscosity. They produce a strong film after drying on the skin, with good resistance against microbial growth. They can be used to prepare lubricating jellies and sterile jellies as they can withstand autoclaving temperature. An example is lignocaine jelly.
7. **Clays:** The preparations containing 7–20% of bentonite can be used as dermatological bases. The main disadvantages are that they form opalescent jellies and lack attractiveness. Their pH is about 9.0, and hence they are not suitable for application on the skin. The residue formed after application on the skin is powdery and rather silky.

Stability of Jellies

The jellies must be formulated with suitable preservatives such as methyl paraben 0.1–0.2% if intended for long-time use, as the jelling agents used are most likely from natural sources. They must be suitably preserved since all jellies contain large amount of water. Loss of water can quickly lead to scaly form of jellies. Glycerol, propylene glycol, or sorbitol solution may be added. Bases and medicaments that are sensitive to heavy metals are sometimes protected by a chelating agent such as ethylenediaminetetraacetic acid (EDTA).

SUPPOSITORIES

Learning Objectives

- Introduction to suppositories and their classification with examples
- Classification of suppository bases with the merits and demerits

Suppositories are unit solid preparations, which may contain one or more active medicaments intended for insertion into the body cavities other than mouth. They are normally used for local action or systemic absorption of the active ingredient. They usually melt, soften, or dissolve at body temperature. They may be inserted into rectum, vagina, urethra, nose or ear cavity.

Advantages of Suppositories

1. Suppositories are extensively used as a mechanical aid for bowel evacuation, which produces its action by either irritating the mucous membrane of the rectum (e.g., glycerol and bisacodyl) or by mechanical lubrication.
2. Suppositories may be used for local action. Examples are zinc oxide for soothing effect, cinchocaine and benzocaine as local anesthetic, bismuth subgallate, hamamelis extract, and tannic acid as astringents and hydrocortisone and its acetate for anti-inflammatory activity.
3. Suppositories are a reliable and alternative mode of administration of drugs that irritate the gastrointestinal tract, cause vomiting, are destroyed by the hepatic circulation or are destroyed in the stomach by pH changes, enzymes.

Types of Suppositories

1. **Rectal suppositories:** These are the preparations meant for introduction into the rectum for their local or systemic effect. They are tapered at one or both ends and usually weigh about 2 g. The rectal suppositories meant for children are smaller in size with a weight of 1 g.
2. **Vaginal suppositories (Pessaries):** They are semisolid bodies meant for introduction into vagina. They are larger than rectal suppositories and vary in weight from 3 g to 6 g or more. They may be conical, rod shaped or wedge shaped and are exclusively used for their local action.
3. **Urethral suppositories (Urethral bougies):** They are meant for introduction into the urethra. They weigh between 2 g and 4 g with length 2–5 inch. They are very rarely used and should be sterile.

4. **Nasal suppositories (Nasal bougies):** They are meant for introduction into nasal cavity. They are similar in shape to urethral bougies and are prepared with glycero-gelatin base.
5. **Ear cones (Aurinaria):** They are miniature bodies meant for introduction into the ear. Theobroma oil is used as a base; these are prepared in a urethral bougies mold and cut according to the required size.

Properties of an Ideal Suppository Base

1. Melt at body temperature or dissolve or disperse in body fluids
2. Release the medicament readily
3. Retain its shape during handling, transportation and storage
4. Nontoxic and nonirritant to the mucous membrane
5. Compatible with any added medicament or additives
6. Stable if heated above its melting point
7. Easily available and economical
8. Easily moldable and should not adhere to the mold
9. Pharmacologically inert

Types of Suppository Bases

The following are the different types of suppository bases:

1. Fatty or oleaginous bases
2. Water-soluble or water-miscible bases
3. Emulsifying bases

Fatty (Oleaginous) Bases

Theobroma oil (Cocoa butter): It is obtained from whole and roasted seeds of cocoa bean. It occurs as a yellowish-white solid with chocolate-like odor. It contains a mixture of glyceryl esters of stearic acid and palmitic, oleic, and other unsaturated fatty acids.

The advantages of this base are as follows:

1. It is solid at normal room temperature but melts in the body as the melting point range is 30–36°C.
2. It liquefies readily on warming and sets rapidly on cooling.
3. It has got good miscibility with many ingredients.
4. It is physicochemically inert, nontoxic and nonirritant.

The following are its disadvantages:

1. It undergoes polymorphism at various preparation temperatures. If cocoa butter is melted and cooled, it solidifies in different crystalline forms depending on the melting temperature, rate of cooling and size or bulk of the mass. The four main polymorphic forms are α, β, β^1, and γ. If melted at a temperature less than 36°C and slowly cooled, it forms stable beta crystals with normal melting point. However, if over-heated, it may produce on cooling unstable gamma crystals, which melt at about 15°C, or alpha crystals, which melt at about 20°C.

2. Cocoa butter contracts enough on cooling to loosen the suppositories in the mold. Sticking may occur, particularly if the mold is inadequately lubricated. This can be overcome by sufficient lubrication of the mold before use.
3. The softening point of cocoa butter is too low for hot climates. To raise the softening point, white beeswax may be added if intended for use in tropical and subtropical countries.
4. Chloral hydrate, which dissolves in theobroma oil, lowers its melting point so that the suppositories are too soft for use. To restore or increase the melting point, a controlled quantity of white beeswax may be added.
5. Slow chemical oxidation of the unsaturated glycerides present in the theobroma oil takes place, leading to rancidification.
6. The base is hydrophobic in nature and has poor water-holding capacity. The water absorption capacity can be improved by the addition of emulsifying agents.

Synthetic fats: A number of hydrogenated oils, such as hydrogenated edible oil, arachis oil, coconut oil, palm kernel oil, and a mixture of oleic and stearic acids are recommended as a substitute of theobroma oil.

The advantages of these synthetic fats over theobroma oil are as follows:

1. They are unaffected by overheating.
2. They have good resistance to oxidation because their unsaturated fatty acids have been reduced.
3. They possess good emulsifying and water-absorbing capacities.
4. Mold lubricant is not required.
5. They produce colorless, odorless and elegant suppositories.

Their main disadvantage is that they should not be cooled in refrigerator because they become brittle if cooled quickly. Certain additives such as 0.05% polysorbate 80 can be used as the remedy.

Water-soluble and Water-miscible Bases

Glycero-gelatin base: The base consists of a mixture of glycerol and water made into a stiff jelly by adding gelatin. It is mainly used for the preparation of suppositories and pessaries. The stiffness of the mass depends upon the proportion of gelatin used, which is adjusted according to its immediate or sustained drug release use. It is hydrophilic in nature and is a tailor-made base for suppositories containing belladonna extract, boric acid, chloral hydrate, iodoform or opium.

Glycero-gelatin base suppositories are less commonly used than the fatty base suppositories because of its following disadvantages:

1. Glycerol exerts laxative action.
2. They are hygroscopic in nature and hence must be carefully stored.
3. Gelatin is incompatible with drugs those precipitate with protein such as tannic acid, ferric chloride and gallic acid.
4. They are more prone to microbial contamination as gelatin is obtained from the animal source.

Soap–glycerin suppositories: In this type of suppositories, gelatin is replaced with curd soap or sodium stearate, which makes the glycerin sufficiently hard for suppositories; moreover, a large quantity of glycerin, up to 95% of the mass, can be incorporated. Furthermore, the soap helps in the evacuation of glycerin. The striking disadvantage is that they are very hygroscopic; therefore, they must be protected from atmosphere and wrapped in waxed paper or tin foil.

Emulsifying Bases

These are synthetic bases and a number of proprietary bases of very good quality are available as desired.

Witepsol: It consists of triglycerides of saturated vegetable acids (chain length C_{12} to C_{18}) with varying proportions of partial esters.

Massa esterium: The base consists of a mixture of mono-, di-, and triglycerides of saturated fatty acids with chain lengths of C_{11} to C_{17}.

Massuppol: It consists of glyceryl esters, mainly of lauric acid, to which a small amount of glyceryl monostearate has been added to improve its water-absorbing capacity.

The following are the advantages of this base:

1. Physical characteristics do not alter on overheating.
2. It does not stick to the mold.
3. Prelubrication of the mold is not necessary
4. It solidifies rapidly.
5. It is less liable to get rancid.
6. It absorbs fairly large amount of aqueous liquids.

Preparation of Suppositories

Learning Objectives

- Importance and definition of displacement value
- Methods of manufacture of suppositories
- Evaluation tests for suppositories

Displacement Value

The volume of a suppository from a particular mold is uniform but its weight will vary because the densities of medicaments usually differ from the density of the base. Hence, it becomes necessary to calculate the displacement value of the base to be used for the particular medicament.

Definition: The number of parts of the medicament that displaces one part by weight of the base is known as the displacement value of that drug.

Calculation of Displacement Value of Medicament

Prepare and weigh 10 suppositories containing base alone = [A] g
Prepare and weigh 10 suppositories containing 40% of medicament = [B] g
Calculate the amount of base present in the medicated suppositories = [C] g
Calculate the amount of medicament present in the medicated suppositories = [D] g
Calculate the amount of base displaced by [D] g of medicament = [$A - C$] g

Displacement value of medicament $[DV] = \dfrac{[D]}{[A-C]}$

Lubrication of the Mold

If the mold cavities are imperfect, poorly polished, or scratched, it becomes difficult to remove the suppositories without damaging their surfaces. So, lubrication of the molds is necessary. In case of greasy or oily base, water-soluble lubricants are required. For example, the following is the composition of lubricant solution for cocoa butter:

Soft soap	10 g
Glycerol	10 ml
Alcohol (90%)	50 ml

For water-soluble or water-miscible bases, oily lubricant may be used. For example, for glycerogelatin base, liquid paraffin or arachis oil may be used as the lubricant.

Methods of Manufacture of Suppositories

1. **Hand molding method:** Cocoa butter is grated into small pieces. The drug is triturated into a very fine powder in a mortar. The drug and a portion of the cocoa butter are mixed with few drops of vegetable oil. The remaining cocoa butter is added by geometric dilution and triturated with pressure. The heat generated by trituration results in a plastic mass with cohesive property. The mass is scrapped from the mortar with a spatula and rolled into a ball. An ointment tile or slab is taken and dusted lightly with starch powder; the ball is placed on it and rolled with a flat-faced spatula to form a cylindrical mass. The cylinder is cut into desired number of pieces with a sharp blade. One end of the suppository is held firmly with a finger and the other end is tapered with the spatula to give the shape of suppository.
2. **Compression molding:** In this method, compression mold instrument is used. This is especially suitable for thermolabile drugs. The drug is finely powdered and mixed intimately with the grated cocoa butter. The mixture is filled into a chilled cylinder. The mixture is pressed within the die cavity of the cylinder by a piston until a pressure is felt. Then, the formed suppositories are ejected from the other end of the cylinder.
3. **Pour molding (Fusion method):** This is the mostly widely used method of preparing suppositories. A weighed quantity of the drug is powdered in a mortar. Carefully grated cocoa butter is taken into a china dish and heated in a water bath. When two-thirds of the portion is melted, the china dish is taken out of the heat source. The rest of the mass is melted by thorough stirring with a glass rod. The drug is incorporated into the china dish and stirred thoroughly to mix with the "creamy" base. The melted medicated base is then poured into previously lubricated mold. The mold is allowed to congeal and then placed on the ice bath for 30 minutes to harden. It is taken out and the surface is trimmed off with a sharp blade dipped in hot water. The mold is opened and the suppositories are expelled out by gentle pressure with the finger.
4. **Automatic molding machine:** Large-scale batch process with high output ranging from 3500 to 6000 suppositories per hour can be carried out by using automatic molding machine. The manufacturing cycle process includes the following steps:
   (a) The prepared mass is filled into a filling hopper where it is continuously mixed and maintained at constant temperature.
   (b) The suppository molds are lightly lubricated by brushing or spraying a lubricant solution.

(c) The molten mass is filled into the molds to a slight excess.
(d) The mass is cooled to solidify and the excess material is scrapped off and collected for reuse.
(e) In the ejecting section, the mold is opened and the suppositories are gently pushed out by steel rods.
(f) The mold is closed and then moved to the initial step for the cycle process to continue.

Packaging of Molded Suppositories

The suppositories should be wrapped or they must be placed in a tightly closed partition container in such a condition that they do not touch each other. Suppositories in contact may fuse with one another or with the container at room temperature. Packing materials used are aluminum foils, paper strip or plastic strips. Suppositories containing hygroscopic or volatile material are packed in a glass or plastic containers. Bulk suppositories are not individually wrapped. They are placed in sectioned cardboard boxes or plastic containers that hold 6 or 12 suppositories.

In the method using the latest technology, the suppositories are individually molded in their wrapping material. Either plastic or aluminum foil, propylene or lacquer laminate is used. In plastic wrapping, the plastic is thermoformed into the shape of the mold. The molten mass is injected through the top end and the top portion is cooled and sealed. In aluminum foil method, two aluminum foils are embossed and sealed to give the shape of a mold; the mass is injected at the top and then the top is cooled and sealed.

The main advantage of this packaging system is that even if the suppositories melt at a higher storage temperature, their shapes are retained and they can be used by just cooling them again.

Quality Control Tests for Suppositories

Visual Inspection

The suppositories are visually inspected for its physical appearance, size, shape and texture. Individual suppositories should be examined for cracks and pits due to entrapment of air in the molten mass.

Disintegration Test

The disintegration test can be determined by using the tablet disintegration test apparatus with necessary modification in the test media. According to BP, the disintegration test determines whether the suppositories or pessaries soften or disintegrate within the prescribed time when placed in a liquid medium in the experimental conditions described here. Disintegration is considered to be achieved under the following conditions:

1. Dissolution is complete.
2. The components of the suppository or pessary have separated. Melted fatty substances collect on the surface of the liquid, insoluble powders fall to the bottom, and soluble components dissolve. Depending on the type of preparation, the components may be distributed in one or more of these ways.
3. There is softening of the sample, which may be accompanied by appreciable change of shape without complete separation of the components. The softening is such that the suppository or pessary no longer has a solid core offering resistance to the pressure of a glass rod.
4. Rupture of the gelatin shell of rectal or vaginal capsules occurs allowing release of the contents.
5. No residue remains on the perforated disk, or if a residue remains, it consists only of a soft or frothy mass, having no solid core offering resistance to the pressure of a glass rod (vaginal tablets).

Three suppositories or pessaries are used for the study. To pass the test, all the samples must have disintegrated.

Uniformity of Mass

Weigh 20 suppositories individually and calculate the average mass. When the suppositories are weighed singly, the deviation of individual mass from the average mass should not exceed the limits as indicated in Table 7.4.

Table 7.4 Deviation of Individual Mass of Suppositories from Average Mass

Deviation %	*Number of Suppositories*
±5	Minimum 18
±10	Maximum 12

Not more than two of the individual masses should deviate from the average mass by more than 5% and none deviates by more than 10%.

Procedure: The steps for determining the uniformity of mass are as follows:

1. Weigh 20 suppositories individually (w_1, w_2, w_3, …, w_{20}).
2. Weigh all the suppositories together (W).
3. Calculate the average weight (W/20).
4. **Limit:** Not more than two suppositories differ from the average weight by more than 5%, and no suppository differs from the average weight by more than 10%.

$$\text{Upper limit} = \text{Average weight} + \frac{5 \times \text{Average weight}}{100}$$

$$\text{Lower limit} = \text{Average weight} - \frac{5 \times \text{Average weight}}{100}$$

Not more than two of the suppositories differ from the average weight by more than the error percentage listed. If more than two suppositories are different from the average weight by 5%, calculate double the percentage error as follows:

$$\text{Upper limit} = \text{Average weight} + \frac{10 \times \text{Average weight}}{100}$$

$$\text{Lower limit} = \text{Average weight} - \frac{10 \times \text{Average weight}}{100}$$

Uniformity of Drug Content

In a sample of 10 units, each suppository should contain within ±15% of the average amount of active ingredient. However, if up to three individual units deviate by more than ±15% but are within ±25% of the average amount of the active ingredient, a further 20 units drawn from the same original sample as the first 10 units should be examined. The preparation under test complies only if the amount of active ingredient in not more than 3 out of 30 units deviates by more than ±15% of the average amount. None of the units should deviate by more than ±25% of the average amount.

Melting Point Determination Test

The temperature at which the partially melted substance begins to rise in the tube is regarded as the melting point.

Procedure: Insert one end of a glass capillary tube into the melted substance so that a column of substance column of 8–12 mm high is obtained in the tube. Cool the tube to 15°C and maintain the temperature at 15–17°C for not less than 16 hours. Attach the tube to a thermometer in a heating vessel containing water at 15°C or dip it in a water bath such that the lower end of the column of substance is 30 mm below the surface of water. Heat the water with constant stirring or regulate the temperature of the water bath slowly so that the temperature rises at a rate of 2°C per minute. Suppositories are melted rapidly at a temperature not more than 10°C above the point of complete fusion.

Liquefaction or Softening Time Test

This test is mainly performed for rectal suppositories. In this test, a standard glass rod is placed on a suppository held in a U-tube apparatus, which is immersed in a constant water bath maintained at 37°C. The time taken by the glass rod to penetrate from the surface of the suppository to the bottom end of the U-tube is recorded as the softening time.

Fragile or Breaking Test

This test is performed to determine the tensile strength of the suppository to withstand mechanical shocks during handling, transit and storage.

Procedure: The breaking test apparatus is used for this purpose. It consists of a double-wall chamber. Water is pumped through the walls of the chamber. The inner chamber consists of a disk, which holds the suppositories. A rod is attached to this disk. The other end of the rod consists of another disk on which weights are placed gradually and increased at one-minute intervals. The weights are added until the suppository crumbles.

All the weights used are added, which gives the tensile strength. Likewise, few more suppositories are tested and the average tensile strength is calculated. Tensile strength indicates the maximum force that the suppository can withstand during production, packing and handling. Large tensile strength indicates a lesser tendency to fracture.

Melting Range Test

It is a measure of the time taken for the entire suppository to melt when immersed in a constant-temperature (37°C) water bath. The apparatus commonly used for measuring the melting range of the entire suppository is the USP tablet disintegration apparatus.

Procedure: The suppository is completely immersed in the constant-temperature water bath, and the time for the entire suppository to melt or disperse in the surrounding water is measured.

The suppository is considered disintegrated under the following conditions:

1. It is completely dissolved.
2. It is dispersed into its component part.
3. There is a soft “change in shape” with the formation of core, which is not resistant to pressure with glass rod.

Both macromelting and micromelting ranges are determined.

1. **Macromelting range:** It is a measure of the thermal stability of the suppository. It is the time taken by the entire suppository to melt in a constant-temperature water bath. The test is conducted using the tablet disintegration apparatus. The suppository is immersed in a constant-temperature water bath and the melting range is recorded.
2. **Micromelting range:** The melting range of the fatty base is measured in capillary tubes.

Dissolution Studies

It is the amount of dosage form that gets dissolved in body fluid in unit time. It is a measure of the rate of drug release from the suppository. Two types of apparatus are available for testing the dissolution rate:

1. **Suppository dialysis cell:** Lipophilic suppositories are tested using the suppository dialysis cell, which is also known as the modified flow-through cell.
2. **Stationary basket, rotating paddle, or basket apparatus (USP dissolution test apparatus):** Hydrophilic suppositories are tested using stationary basket or rotating paddle apparatus.

CREAMS

Learning Objectives

- Introduction to creams and the types of creams
- Ideal qualities of a cream, with its merits and demerits

Creams are homogeneous, semisolid preparations consisting of opaque emulsion systems. Their consistency and rheological properties depend on the type of emulsion, either w/o or o/w, and on the nature of the solids in the internal phase. Creams are intended for application to the skin or certain mucous membranes for protective, therapeutic or prophylactic purposes, especially where an occlusive effect is not necessary. The term "cream" is most frequently used to describe soft, cosmetically acceptable types of preparations.

Definition: Pharmaceutical creams are semisolid preparations containing one or more active agents dissolved or dispersed in either a w/o emulsion or an o/w emulsion or in other types of water-washable base. Creams find primary application in topical skin products and are also used rectally and vaginally.

Advantages of Creams

1. They promote prolonged contact at the site of application than any other semisolid dosage forms.
2. They are nonsticky in nature and are easily washable.
3. Creams can dry the injured area quickly than any other semisolid preparations.
4. They have distinct three-dimensional thixotropic properties.
5. They are nonirritating on application to the skin.
6. They are not expensive.

Disadvantages of Creams

1. They are less hydrophobic than other semisolid preparation; hence, the risk of contamination is high.
2. They are less viscous than other semisolid preparations.

Criteria of a Good Quality Cream

1. It should have high affectivity.
2. It should show rapid onset of action.
3. It should be biocompatible and biomiscible.
4. It should be free from grittiness.
5. It should be smooth.
6. It should be readily washable.
7. It should be nonirritant.
8. It should be nonallergic.
9. It should be nontoxic.
10. It should be physically and chemically stable.

Classification of Creams

1. **Cleansing creams:** These are semisolid o/w emulsion preparations containing mineral oil, which imparts cleansing action.
2. **Cold creams:** These are semisolid w/o emulsion preparations; when applied to the skin surface, water gets evaporated and phase inversion occurs.
3. **Foundation creams:** The main ingredient of these creams is humectants such as lanolin and mineral oil, which help in forming an invisible film.
4. **Night and massaging creams:** These creams prevent drying of the skin by providing nourishment and proteins.
5. **Vanishing creams:** These are o/w semisolid emulsions.
6. **All-purpose creams:** These are for outdoor purposes and are more oily preparations.

Cold Cream

Cold cream is a semisolid white w/o emulsion prepared with cetyl ester wax, white bees wax, mineral oil, sodium borate, and purified water. Sodium borate combines with the free unsaturated fatty acids present in the waxes to form sodium salts of fatty acids (soaps), which act as emulsifiers. Cold cream is employed as an emollient and ointment base. For example, eucerin cream is a w/o emulsion of petrolatum, mineral oil, mineral wax, wool wax, alcohol, and bronopol. It contains urea as an active ingredient and is used to help rehydrate dry and scaly skin.

Example:

W/o emulsion base formula

White wax	12%
Cetyl ester max	12%
Mineral oil	56%
Sodium borate	0.5%
Purified water	19%

Lanolin type

White bees wax	15.5%
Cetyl ester wax	6.05%
Lanolin	4.5%
Mineral oil	42.5%
Sodium borate	1%
Perfume	0.5%
Water	30%

Vanishing Creams

Vanishing creams are also called as stearate creams. Chemically, they are o/w emulsions consisting of a stearic acid, an alkali, a polyol and water. The alkali forms a soap with stearic acid, forming an *in situ* emulgent during the preparation, thereby producing a stable emulsion. The polyol (e.g., glycerin) makes the cream more spreadable and acts as a humectant to prevent the cream from drying out and cracking during storage in its container. Packaging the cream in an airtight screw-top jar or collapsible tube is also important in maintaining its water content. The product is noted for its smooth, dry feel on the skin and its pearly appearance.

Earlier, carbonates or bicarbonates were used as the alkali. These release carbon dioxide during the production process, resulting in a foamy consistency. Some of the carbon dioxide will quickly escape, but small bubbles will remain and rise to the top of the mixture causing the cream to sink. Using hydroxides as the alkali avoided this problem and potassium hydroxide became a favorite in many formulations.

Example:

O/w emulsion formula (vanishing creams)

Formula 1

Stearic acid	17%
Sodium carbonate	0.5%
Potassium hydroxide	0.5%
Glycerin	6%

Water	71%
Alcohol	4.5%
Perfume	0.5%

Formula 2

Stearic acid	22.5%
Triethanolamine	1.5%
Potassium hydroxide	1%
Glycerin	6%
Water	69%

Ingredients are separated based on solubility; for example oil-soluble ingredients are taken in a china dish and water-soluble ingredients are taken in a beaker separately. Both the contents are heated to 70°C and the molten oily phase is transferred into the aqueous phase by continuous stirring, which is continued until it gets solidified and comes down to room temperature. At the temperature below 40°C, perfume is added to the solid matter and spread homogenously; this is done to prevent the free escape of perfumes as they are highly volatile at higher temperature. Furthermore, the homogenization of the product can be made by transferring the contents of the product and triturating in a glass pestle and mortar. Figure 7.1 gives the process flowchart of cream manufacture.

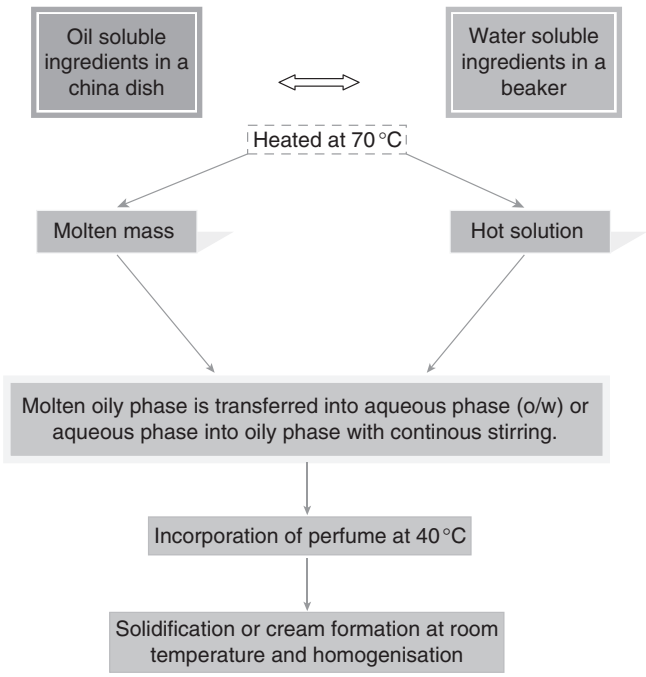


Figure 7.1 Process Flowchart of Cream Manufacture

Tables 7.5 and 7.6 detail the differences between cold and vanishing creams and ointment and cream, respectively.

Table 7.5 Differences between Cold and Vanishing Creams

Cold Cream	*Vanishing Cream*
1. It is a w/o semisolid emulsion.	It is an o/w semisolid emulsion.
2. It is meant for cleansing, massaging and moisturizing purposes.	It is used as a foundation cream before applying makeup.
3. It is more oily and greasy in nature.	It is less greasy and oily in nature.
4. It is not readily washable by water.	It is readily soluble in water.
5. There is no need for preservatives.	It requires preservatives.
6. It gives a cooling sensation.	It leaves an immiscible layer.
7. It does not show any pearliness, luster, and shine.	It shows pearliness, luster, and shine, because stearic acid crystals shine on incidence of light.
8. It is nonocclusive.	It is semiocclusive.
9. Humectants are not used.	Humectants are added.

Table 7.6 Differences between an Ointment and a Cream

Ointment	*Cream*
1. Ointment bases are highly hydrophobic and so they are sticky in nature.	Cream is not so sticky
2. It is not readily washable as it is sticky and greasy in nature.	It is readily washable.
3. It does not show prolonged contact at the site of action.	It shows prolonged contact at the site of action.
4. Injured area dries slowly by ointment.	Injured area dries quickly by creams.

Evaluation Tests for Creams

As creams are widely used for various body parts, general tests such as qualitative and quantitative tests should be done.

1. **Viscosity:** Measurement of viscosity of creams during manufacturing process determines the quality of the product. Viscosity of creams is non-Newtonian in nature; so, it should remain constant during its shelf life. It can be determined using "Brookfield viscometer."
2. **Patch test or sensitivity test:** The sensitivity test for the final formulated cream should be done after application to the different parts of skin surfaces. It should be observed for any skin rashes, itching, irritation, or redness for a period of 7–14 days.

3. **Biological testing:** This test is mainly performed for products containing hormones, vitamin preparations, and antiseptics.
4. **Cooling time and total stirring time:** These two factors are used to determine the consistency, stability and viscosity of creams.
5. **Peroxide stability test in creams:** In this test, 1 g of cream is taken in a test tube and subjected to heating at a constant temperature of 95°C for 24 h. Care should be taken to ensure that the water level in the bath meets the upper surface of the cream in the test tube. Then, the contents in the test tube are emptied into an 250 ml volumetric flask and subjected to peroxide content determination by using the formula

   Percentage stability = (Final H_2O_2 concentration/Initial H_2O_2 concentration) × 100

   The stability of the peroxide cream should be more than 95%.

GELS

Learning Objectives

- Introduction to gels and the types of gels
- Discussion on gelling agents
- Evaluation of gels

Gels are semisolid preparations usually homogeneous and clear, consisting of a liquid phase within a three-dimensional polymeric matrix that is physically or sometimes chemically cross-linked by suitable gelling agents. Gels are applied to the skin or certain mucous membranes for various purposes such as protective, therapeutic or prophylaxis.

Alternatively, it is a coherent system in which a liquid phase is entrapped within a polymeric matrix (natural or synthetic gum) of high degree physical or chemical cross-linking. Gels are transparent or translucent, nongreasy semisolid preparations. Some are as transparent as water, in an aesthetically pleasing state, whereas others are turbid as the polymer is present in colloidal aggregates that disperse light. They are mainly used for medication or lubrication.

Hydrophobic gels: Hydrophobic gel (oleogel) bases usually consist of liquid paraffin with polyethylene or fatty oils gelled with colloidal silica or aluminum or zinc soaps.

Hydrophilic gels: Hydrophilic gel (hydrogel) bases usually consist of water, glycerol, or propylene glycol gelled with suitable agents such as tragacanth, starch, cellulose derivatives, carboxyvinyl polymers, and magnesium aluminum silicates.

Properties of Gels

1. **Thixotropy:** Gels become fluid when agitated, but resolidify on resting. In general, gels are apparently solid, jellylike materials. By replacing the liquid with gas, it is possible to prepare

aerogels, possessing exceptional properties such as very low density, high specific surface area, and excellent thermal insulation properties.

2. **Syneresis:** On standing for some time, the gel often shrinks because some of the liquid is squeezed out of the system.
3. **Swelling:** This is exactly opposite to syneresis, wherein the gel takes up some liquid and increases in volume.
4. **Imbibition:** The gel takes up a certain amount of liquid with no considerable increase in volume.

Common gelling agents used are polyvinyl alcohol, sodium polyacrylate, acrylate polymers, and copolymers with an abundance of hydrophilic groups.

Types of Gels

Figure 7.2 shows the classification of gels.

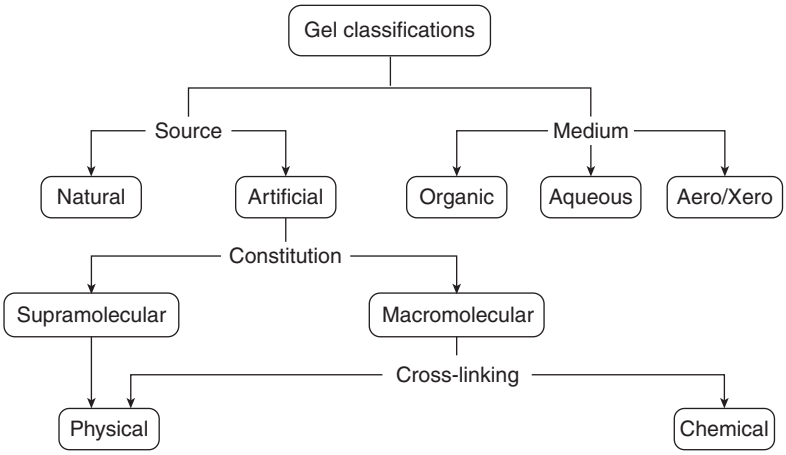


Figure 7.2 Classification of Gels

Hydrogels

It is a network of hydrophilic polymer chains, sometimes occurring as a colloidal gel in which water is the dispersion medium. The polymers may be of natural or synthetic origin.

The following are the uses of hydrogels:

1. They are used as scaffolds in tissue engineering. This form may contain human cells to repair tissues.
2. Hydrogel-coated wells have been used for cell culture.
3. Environmentally sensitive hydrogels (smart gels or intelligent gels) have the ability to sense changes in pH, temperature or concentration of metabolite and release their load as result of such a change.

4. These are used in sustained-release drug delivery systems.
5. They provide absorption, desloughing and debriding of necrotic and fibrotic tissues.
6. They can be used as biosensors as well as in drug delivery systems (DDS).
7. They are used in disposable diapers where they absorb urine and in sanitary napkins.
8. Contact lenses are designed using silicone hydrogels and polyacrylamides.
9. They are used in EEG and ECG medical electrodes.
10. They are used in water gel explosives.
11. They are used in rectal drug delivery and diagnosis.
12. They are used in breast implants.
13. They are used in glues.
14. They are used in the preparation of granules for holding soil moisture in arid areas.
15. Wound gels are used for helping to create or maintain a moist environment.
16. They are used for reservoirs in topical drug delivery

Organogels

These are noncrystalline, nonglassy, thermoreversible (thermoplastic) solid materials composed of a liquid organic phase entrapped in a three-dimensionally cross-linked network. The liquid may be an organic solvent, mineral oil or vegetable oil. These systems are based on self-assembly of the structurant molecules.

Organogels find potential applications in pharmaceuticals, cosmetics, art conservation and food. An example of formation of an undesired thermoreversible network is the occurrence of wax crystallization in petroleum.

Gel-forming Substances or Gelling Agents

Polymers are used to give the three-dimensional structural network, which is highly essential for the preparation of gels. Gel-forming polymers are classified as follows:

1. **Natural polymers**
   (a) Proteins such as collagen and gelatin
   (b) Polysaccharides such as agar, alginate acid, sodium or potassium carrageenan, tragacanth, pectin, guar gum, cassia tora, xanthan and gellum gum
2. **Semisynthetic polymers:** Cellulose derivatives such as carboxymethyl cellulose, methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose and hydroxyethyl cellulose.
3. **Synthetic polymers**
   (a) Carbomers such as Carbopol 940 and Carbopol 934
   (b) Poloxamer
   (c) Polyacrylamide
   (d) Polyvinyl alcohol
   (e) Polyethylene and its copolymers
4. **Inorganic substances**
   (a) Aluminum hydroxide
   (b) Bentonite

5. **Surfactants**
   (a) Cebrotearyl alcohol
   (b) Brij-96

Methods of Preparation of Gels

The following are the methods used for preparation of gels:

1. Fusion method
2. Cold method
3. Dispersion method

Evaluation of Gels

1. **Measurement of pH:** The pH of various gel formulations can be determined by using digital pH meter. One gram of gel is dissolved in 100 ml distilled water and stored for two hours. The measurement of pH of each formulation is done in triplicate and average values are calculated.

2. **Drug content:** In this method, 1 g of prepared gel is mixed with 100 ml of drug soluble or extractable suitable solvent. Aliquots of different concentrations are prepared by suitable dilutions after filtering the stock solution and the absorbance is measured. Drug content will be calculated using the equation obtained by linear regression analysis of calibration curve.

3. **Viscosity:** Brookfield viscometer is used for the measurement of viscosity of the prepared gel. The gel is rotated at different values of rpm. At each speed, the corresponding dial reading is noted. The viscosity of the gel is obtained by multiplication of the dial reading and the factor given in the Brookfield viscometer catalogues.

4. **Spreadability:** One of the criteria for a gel to meet the ideal quantities is that it should possess good spreadability. It is the term expressed to denote the extent of area to which gel readily spreads on application to skin or affected part. The therapeutic efficacy of a formulation also depends upon its spreading value.

   Spreadability (S) is expressed in terms of time in seconds taken by two slides to slip off from gel placed in between the slides under the direction of certain load. Lesser the time taken for separation of two slides, better the spreadability. It is calculated by using the following formula:

   $$S = ML/T$$

   where M = Weight tied to upper slide

   L = Length of glass slides

   T = Time taken to separate the slides

5. **Extrudability study:** The formulations are filled in the collapsible tubes after the gels are set in the container. The extrudability of the formulation is determined in terms of weight in grams required to extrude a 0.5 cm ribbon of gel in 10 seconds.

6. **Skin irritation test:** Guinea pigs (400–500 g) of either sex are used for testing of skin irritation. The animals are maintained on standard animal feed and have free access to water. They are kept under standard conditions. Hair is shaved from the back of guinea pigs and an area of 4 cm^2 is marked on both the sides; one side would serve as control and the other side as test. Gel is applied (500 mg/guinea pig) twice a day for seven days and the site is observed for any sensitivity; the reaction, if any, will be graded as 0, 1, 2, and 3 for no reaction, slight patchy erythema, slight but confluent or moderate but patchy erythema, and severe erythema with or without edema, respectively.
7. ***In vitro* diffusion studies:** The drug diffusion studies of the prepared gels can be carried out in Franz diffusion cell for studying the drug permeation release of gels through a cellophane membrane or a rat skin or pork skin membrane. Gel sample (0.5 g) is taken and the diffusion studies are carried out at 37 ± 1°C using phosphate buffer (pH 7.4) as the dissolution medium. At predetermined time intervals, known volume of sample is withdrawn, and each sample is replaced with equal volume of fresh dissolution medium. Then, the samples after suitable dilution are analyzed by analytical methods to determine the drug flux.
8. ***In vivo* studies:** The pharmacokinetic and pharmacodynamic studies on suitable animal models can be studied after obtaining permission from institutional animal ethical clearance committee.
9. **Stability:** The stability studies are carried out for all gel formulations by freeze–thaw cycling. In this, syneresis is observed by subjecting the product to a temperature of 4°C for one month, at 25°C for one month, and at 40°C for one month. After this, the gel is exposed to ambient room temperature and liquid exudates separation is noted.

POULTICE

Learning Objective

- Introduction to poultices, their types and applications

Poultice, which is also known as cataplasms, is a soft, viscous, and wet or moist mass to be heated and medicated. This has to be spread on cloth over the skin for the treatment of an aching, inflamed, or painful part of the body. It can be used on wounds such as cuts. It can also be a porous solid filled with solvent used to remove stains from porous stones such as marble or granite.

The word "poultice" comes from the Latin *puls* or *pultes*, meaning "porridge."

Many ready-made commercial poultices are also available. Some of these may be labeled as "drawing salves." Poultices may also be heated and placed on an area where extra circulation is desired.

Types of Poultice for Boils

1. **Bran poultice:** It is useful to reduce inflammations in boils. The poultice consists of mixing of bran with hot water and applying it on the boil head warm to the extent of tolerance.
2. **Bread and milk:** It is used to develop heads in pus-filled boils so that the pus can easily flow out from the boil leading it to dry up soon. Bread soaked with milk is smashed and then applied on the head as poultice.

3. **Cabbage poultice:** This poultice consists of a paste made by smashing raw or cooked cabbage. A thick coating of the cabbage poultice on a boil is to be covered with a warm towel. This poultice is highly effective as a detoxification agent and is to be applied for 10 minutes at a stretch.
4. **Carrot poultice:** It is highly beneficial for acne, cysts, and boils. The poultice is made up of boiled carrot. The carrot is first boiled until it becomes soft and then turned into a pulp. The pulp of the carrot is then applied on the boil head to allow the pus to flow out.
5. **Clay poultice:** It is a very effective way to get rid of inflammations that are related to the development of boils. The clay is at first cleaned by removing impurities and then is converted into a paste by adding water or cider vinegar (Kaolin Poultice B.P.C.).

RIGID FOAMS

Foams are systems in which air or some other gas is emulsified in a liquid phase to the point of stiffening.

Examples are shaving creams, whipped creams and aerosolized shaving creams.

PLASTERS

Learning Objective

- Introduction to plasters and their applications

Plasters are substances of either solid or semisolid masses, intended for external application and are made of such material and consistency as to adhere to the skin and thereby attach and retain as dressing. They promote prolonged contact of the drug with the skin. They are made by incorporating medicaments in resinous or waxy bases, which are melted and spread on suitable backing material for the following purposes:

1. To afford protection and mechanical support
2. To furnish an occlusive and macerating action
3. To enhance the drug–skin surface contact time

Plasters are available in different shapes meant for application on different regions of the body. Examples are ear plaster, breast plaster, back plaster, chest plaster and shoulder plaster.

RECENT ADVANCES IN SEMISOLIDS

Learning Objective

- Introduction to recent advancements in the topical drug delivery systems

Advances in semisolid dosage form facilitate modified release of drug as well as flexibility in route of administration.

Ointments

Rectal Ointment

It is used for the symptomatic relief against anal and perianal pruritus, pain and inflammation associated with hemorrhoids, anal fissure, fistulas and proctitis. Rectal ointment should be applied several times in a day according to the severity of the condition. For intrarectal use, the ointment has to be applied with the help of a special applicator.

Creams

Creams Containing Microspheres

Albumin microsphere containing vitamin A can be administered by using creams topically. The *in vitro* and *in vivo* drug release of a microencapsulated and nonmicroencapsulated vitamin A cream was studied. The *in vivo* study in six volunteers revealed that these microspheres were able to remain on the skin for a long period of time and as a consequence they were able to prolong the release of vitamin A.

Lamellar Face Creams

These are liquid paraffin-in-water emulsions prepared from cetrimide or fatty alcohol mixed emulsifiers and ternary systems formed by dispersing the mixed emulsifier in required quantity of water. The cationic emulsifying wax shows phenomenal swelling in water and this swelling is due to electrostatic repulsion, which can be suppressed by the addition of salt and can be reduced by changing the surfactant counter ion.

Creams Containing Lipid Nanoparticles

Occlusion of cream is an important criterion since it increases the penetration of topical drugs. This can be achieved by using oils and fats such as liquid and semisolid paraffin in large quantities. However, such formulations have the limitations of poor cosmetic properties since they have a greasy feel and nonglossy appearance.

The development of a w/o cream containing small particles of solid paraffin was studied. However, this nanodispersion revealed a rough texture when applied. The development of a w/o cream wherein the aqueous phase was divided into small droplets solved this problem. Nanoparticles are incorporated in the aqueous phase. Hence, the oil phase in which the water droplets are dispersed serves as a lubricant for nanoparticles, thereby preventing a rough feel during application.

Gels

Controlled Release Gels

Drug delivery to nasal or ocular mucosa for either local or systemic action suffers from many obstacles. Gel formulations with suitable rheological and mucoadhesive properties increase the contact time at the site of absorption. However, drug release from the gel must be sustained, if benefits are to be gained from the prolonged contact time.

Gelrite gels were formulated in simulated tear fluid at concentrations of polymer as low as 0.1% and it was shown that sodium was the most important gel-promoting ion *in vivo*.

It was possible to control the release of uncharged drug substances by including surfactants that form micelles in the gel. The release depends on lipophilic interactions between the drug and the polymer and/or the micelles.

Controlled-release formulations of charged drugs could be designed by mixing the drugs with oppositely charged surfactants in certain fixed ratios. In this way, vesicles in which the drug and surfactant constituted the bilayer formed spontaneously. The gels were evaluated using porcine nasal mucosa; from the results it was found that the rate of transport of drugs through the mucosa could be controlled by the rate of release from the formulation.

Organogels

Sorbitan monostearate, a hydrophobic nonionic surfactant, gels a number of organic solvents such as hexadecane, isopropyl myristate and a range of vegetable oils. Gelation is achieved by dissolving or dispersing the organogelator in hot solvent to produce an organic solution or dispersion, which on cooling sets to the gel state. Cooling the solution or dispersion causes a decrease in the solvent–gelator affinities, such that at the gelation temperature the surfactant molecules self-assemble into toroidal inverse vesicles. Further cooling results in the conversion of the toroids into rod-shaped tubules. Once formed, the tubules associate with others and a three-dimensional network is formed, which immobilizes the solvent and thus organogel is formed. The sorbitan stearate and palmitate organogels may have potential applications as delivery vehicles for drugs and antigens.

Extended Release Gels

TIMERx is a controlled release technology consisting of an agglomerated, hydrophilic complex that, when compressed, forms a controlled-release matrix. The matrix, consisting of xanthan and locust bean gums (two polysaccharides) combined with dextrose, surrounds a drug core. In the presence of water, interactions between the matrix components form a tight gel while the inner core remains unwetted. The drug is encapsulated in the pores of the gel, and as the matrix travels through the patient's digestive system, the tablet swells and begins to erode. This erosion allows the drug to "back-diffuse" out through the gel matrix at a controlled rate until the matrix erodes and a majority of the drug is released. The fundamental component controlling the rate of release lies in the properties of the gel matrix. The advantages of this system include predictable modified release profile such as zero order or first order or initial immediate release kinetics; moreover, it can be produced on standard manufacturing equipment.

Amphiphilic Gels

Amphiphilic gels can be prepared by mixing the solid gelator such as sorbitan monostearate or sorbitan monopalmitate and the liquid phase such as liquid sorbitan esters or polysorbate and heating them at 60°C to form a clear isotropic sol phase, and cooling the sol phase to form an opaque semisolid at room temperature. Amphiphilic gel microstructures consist mainly of clusters of tubules of gelator molecules that had aggregated upon cooling of the sol phase, forming a three-dimensional network throughout the continuous phase. The gels demonstrate thermoreversibility at skin surface temperature and the gels soften considerably, enabling easy topical application. Hence, thixotropic surfactant gels (amphiphilogels) with suitable physical properties are ideal for topical use.

Hydrophilic Gels

An important group of gels used in pharmacy are hydrophilic gels or hydrogels, usually made of hydrophilic polymers, which gellify under certain conditions and polymer concentrations. Attention of pharmaceutical research now concentrates primarily on hydrophilic gels, as this dosage form seems to be prospective for the development of modern drugs based on systems with prolonged and controlled release of active ingredients.

Nonaqueous Gels

Ethylcellulose was successfully formulated as a nonaqueous gel with propylene glycol, dicaprylate or dicaprate. The novel nonaqueous gel exhibited rheological profiles corresponding to a physically cross-linked three-dimensional gel network with suitable mechanical characteristics for use as a vehicle for topical drug delivery. The gel matrices exhibited prominent viscoelastic behavior, yield stress, and thixotropy.

Bioadhesive Gels

Chitosan bioadhesive gel was formulated for nasal delivery of insulin. A nasal perfusion test was carried out to study the toxicity of four absorption enhancers, namely saponin, sodium deoxycholate, EDTA and lecithin. Considering *in vitro* and *in vivo* studies, the formulated gel could be a useful preparation for controlled delivery of insulin through the nasal route.

Emulgel

An emulgel is basically a gellified emulsion. It is prepared by mixing an o/w type or w/o type emulsion with a gelling agent. This approach has been applied to numerous drug categories, such as antifungal agents, anti-inflammatory agents, anti-acne agents and corticosteroids. Emulgel formulations offer several advantages over the conventional topical formulations, such as creams, ointments, lotions, and powders. Emulgels allow dual control of drug release from the formulation, that is, emulsion and gel. Incorporation of the emulsion into a gel enhances its stability. It is well suited for the administration of hydrophobic drugs. O/w emulsions may be formulated but a water washable base is intended, such as for cosmetic purposes, whereas w/o type emulsions are a good choice for the treatment of dry skin and emollient application.

Lipid Nanoparticles Incorporated Gel

Solid–lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) are two main types of lipid nanoparticles. Drug delivery from these colloidal systems has unique characteristics when compared to the delivery from traditional topical and dermatological formulations. The small size of lipid nanoparticles ensures close contact with the stratum corneum and increases the amount of encapsulated compounds penetrating into the skin. These nanoparticles have distinct occlusive properties due to the formation of an intact film on the skin surface upon drying, which decreases transepidermal water loss and favors the drug penetrating through the stratum corneum. The advantages of these carriers include negligible skin irritation, controlled release and protection of active substances. They can also be used for controlled drug delivery.

Microemulsion Gel

Microemulsions are thermodynamically stable, isotropically clear dispersion of two immiscible liquids, such as oil and water, stabilized by an interfacial film of surfactant molecules, with a size range

of 5–200 nm and have very low interfacial tension. Because of their unique solubilization properties, microemulsions have attracted increasing attention as potential drug delivery systems, either as vehicles for topical applications or as bioavailability enhancers for poorly water-soluble active pharmaceutical ingredients. The advantages associated with microemulsions include their thermodynamic stability, optical clarity, ease of preparation, and high diffusion and absorption rates when compared with solvents without the surfactant system.

Thermosensitive Sol–Gel Reversible Hydrogels

They are aqueous polymeric solutions at lower temperature and undergo reversible sol-to-gel transformation under the influence of environmental temperature conditions such as room or body temperature. The gels can be prepared using thermoresponsive polymers such as poloxamers.

The advantages of these hydrogels over conventional hydrogels are as follows:

1. Ease of mixing pharmaceutical solutions than semisolids
2. Biocompatibility with biological systems
3. Convenient to administer
4. Controlled manner of release
5. Immobilization of cells
6. Tissue engineering

Complexation Gels

The use of pH-responsive poly (methacrylic-g-ethylene glycol) hydrogels as oral delivery vehicles for insulin was evaluated. Insulin was loaded into polymeric microspheres and administered orally to healthy and diabetic Wistar rats. In the acidic environment of the stomach, the gels were unswollen due to the formation of intermolecular polymer complexes. The insulin remained in the gel and was protected from proteolytic degradation.

Niosomes

These are nonionic surfactant vesicles having a bilayer structure formed by the self-assembly of hydrated surfactant monomers. The bilayer is multilamellar or unilamellar and enclose aqueous solution of solutes and lipophilic components. Niosomes are formed by the hydration of nonionic surfactant dried film, resulting in imbibing or encapsulating the hydrating solution. The major component of niosomes is a nonionic surfactant. This gives an advantage of being more stable when compared to liposomes, thus overcoming problems such as susceptibility to oxidation, high cost, difficulty in procuring and high purity levels, which can influence the size, shape and stability of the vesicles. Niosomes can entrap both hydrophilic and lipophilic drugs in aqueous layer and vesicular membrane, respectively. Niosomes can serve as drug depots in the body, which release the drug in a controlled or sustained manner. They improve the oral bioavailability of poorly soluble drugs and also enhance the skin permeability of drugs when applied topically.

Microsponges

These can be defined as microscopic spheres capable of absorbing skin secretions. They contain particles of size 10–25 microns in diameter and are capable of entrapping a wide range of ingredients in a single microsponges system and releasing them at desired rates. Drug release from microsponges is done by external stimuli such as pH, temperature and rubbing. It has several advantageous over the other topical

preparations in being nonallergenic, nontoxic, nonirritant and nonmutagenic in nature. Microsponges can be used in sunscreens, creams, ointments and over-the-counter skin care preparations.

Liposomes

These are microscopic spheres with an aqueous core surrounded by one or more outer shells consisting of lipids arranged in a bilayer configuration. Liposomes can encapsulate hydrophilic and lipophilic drugs and protect them from degradation. They also have an affinity to keratinize horny layer of skin and can penetrate deeper into skin to give better absorption. Applied on the skin, liposomes may act as a solubilizing matrix for poorly soluble drugs, a penetration enhancer and a local drug depot. Topical liposome formulations could be more effective and less toxic than conventional formulations. The liposome gel formulations could act as prolonged and controlled release topical dosage forms, which may lead to improved efficiency and better patient compliance.

PATENTED TECHNOLOGIES IN SEMISOLIDS

Delivery of Monoclonal Antibody Using Semisolid Dosage Form

Lysostaphin was formulated into a hydrophilic cream, which forms an emulsion with the secretions of the nasal mucosa. Aqueous formulations were made containing the mucoadhesive polymers polystyrene sulfonate and chitosan. The results demonstrated that cream and polymer delivery systems significantly decreased the clearance rate of lysostaphin from the nose, thereby enhancing their therapeutic potential for eradicating *Staphylococcus aureus* nasal colonization.

Topical Delivery of Vitamin A

Burst release as well as sustained release of vitamin A can be obtained by using SLN suspensions. Burst release can be useful to improve the penetration of a drug. Sustained release becomes important with active ingredients that are irritating at high concentrations or to supply the skin over a prolonged period of time with a drug.

Glyceryl behenate SLN suspensions were loaded with vitamin A and the release profiles were studied using Franz diffusion cells to assess the release kinetic over a period of 24 hours.

Delivery of Epidermal Growth Factor by Topical Route

The effect of a topical recombinant human epidermal growth factor (rhEGF) ointment on the rate of wound healing and skin re-epithelialization in a rat full thickness wound model was carried out when rhEGF was applied topically to verify whether or not the rhEGF treatment affects both myofibroblast proliferation and collagen synthesis in the dermis. The results indicated significantly enhanced wound closure.

Topical Medications for Orofacial Neuropathic Pain

A vehicle-carrier agent (pluronic lecithin organogel) that can penetrate the mucosa and cutaneous tissues and carry the active medication with it to the treatment site was developed. Because of its rapid onset and low side effect profile, topical medication offered a distinct advantage over systemic administration for those orofacial disorders that are regional, near the surface and chronic.

Foam Drug Delivery

Pharmaceutical foams are pressurized dosage forms containing one or more active ingredients, which, upon valve actuation, emit a fine dispersion of liquid and/or solid materials in a gaseous medium. Foam formulations are generally easier to apply, less dense, and spread more easily than other topical dosage forms.

Foams may be formulated in various ways to provide emollient or drying functions to the skin, depending on the formulation constituents. Probably the most convincing argument for the use of foams is the ease of use by the patient and consumer acceptance. Most foam dosage forms used in dermatology to date have incorporated corticosteroids, although some products have also been used to deliver antiseptics, antifungal agents, anti-inflammatory agents, local anesthetic agents, skin emollients, and protectants.

REVIEW QUESTIONS

Answer in Detail

1. Give various types of ointment bases. How are ointments formulated and the quality control tests performed?
2. Explain how rectal suppositories are formulated, packed, and stored.
3. Explain in detail the recent advancements and patented technologies in the topical drug delivery systems.

Answer in Brief

1. Discuss the mechanism of drug penetration through the skin.
2. Explain the physical methods to enhance topical drug delivery.
3. Write a note on the evaluation methods for ointments.
4. Differentiate between ointments and pastes.
5. Discuss in detail the different methods of preparation of suppositories.
6. Write a note on the types of ointment bases.
7. Explain the various types of suppositories.
8. Write a note on jellies.
9. Discuss briefly the suppository bases.
10. What are jellies? How do they differ from ointments? Mention their uses.
11. Write a note on pastes.
12. Explain the preparation of cocoa butter suppositories.
13. How do jellies differ from gels? Mention the uses of gels.
14. What are the different types of gelling agents?
15. Write a note on vanishing creams.
16. Differentiate between vanishing and cold creams.

Answer in One or Two Sentences

1. What are penetration enhancers? Give examples.
2. Mention the ideal properties of an ointment.

3. What are the various types of ointment bases?
4. Mention the types of ointments.
5. Mention the differences between pastes and jellies.
6. How will you evaluate semisolid dosage forms?
7. Define the terms (a) ointments and (b) occlusive layer.
8. Classify the different types of jellies with examples.
9. What is the significance of displacement value in suppository formulations?
10. What is displacement value? State its importance?
11. Define suppositories and pessaries.
12. Name the different types of suppositories.
13. Mention the components of a cold cream.
14. Define poultices with examples.
15. What are plasters? Mention their applications.

Multiple Choice Questions

1. Which of the following is not a route for percutaneous drug absorption?
   (a) Transepidermal route (b) Transfollicular route
   (c) Diffusion across the stratum corneum (d) Active transport
2. Which of the following is not classified under semisolid dosage forms?
   (a) Linctus (b) Gels (c) Pastes (d) Ointments
3. Which of the following is not a mechanism for action of permeation enhancers?
   (a) Disordering the lamellar packing of the stratum corneum
   (b) Increasing the solubility of the drug
   (c) Reducing the volatility of the drug
   (d) Increasing the thermodynamic activity of the drug
4. Which of the following is a technique for percutaneous transport of charged molecules by application of electric current through the ionic drug solution?
   (a) Electroporation (b) Phonophoresis (c) Iontophoresis (d) Sonophoresis
5. Which of the following is a technique for percutaneous transport using low frequency ultrasound waves?
   (a) Electroporation (b) Phonophoresis (c) Iontophoresis (d) Sonophoresis
6. Ointments intended to produce a local effect on the skin surface are called as _____.
   (a) epidermic ointments (b) diadermic ointments
   (c) endodermic ointments (d) physiologic ointments
7. Ointments intended to produce a systemic action are called as _____.
   (a) epidermic ointments (b) diadermic ointments
   (c) endodermic ointments (d) physiologic ointments
8. Which of the following is an example for an emollient ointment?
   (a) Hydrocortisone ointment (b) Salicylic acid ointment
   (c) Sulfur ointment (d) Paraffin ointment
9. Which of the following is not an absorption ointment base?
   (a) Wool alcohol (b) Hard paraffin (c) Lanolin (d) Beeswax
10. Which of the following is an example for a water-soluble base?
    (a) Wool alcohol (b) Macrogols (c) Soft paraffin (d) Cholesterol

11. Which of the following is not a method for preparation of ointments?
    (a) Fusion (b) Trituration (c) Compression (d) Emulsification
12. Which of the following ointment is prepared by chemical reaction?
    (a) Nonstaining iodine ointment (b) Whitfield's ointment
    (c) Simple ointment (d) Coal tar ointment
13. Which of the following statements is true?
    (a) Pastes are greasier than ointments.
    (b) Pastes contain greater concentration of solids than ointments.
    (c) Pastes are transparent semisolid preparations.
    (d) Pastes are prepared using absorption bases.
14. Which of the following are transparent or translucent, nongreasy, semisolid preparations?
    (a) Suppositories (b) Ointments (c) Pastes (d) Jellies
15. Which of the following dosage forms are classified under unit dose semisolid preparation?
    (a) Creams (b) Pastes (c) Suppositories (d) Jellies
16. Polymorphism is a specific disadvantage of which of the following suppository bases?
    (a) Theobroma oil (b) Glycero-gelatin base
    (c) Witepsol (d) Massupol
17. Displacement value can be defined as _____.
    (a) one part of the medicament that displaces one part of the base
    (b) the number of parts of the medicament that displaces one part of the base
    (c) the number of parts of the base that displaces one part of the medicament
    (d) one part of the base that displaces one part of the medicament
18. Which of the following is a disadvantage of glycerol-gelatin base?
    (a) Leakage from body cavities (b) Polymorphism
    (c) Rapid solidification (d) Laxative action
19. Which of the following is not a method for the preparation of suppositories?
    (a) Emulsification (b) Hand molding
    (c) Compression molding (d) Pour molding
20. Which of the following statements about cold creams is false?
    (a) They are w/o emulsions. (b) They are not readily washed with water.
    (c) They give a cooling sensation. (d) They are also called stearate creams.
21. Which of the following is an oil-in-water emulsion?
    (a) Vanishing cream (b) Cold cream (c) Jellies (d) Gels
22. Which of the following semisolid preparation is heated before use?
    (a) Gels (b) Ointments (c) Poultice (d) Creams

ANSWERS TO MULTIPLE CHOICE QUESTIONS

1. (d)	2. (a)	3. (c)	4. (c)	5. (d)
6. (a)	7. (b)	8. (d)	9. (b)	10. (b)
11. (c)	12. (a)	13. (b)	14. (d)	15. (c)
16. (a)	17. (b)	18. (d)	19. (a)	20. (d)
21. (a)	22. (c)			

Sterile Dosage Forms

8

INTRODUCTION

Learning Objectives

- Introduction and classification of sterile dosage forms
- Different routes of injection administration

Sterile, pyrogen-free preparations intended to be administered by way of injections are called parenterals. The term "parenteral" is derived from the Greek terms *para* (outside or other than) and *enteron* (intestine) and denotes routes of administration other than the oral route.

The various sterile dosage forms are small and large volume injectables, irrigation fluids, dialysis solutions, biological preparations including vaccines, toxoids, antitoxins and ophthalmic preparations. Sterility is a prerequisite for parenterals because these preparations come into direct contact with the internal body fluids or tissues, where infection can easily occur.

Pyrogens are metabolic endotoxin products of microorganisms, which are lipid substances associated with a polysaccharide or peptide carrier molecule. If these are injected, they increase the body temperature, cause body ache and cutaneous vasoconstriction and increase the arterial blood pressure. Pyrogens are highly thermostable, water soluble and chemically inert. However, they are nonvolatile in nature, which provides a way for their removal.

Table 8.1 provides the differences between exotoxins and endotoxins.

The parenteral routes are used when rapid drug action is required, when the patient is noncooperative or unconscious and unable to accept oral medication, or when the drug is ineffective by other routes. Most of the injections are administered by the physician or nurse in the course of medical treatment, except insulin, which can be self-administered by the patient.

Table 8.1 Differences between Bacterial Exotoxins and Endotoxins

Sl. No	*Exotoxins*	*Endotoxins*
1.	Excreted by both Gram-positive and Gram-negative bacteria into the surrounding medium	An integral part of the outer lipopolysaccharide layer of Gram-negative bacteria and is liberated upon disintegration of the bacterial cell wall
2.	Protein in nature	Lipopolysaccharide in nature
3.	Heat sensitive	Heat stable
4.	Specific receptors on host target cells	Diverse range of host cells and systems affected
5.	Specific effects in host by treating with formalin	Diverse range of effects in host

PARENTERAL ROUTES OF DRUG ADMINISTRATION

Drugs may be injected into almost any organ or area of the body, including the joints (intra-articular), joint fluid area (intrasynovial), spinal column (intraspinal), spinal fluid (intrathecal), arteries (intra-arterial), heart (intracardiac; in an emergency), into a vein (intravenous), into a muscle (intramuscular), into the skin (intradermal, intracutaneous), or under the skin (subcutaneous, hypodermic) (Fig. 8.1).

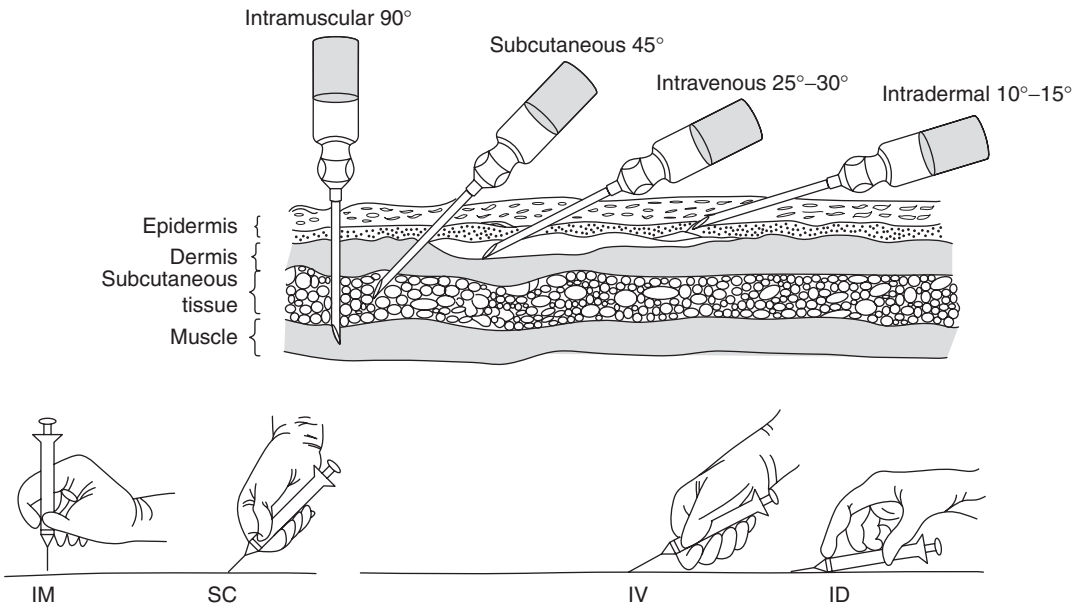


Figure 8.1 Different Sites of Injection Administration

Intravenous Route

The discovery of the intravenous route of administration through hypodermic syringe in the nineteenth century was a revolutionary development in the medical field. Today it is a routine practice in hospitals.

1. The intravenous route ensures rapid action when compared with other routes of administration and may be lifesaving in emergency situations because the drug is administered directly into the blood circulation.
2. The veins of the antecubital area (in front of the elbow) are usually selected for direct intravenous injection.
3. Strict aseptic precautions must be maintained to avoid risk of infection.
4. The injectable solutions, syringes and needles must be sterilized and the point of administration must be disinfected to prevent the entry of bacteria from the skin into the blood through the needle.
5. Both small and large volume parenterals can be administered by the intravenous route.
6. Intravenous preparations must be aqueous in nature. They should mix with the circulating blood and should not precipitate from the solution.
7. Solutions containing nutrients, plasma volume expanders, electrolytes, amino acids and therapeutic agents are administered with a needle or catheter by continuous infusion.
8. According to the needs of the patient, the infusion or flow rate can be adjusted. In general, the flow rate for intravenous fluids is expressed in milliliters per hour and it ranges from 42 ml/h to 150 ml/h.

However, the disadvantages of this route are as follows:

1. In case of an adverse reaction, the drug cannot be easily removed from circulation.
2. Special care must be taken to prevent overdosing or underdosing.
3. Thrombus and embolus formation may be induced by needles and catheters.
4. The parenteral solutions should be sterile and free from particulate matter.

Intramuscular Route

1. Drugs that are administered by this route act less rapidly than those administered through intravenous route but the effect is long lasting.
2. Aqueous or oily solutions or suspensions of drugs can be administered intramuscularly.
3. The rate of absorption depends on the drug properties and formulations.
4. Solutions are more rapidly absorbed than suspensions or oleaginous preparations.
5. Intramuscular injections penetrate deep into the skeletal muscles. The point of injection should be away from the nerves and blood vessels.
6. The point at which the needle enters and deposits the medication might experience injuries such as neural damage, abscess, cyst, embolism and sloughing of the skin to the patients.
7. In adults gluteus maximus is the site for intramuscular injection, whereas in infants and young children, the deltoid muscles of the upper arm or the midlateral muscles of the thigh are the preferred sites for injection.
8. The volume of medication administered may be a maximum of 5 ml in the gluteal region and 2 ml in the deltoid region.

Subcutaneous Route

1. This route is used for injection of small volume parenterals.
2. The preparation is administered beneath the skin, especially in the loose interstitial tissue of the outer upper arm, anterior thigh or lower abdomen.
3. The site of injection is usually changed when frequent injections are required.
4. The skin at the injection site should be thoroughly cleaned before drug administration.
5. The maximum amount of medication that can be injected subcutaneously is about 2 ml because amounts greater than this can cause pain. Syringes of 3 ml capacities and 24 gauge needles are used.
6. Irritating drugs and drugs in thick suspension form may cause abscess or pain.

Intradermal Route

1. Drug substances are effectively injected into the cornium layer, beneath the epidermis. This route is preferred for diagnostic determinations or for desensitization or immunization procedures.
2. The site for intradermal injection is the anterior forearm.
3. For drug administration, a short and a narrow needle is normally employed. The needle is inserted horizontally into the skin with the bevel facing up. The maximum amount of medication that can be injected by this route is about 0.2 ml.

Intra-arterial Route

1. This route is used for inducing rapid drug action in the peripheral area.
2. Injection is made into an artery targeting a particular area.
3. The danger associated with this route is that it may cause gangrene and arterial spasm.

Intrathecal Route

1. Drug substances are injected into the subarachnoid space that surrounds the spinal cord.
2. This route of administration is difficult and causes severe pain to the patients.

OFFICIAL CLASSIFICATION OF INJECTIONS

According to the United States Pharmacopoeia (USP), injectable preparations are classified into five general types:

1. **Injection:** Solutions containing drug substances (e.g., Insulin injection USP)
2. **For Injection:** Dry solids that upon reconstitution with suitable vehicles give solutions and comply with the requirements for injections (e.g., Cefuroxime for injection USP)
3. **Injectable Emulsion:** Drug substances that are dissolved or dispersed in a suitable emulsion medium (e.g., Propofol USP)
4. **Injectable Suspension:** Solids suspended in a suitable liquid medium (e.g., Methylprednisolone acetate suspension USP)
5. **For Injectable Suspension:** Dry solids that upon reconstitution with suitable vehicle give a product that complies with the requirements for injectable suspensions (e.g., Imipenem, meropenem and cilastatin for injectable suspension USP)

The nature of the drug, with respect to certain therapeutic considerations and its physical and chemical properties, decides the form in which the drug is prepared for parenteral use by the manufacturer.

If a drug is unstable in solution, it can be prepared as a dry powder, which is to be reconstituted with the appropriate solvent during the time of administration. For drugs insoluble in water, the injection can be prepared using a suitable nonaqueous solvent, such as vegetable oil or may be prepared as a solution or an aqueous suspension. If an aqueous solution is desired, a water-soluble salt form of the insoluble drug is prepared. Aqueous or blood-miscible solutions may be injected directly into the blood stream. The use of liquids, such as oleaginous injections and suspensions, which are miscible with blood and can interrupt the normal flow of blood, is generally restricted to other than intravenous administration. The onset and duration of action of a drug may be controlled by its chemical form, the physical state of the injection vehicle used and the route of injection administration.

FORMULATION CONSIDERATIONS FOR INJECTABLE PREPARATIONS

Learning Objective

- Factors to be considered for the design of injectables

General Criteria for Design of Suitable Injectable Formulations

1. Drug solubility
2. Selection of the suitable vehicle
3. Volume of administration
4. Route of administration
5. Site of administration
6. Density factor of the injection
7. Isotonicity and pH of the final preparation
8. Sterilization procedures
9. Selection of packaging contents
10. Storage of the product

The following precautions are to be considered when preparing drug solutions and suspensions intended for injection:

1. Solvents or vehicles must meet standards for purity to ensure the safety for injection.
2. The use of buffers, stabilizers and antimicrobial preservatives are restricted in certain parenteral products.
3. The use of colors is strictly prohibited.
4. Parenteral products should meet sterility standards.
5. Solutions for parenteral use must meet pharmacopoeial standards for particulate matter.
6. Parenteral products must be prepared by specially trained personnel in environmentally controlled areas and under strict sanitation standards.
7. Parenteral products are packaged in special high-quality hermetic containers.
8. Each injection container is filled to a volume in slight excess of the labeled volume to be withdrawn. These overfill permits ease of withdrawal and administration of the labeled volumes.

9. Specific labeling requirements are applicable to injections.
10. Sterile powders intended for solution or suspension immediately prior to injection are frequently packaged as lyophilized or freeze-dried powders to permit ease of solution or suspension upon the addition of the solvent or vehicle.

GOOD MANUFACTURING PRACTICES (GMP) REQUIREMENTS FOR STERILE PRODUCTS

1. **Specific Points Relating to Minimizing Risks of Contamination:**
   (a) Microbiological
   (b) Particulate matter
   (c) Pyrogen

2. **Clean Room:**
   (a) The room should undergo 15–20 air exchanges per hour.
   (b) HEPA filters are installed to clean the air entering the room. They are used to remove all airborne particles of size 0.3 microns or larger with an efficiency of 99.97%.
   (c) To minimize the infiltration of airborne contaminants from outside, higher air pressure (positive pressure) within the critical area should be maintained.
   (d) Care should be taken to ensure that airflows do not distribute particles, people, operation process or equipment to a zone of higher product risk. A warning system should be provided to indicate failure in the air supply.
   (e) Adjacent rooms of different grades should have a pressure differential of 10–15 Pascals.
   (f) Counters in the clean room should be made of stainless steel or any other nonporous material, which can be easily cleaned.
   (g) Walls and floors should be free from cracks or crevices and should have tapering corners. The walls, ceiling and floors should be epoxy painted.
   (h) The airflow should move with uniform velocity along parallel lines. The velocity of the airflow should be maintained at 90 ± 20 ft/m^3.
   (i) Controlled temperature and humidity conditions are to be maintained.

3. **Airlocks for Entry:**
   (a) Personnel entry
   (b) Material entry

4. **Separate Areas for Operations:**
   (a) Component preparation
   (b) Product preparation
   (c) Filling and sealing

5. **Air Classification—Grades A, B, C and D:** The air system shall be provided with the appropriate filters such as HEPA for grades A, B and C. The maximum number of particles permitted "at rest" condition shall approximately be as follows:
   (a) Grade A corresponds with class 100, M 3.5, or ISO class 5.
   (b) Grade B corresponds with class 1000, M 4.5, or ISO class 6.

(c) Grade C corresponds with class 10,000, M 5.5, or ISO class 7.
(d) Grade D corresponds with class 100,000, M 6.5, or ISO class 8.

The requirement and limit for the area shall depend on the nature of the operation carried out. The types of operations to be carried out in the various grades are given in Table 8.2.

Table 8.2 Types of Operations to be Carried Out in the Various Grades for Aseptic Preparations

Grade	*Types of Operations for Aseptic Preparations*
A	Aseptic preparation and filling
B	Background room conditions for activities requiring grade A
C	Preparation of solution to be filtered
D	Handling of components after washing

6. **Laminar Airflow Hood:**
   (a) These are clean air workbenches specially designed to ensure the aseptic preparation of sterile products. Laminar airflow hoods are generally used in combination with clean rooms.
   (b) The airflow rates would be 0.3 m/sec (vertical) and 0.45 m/sec (horizontal)
   (c) Laminar airflow velocity satisfactorily sweeps the area but does not create unacceptable turbulence.

FORMULATION OF INJECTABLES AND ADDITIVES

Learning Objectives

- Formulation of sterile dosage forms
- Manufacture of small and large volume parenterals
- Packaging contents used in injectables

Vehicles for Injections

Vehicles used for parenteral preparations should possess the following characteristics:

1. They should be well tolerated by the body.
2. They should be easy to handle during formulation.
3. They should be capable of dissolving the drug.
4. They should be sterile and pyrogen-free.
5. They should have optimum viscosity.

Vehicles used for parenteral preparations are classified as follows:

1. Aqueous vehicles
2. Nonaqueous vehicles

Aqueous Vehicles

1. **Water for Injection USP:** Figure 8.2 shows the water for injection flow chart:

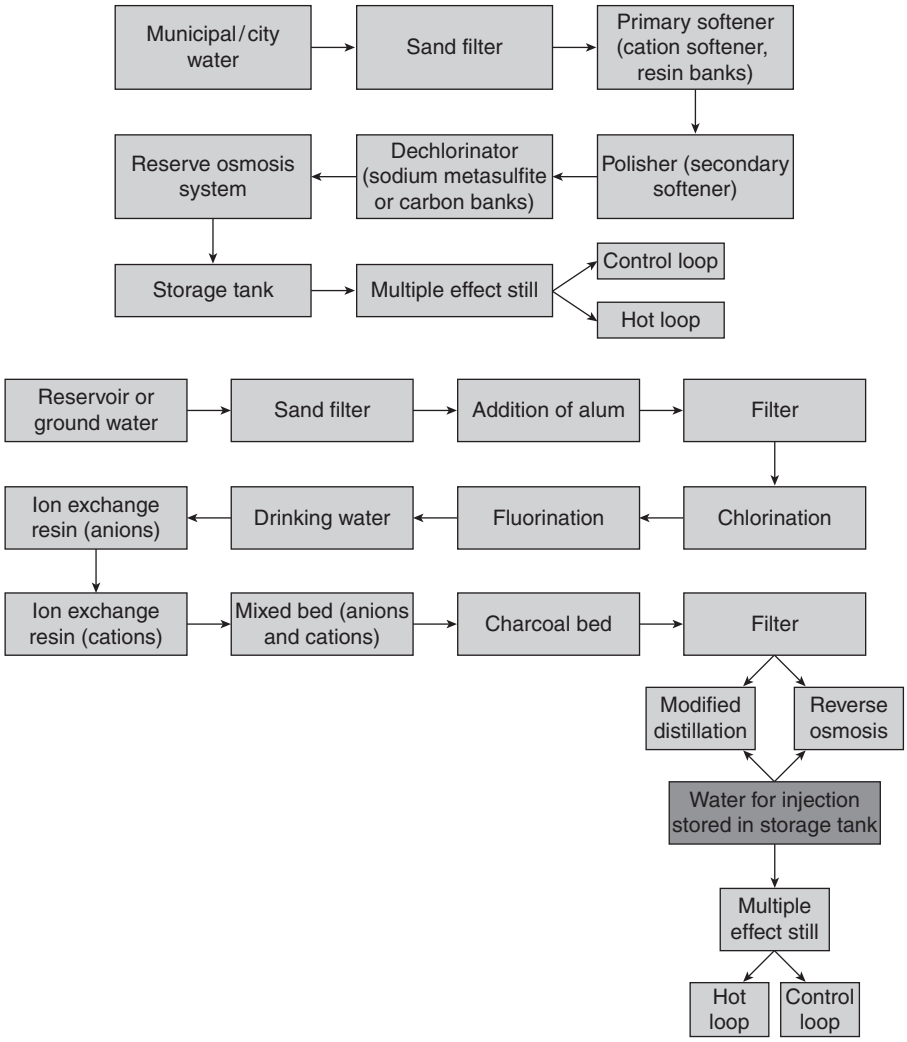


Figure 8.2 Preparation of Water for Injection

(a) The most frequently used solvent in the large-scale manufacturer of injections is *water for injection USP.*
(b) This water is purified by distillation or by reverse osmosis and meets the same standards for the presence of total solids as that of *purified water,* which is not more than 1 mg/100 ml of water for injection USP, and may not contain added substances.
(c) Although water for injection is not required to be sterile, it must be pyrogen-free.

(d) This water can be used in the manufacture of injectable products that are terminally sterilized after preparation.
(e) Water for injection is intended to be used within 24 hours after collection. It should be collected in sterile and pyrogen-free containers.

2. **Sterile Water for Injection USP:**
   (a) Sterile water for injection USP is packaged in single-dose containers not exceeding 1 liter capacity.
   (b) It must be pyrogen-free and should have an allowable endotoxin level, which is not more than 0.25 USP endotoxin units per milliliter.
   (c) It should not contain any antimicrobial agent or other added substance.
   (d) This water may contain slightly more total solids than water for injection because of the leaching of solids from the glass-lined tanks during sterilization.
   (e) This water is intended to be used as a vehicle for already sterilized and packaged injectable medications.
   (f) This water is used for reconstitution of antibiotics. It is aseptically added to the vial of medication to prepare the desired injection. For instance, a suitable injection may be prepared from the sterile dry powder ampicillin sodium USP by aseptic addition of sterile water for injection.

3. **Bacteriostatic Water for Injection USP:**
   (a) Bacteriostatic water for injection USP is sterile water for injection containing one or more suitable antimicrobial agents.
   (b) It is packaged in prefilled syringes or in vials containing not more than 30 ml of the water.
   (c) The label must state the names and proportions of the antimicrobial agents.
   (d) This water is employed as a sterile vehicle in small volume parenterals.
   (e) Bacteriostatic agents are preferred for multiple-dose parenterals.
   (f) Because of the presence of antimicrobial agents, this water must be used only in parenterals that are administered in small volumes.
   (g) Bacteriostatic agent or agents must be chemically compatible with the particular medicinal agent being dissolved or suspended.
   (h) This type of water should not be used in neonates.

4. **Sodium Chloride Injection USP:**
   (a) Sodium chloride injection USP is a sterile isotonic solution of sodium chloride in water for injection.
   (b) It contains no antimicrobial agents but has approximately 154 mEq each of sodium and chloride ions per liter.
   (c) It may be used as a sterile vehicle in solutions or suspensions of drugs for parenteral administration.
   (d) It is frequently used as a catheter or intravenous line flush. Catheters or intravenous lines are constantly used to infuse fluids and intravenous medications and draw blood for laboratory analysis. Usually, 2 ml is used to flush the line after each use or every eight hours if the line is not used.

5. **Bacteriostatic Sodium Chloride Injection USP:**
   (a) Bacteriostatic sodium chloride injection USP is a sterile isotonic solution of sodium chloride in water for injection.

(b) It contains one or more suitable antimicrobial agents, which should be mentioned on the label.
(c) Sodium chloride 0.9% renders the solution isotonic.
(d) When this solution is used as a vehicle, care must be exercised to ensure compatibility of the drug with the preservative and sodium chloride.
(e) It can also be used to flush a catheter or intravenous line to maintain its potency.
(f) It should not be used in neonates.

6. **Ringer's Injection USP:**
   (a) Ringer's injection USP is a sterile solution of sodium chloride, potassium chloride, and calcium chloride in water for injection.
   (b) The three agents are present in concentrations similar to those of physiologic fluids.
   (c) Ringer's is employed as a vehicle for other drugs or alone as an electrolyte replenisher and plasma volume expander.
   (d) Lactated Ringer's injection USP is a sterile solution of sodium chloride, potassium chloride, calcium chloride and sodium lactate in water for injection.
   (e) This injection is used as a fluid and electrolyte replenisher and as systemic alkalizer.

Nonaqueous Vehicles

Although an aqueous vehicle is generally preferred for an injection, it may be unacceptable if the drug has limited water solubility or is susceptible to hydrolysis. When such physical or chemical factors limit the use of an aqueous vehicle, then the only alternative is to use nonaqueous vehicles.

Examples of nonaqueous solvents employed in parenteral products are fixed vegetable oils, glycerin, polyethylene glycols, propylene glycol, alcohol, ethyl oleate, isopropyl myristate and dimethyl acetamide.

Characteristics of Nonaqueous Vehicles: A nonaqueous vehicle should have the following characteristics:

1. It must be nonirritating, nonsensitizing and nontoxic in the amounts administered.
2. It must not exert a pharmacological activity of its own.
3. It should not adversely affect the activity of the drug.
4. It should be physically and chemically stable at various pH levels.
5. Its viscosity must allow ease of injection and good syringibility.
6. Its fluidity must be maintained over a fairly wide temperature range.
7. Its boiling point should be sufficiently high to permit heat sterilization.
8. It should be miscible with body fluids.
9. It should have low vapor pressure to avoid problems during heat sterilization.
10. It should have constant purity or should be capable of purification.

Nonaqueous vehicles may be used provided they are safe in the amounts administered and do not interfere with the therapeutic efficacy of the preparation or with its response to prescribed assays and tests.

The USP specifies restrictions on the use of fixed vegetable oils in parenteral products. The oils used must remain clear when cooled to 10°C to ensure the stability and clarity of the product during refrigeration. They must not contain mineral oil or paraffin, as these materials are not absorbed by body tissues.

Examples of fixed oils used in injections are corn oil, cottonseed oil, peanut oil and sesame oil.

Preservatives

1. Preservatives are used in concentrations that prevent the growth of or kill microorganisms.
2. Many of the preservatives are toxic in large amounts or irritating when parenterally administered. Therefore, special care must be exercised when selecting preservative agents.
3. The maximum limit of certain preservatives used in parenteral products is as follows:

Cationic surface-active compounds	0.01%
Chlorobutanol, cresol, and phenol	0.5%
Sulfite, bisulfite, or metabisulfite of potassium or sodium	0.2%

4. In addition to the stabilizing effect of the additives, the air accompanying the injectable product is frequently replaced with an inert gas, such as nitrogen, to prevent oxidation and to enhance the stability of the product.

Buffers

1. Buffers are solutions that resist any change in pH upon addition of small amounts of acid or alkali.
2. The solubility and stability of the preparation is significantly affected by the pH of the preparation. The ideal pH of a parenteral product is 7.4. Variations from this pH may cause tissue necrosis and extreme pain while administration.
3. The usual pH range for parenteral preparations is between 3.0 and 10.5. This is because the blood itself can act as a buffer and can dilute and distribute the solution rapidly in the circulatory system.
4. The commonly employed buffers are acetic acid, lactic acid, maleic acid, sodium phosphate dibasic, sodium acetate, sodium bicarbonate and tartaric acid.
5. The concentration of buffer used ranges from 0.1% to 2.0%.

Antioxidants

1. Many drugs in aqueous solutions are easily degraded by oxidation and hence an antioxidant should be incorporated in the formulation.
2. Bisulfites and metabisulfites are the commonly used antioxidants in aqueous injections.
3. Antioxidants must be carefully selected for use in injections to avoid interaction with the drug.
4. In addition to antioxidants, parenterals may also contain chelating or sequestering agents, such as EDTA or citric acid, to remove trace elements, which catalyze oxidative degradation.

Tonicity Contributors

1. Parenteral products should be isotonic with the blood in order to reduce tissue damage and irritation.
2. Tonicity adjustment can prevent hemolysis of blood cells and electrolyte imbalance.
3. Hypotonic solutions can cause hemolysis of the RBCs while hypertonic solutions can cause crenulation of the RBCs.
4. Hypertonic solutions should be diluted with water prior to administration.

5. The tonicity of the solution shall be calculated by sodium chloride equivalence method or freezing point depression method.
6. Suitable tonicity adjusting agents used are sodium chloride, urea or dextrose.

Wetting Agents

1. Wetting agents will facilitate the dispersion of drug in the vehicle, especially in case of aqueous suspensions.
2. It reduces the contact angle between the surface of the particle and the vehicle.
3. Surfactants with a hydrophilic lipophilic balance (HLB) value between 7 and 9 will serve as effective wetting agents.
4. The usual concentration of wetting agent is 0.05%–0.5%.
5. Use of excess quantity may cause foaming and caking and may impart undesirable odor to the formulation.

Miscellaneous Additives

Apart from the ingredients discussed above, the other additives that are commonly included in the parenteral preparations are flocculating agents, surfactants, emulsifying agents, and suspending agents depending upon the formulation requirement.

Containers

Containers for parenteral products are produced from one of the following three types of glasses or from one of a variety of plastic materials.

Types of glass

Type I (Borosilicate Glass): This is commonly known as neutral glass. It has a high resistance to hydrolysis and can withstand autoclaving, weathering and solutions of pH up to 8. It can be used for all types of preparations and especially for analytical glass apparatus.

Type II (Treated Soda Lime Glass): Containers may be treated with moist sulfur dioxide at high temperature to create a neutral surface film with high hydrolytic resistance. This type of glass has lower resistance to autoclaving than type I glass. It can be used for products containing aqueous phase as the solvent.

Type III (Soda Lime Glass): This offers very little resistance to hydrolysis and should only be used for powders for reconstitution prior to injection and for nonaqueous preparations.

Glass ampoules are the most commonly used single-dose containers and can range from sizes of 1–50 ml. For aqueous solutions, neutral glass is used. After filling, glass ampoules are sealed by fusion of the glass and hence it becomes tamper proof and there is no danger of entry of microorganisms. Amber-colored glass ampoules are available for light-sensitive products. Clear ampoules may be used, provided the ampoules are packaged in a light-resistant box.

Glass vials sealed by rubber closures are commonly used as multidose containers. The rubber closure is held in place by an aluminum sealing ring. The rubber closure permits the penetration of a syringe needle to allow the withdrawal of a dose of injection.

Plastics

Glass containers have been replaced to a greater extent with plastic containers as they are lightweight and stable against breakage. Nowadays, glass is used only for those products that are not compatible with plastic. Plastics are polymers that can be shaped when softened and then hardened to produce the desired shape and structure. Flexible containers fabricated from modified polyethylenes, polycarbonates, polypropylenes, polyesters, polyolefins, teflon and polyvinyl chlorides are used in parenterals.

Closures for Parenterals

Elastomeric closures or rubbers are commonly used for parenterals because of their compressibility and resealability properties. They can be easily penetrated by a hypodermic needle and the puncture reseals after the withdrawal of the needle.

They are impermeable to water vapor and other gases. They reduce the particulate level or extractables in the preparation and are resistant to multiple puncturing, solvents and radiation.

The selection of a rubber closure should be based on buffers used in the preparation, color and pH of product, nature of drug, method of sterilization, concentration of preservative used and nature of vehicle used.

GENERAL METHOD OF PARENTERAL MANUFACTURE

Figure 8.3 shows the process flowchart of parenteral manufacture.

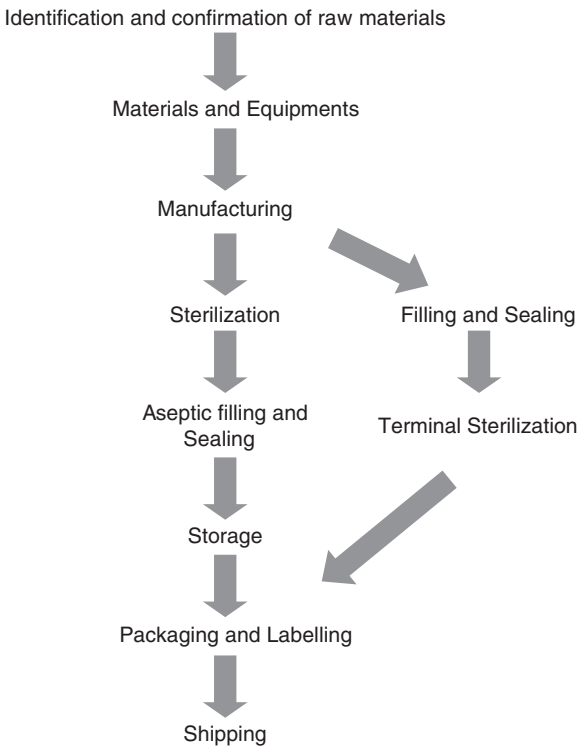


Figure 8.3 Process Flow Chart of Parenteral Manufacture

Figure 8.4 indicates the overview of the steps of manufacturing process of parenterals.

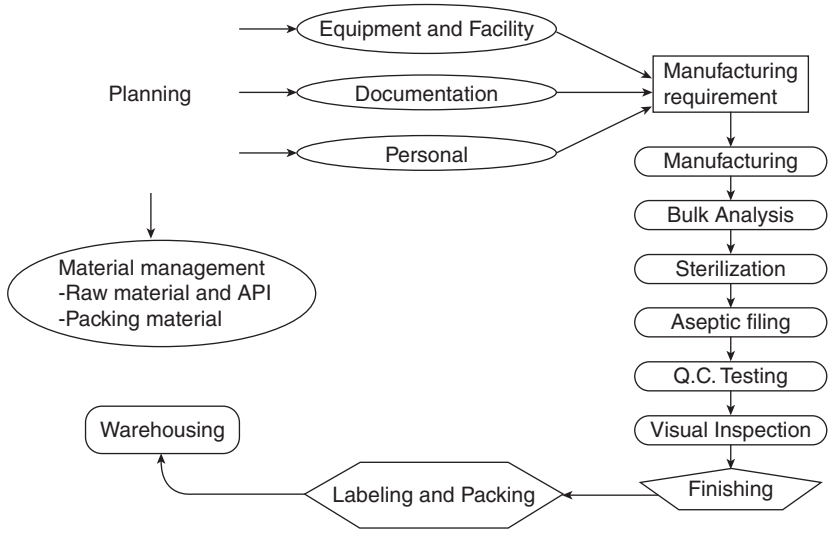


Figure 8.4 Overview of Manufacturing Process of Parenterals

Figure 8.5 shows the flow of materials through the parenteral unit.

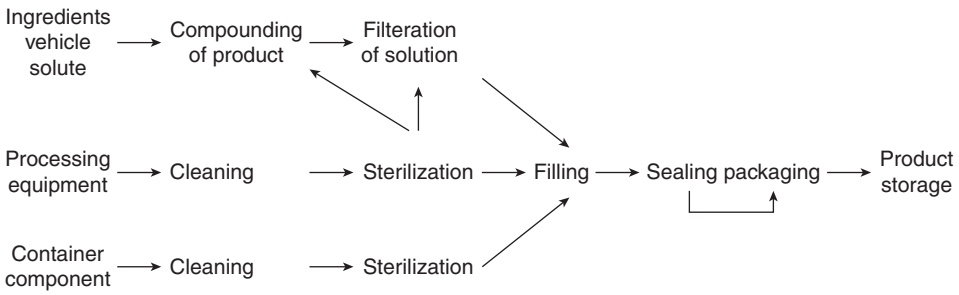


Figure 8.5 Material Flow in Parenteral Unit

Storage and Labeling

Ampoules are labeled by direct printing on the glass. For small-scale dispensing, a paper label is used and it should contain information such as the following:

1. Strength expressed in terms of the amount of active ingredient in a suitable dose volume
2. Name and concentration of any added substance
3. Warning that a single-dose preparation should be discarded after use
4. Special directions for preparation of a particular product, for example, powders for reconstitution prior to use and concentrated solutions for dilutions prior to use

5. Expiry date
6. Storage conditions

Preparations intended to be used as dialysis, hemofiltration or irrigation solutions should meet the standards for injections except that the label should bear a warning that the solution is not intended for intravenous infusion. Any injection containing particulate matter should be discarded. Injections prepared from chemically pure medicinal agents and stable at room temperature need not be stored under special conditions. However, all biologic products such as insulin injection, vaccines, toxoids, toxins and related products should be stored in a refrigerator.

Units of Concentration

The concentration of the components in parenteral products may be expressed in various ways such as percentage weight/volume, weight per unit volume and millimoles per unit volume.

Single-dose Preparations

Single-dose preparations are defined as the volume of injection in a single-dose container sufficient to permit the withdrawal and administration of a nominal dose.

Multiple-dose Preparations

Multiple-dose preparations are multidose injections containing a suitable antimicrobial preservative at an appropriate concentration.

Large Volume Parenterals (LVP)

Large volume parenterals can be classified into the following categories:

1. **Hyperalimentation Solutions:** These are used for administration of large amounts of nutrients such as carbohydrates and amino acids to a patient who is unable to take food orally for several weeks.
2. **Cardioplegia Solutions:** These are electrolyte solutions used in heart surgery to prevent ischemic injury to the myocardium. The electrolyte composition is intended to maintain diastolic arrest.
3. **Peritoneal Dialysis Solutions:** These are meant for continuous infusion into the abdominal cavity to aid removal of toxic substances such as drug overdose or to accelerate the normal kidney excretion in case of kidney dysfunction. These solutions contain glucose and have an ionic content similar to extracellular fluid.
4. **Irrigating Solutions:** These are used to irrigate, flush and clean body cavities (such as urinary bladder) and wounds.

Parenteral Suspensions

Suspensions for parenteral use are required when the drug is insoluble or poorly soluble in the aqueous vehicle. These are preferred for depot release of drug.

Some of the parameters to be considered while formulating suspensions are wettability, rate of sedimentation, caking, size and shape of particles, syringibility, and thixotropic nature of the suspensions. Recrystallization of drug particle should be done followed by its size reduction. All the ingredients should be sterilized prior to manufacturing. Manufacturing, filling and packing should all be carried out under aseptic conditions.

Suspensions can be aqueous or oily in nature and are usually administered by IM or SC route. The rate of drug release from suspension is based on factors such as dissolution of the drug, partition coefficient, blood perfusion, diffusion of drug through the adipose layer, depth of injection and composition of muscle and adipose tissues.

Some examples are chloramphenicol injection B.P. and methylprednisolone acetate injection B.P.

Parenteral Emulsions

Sterile emulsions are required when the drugs are immiscible with the vehicle systems and when fatty substances should be administered intravenously. Emulsions should be formulated with a globule size range of 0.5–1 microns. Surfactants are commonly employed to emulsify the oily liquid and aqueous phase. They should be nontoxic and easy to sterilize.

Examples of such surfactants are lecithin and polysorbate. The important variables that should be taken into consideration are globule size, surface charge, zeta potential, pH, concentration of emulsifier and preservatives. All the ingredients should be sterilized prior to manufacturing. Manufacturing, filling and packing should be carried out under aseptic conditions.

Dry Powder Parenterals (Reconstituted Powders)

Dry powders for injection are a popular parenteral dosage form for drugs that cannot be formulated into ready-to-use injectables because of their instability in aqueous solution. Depending on their formulation strategy, dry powders for injection can be formulated by two strategies.

The first strategy is lyophilization (freeze-drying), where the primary pack allows the formulation of drugs that are thermolabile or unstable in aqueous solution. However, lyophilization normally yields an amorphous or partially amorphous product, which leads to solid-state instability.

The second strategy is the preparation of a more stable crystalline stage that can be obtained by crystallization in aseptic conditions and can be maintained by directly filling the sterile dry-powder drug into pre-sterilized vials. Dry powders for injections are relatively simple formulations with regard to the number of excipients and the manufacturing process.

Filling of Parenterals

Blow–Fill–Seal Technology

Blow–fill–seal (BFS) technology is an automated process by which containers are formed, filled and sealed in a continuous operation.

Most BFS machines operate using the following steps:

1. **Extrusion:** An endless sterile plastic tube is continuously extruded from the melted granulate in the filling cavity of the mold.

2. **Blowing:** Final container is produced by blowing sterile air at high pressure.
3. **Filling:** After the container is formed inside the mold, sterile liquid product is introduced into the container.
4. **Sealing:** The filled container is sealed in place by closing the seal-mold form onto the container top.
5. **Mold Opening:** Upon completion of filling and sealing steps, the mold is separated, producing the sterile filled and sealed container.

Advantage Over Conventional Filling Process

1. There is no need to purchase and stock a range of pre-fabricated container and closures.
2. Cleaning and sterilizing pre-fabricated container and closures are not required.
3. The cost of material, transport, storage and inventory control is reduced.
4. Validation requirements are reduced.
5. There is a large choice in the shapes of necks and opening devices.
6. Less labor is involved.
7. The code number and variables can be molded into the container.
8. With BFS process, a one-piece aseptically filled container with a built- in safety seal is produced.
9. The BFS process is suitable for thermolabile products.

TOTAL PARENTERAL NUTRITION

Parenteral nutrition is the infusion of enough basic nutrients to achieve active tissue synthesis and growth. It is characterized by the long-term intravenous feeding of protein solutions containing high concentrations of dextrose (approximately 20%), electrolytes, vitamins and in some instances insulin.

Table 8.3 provides the composition of total parenteral nutrition.

Table 8.3 Composition of Total Parenteral Nutrition

Ingredients	*Quantity*		
	Normal Patient	*High Stress*	*Fluid-restricted*
Amino acids	85 g	128 g	75 g
Dextrose	250 g	350 g	250 g
Lipids	100 g	100 g	50 g
Na^+	150 mEq	155 mEq	80 mEq
K^+	80 mEq	80 mEq	40 mEq
Ca^{2+}	360 mg	360 mg	180 mg
Mg^{2+}	240 mg	240 mg	120 mg
Acetate	72 mEq	226 mEq	134 mEq
Cl^-	143 mEq	145 mEq	70 mEq
P	310 mg	465 mg	233 mg
Trace elements	5 ml	5 ml	5 ml

The following are the salient features of parenteral nutrition:

1. The individual components and amounts vary with the patient's needs.
2. The large proportion of dextrose increases the calorific value of the solution while keeping the volume required to be administered to a minimum.
3. The solution is administered slowly through a large vein, such as the superior vena cava. This permits rapid dilution of the concentrated hyperalimentation fluid and minimizes the risk of tissue or cellular damage due to the hypertonicity of the solution.
4. Calcium usually as calcium gluconate and phosphate with potassium or sodium phosphate are frequently present in parenteral admixtures. They tend to form precipitates because of concentration of the individual ions, salt form of the calcium, concentration and type of amino acids, concentration of the dextrose, temperature and pH, presence of other additives, and the order of mixing. Hence the methods of manufacture and storage conditions should be optimized.

IRRIGATION AND DIALYSIS SOLUTIONS

1. Solutions for irrigation of body tissues and for dialysis are subject to the same stringent standards as parenteral preparations.
2. The difference is in use. Irrigation and dialysis solutions are not injected into the vein but are used outside the circulatory system.
3. Since they are used in large volumes, they are packaged in large containers.
4. Irrigation solutions are used to wash wounds, surgical incisions, body tissues or body cavities.
5. Dialysis solutions are similar to intravenous bags and irrigation solutions and are dispensed in screw-capped containers or bags.
6. Dialysis is the separation of substances in solution from one another by taking advantage of their differing diffusibilities through membranes.
7. Peritoneal dialysis solutions allow to flow into the peritoneal cavity are used to remove toxic substances normally excreted by the kidney. In cases of poisoning or kidney failure and in patients awaiting renal transplants, dialysis is an emergency lifesaving procedure. Such solutions contain dextrose as a major source of calories, vitamins, minerals, electrolytes with amino acids or peptides as a source of nitrogen.
8. The solutions are made to be hypertonic with dextrose to plasma to avoid the absorption of water from the dialysis solution into the circulation.
9. The semipermeable peritoneal membrane restricts the movement of formed elements and large molecules but allows the movement of smaller molecules in both directions across the membrane according to the concentration on each side of the membrane, with net movement occurring in the direction of the concentration gradient.
10. Intraperitoneal instillation of dialysis solutions containing physiologic concentrations of electrolytes allows for movement of water, toxic substances, and/or metabolites across the membrane in the direction of the concentration gradient, removing these substances from the body following drainage of the solution from the peritoneal cavity.
11. Hemodialysis is employed to remove toxins from the blood. In this method, the arterial blood is passed through a polyethylene catheter through an artificial dialyzing membrane bathed in an electrolyte solution. Following the dialysis, the blood is returned to the body circulation through a vein.

METHODS OF STERILIZATION OF PARENTERAL PRODUCTS

Learning Objective

- Classification and process of sterilization methods

The process of sterilization signifies a complete removal of all living microorganisms from the preparation. It also indicates the killing of all living, micro-organisms including their spores. The common methods of sterilization of pharmaceuticals are as follows:

1. Moist heat sterilization
2. Dry heat sterilization
3. Filtration sterilization
4. Gas sterilization
5. Ionizing radiation sterilization

Depending upon the nature of the pharmaceutical preparation, a suitable method of sterilization is selected.

Moist Heat Sterilization

The method of moist heat sterilization is based on the steam under pressure. An autoclave is used for this purpose. Moist heat sterilization is the method preferred for the pharmaceutical products that can withstand heat. Microorganisms are coagulated and destroyed at a lower temperature in the presence of water. The mechanism of microbial destruction in moist heat is by denaturation and coagulation of the organism's essential protein, which occurs by the hot moisture in the microbial cell that permits destruction at relatively low temperature. Increase in pressure helps in killing the microbes in combination with the temperature. Under atmospheric conditions it is not possible to increase the temperature of steam above 100°C. Hence, pressure is employed to achieve a higher temperature. An autoclave is fitted with temperature, pressure and time gauges which help the operator to fix the sterilization conditions required for different sterilizing substances. The usual steam pressures, the temperatures obtainable under these pressures, and the approximate length of time required for sterilization after the system reaches the indicated temperatures are provided in Table 8.4.

Table 8.4 Sterilization Conditions by Autoclaving

Steam Pressure (lb pressure)	*Temperature (°C)*	*Temperature (°F)*	*Time for Sterilization (min)*
10	115.5	240	30
15	121.5	250	20
20	126.5	260	15

Moist heat sterilization is applicable to preparations that can withstand heat under pressure; examples are ampoules containing solutions, sealed empty vials containing small quantity of water, bulk

solutions, glassware, surgical dressings and instruments. However, it is not applicable to exposed powders that may be damaged by the condensed moisture and oils, fats, oleaginous preparations and other preparations that are not penetrated by the moisture.

Dry Heat Sterilization

This method of sterilization is usually carried out in ovens such as hot air oven, which are normally heated by electricity or gas and are thermostatically controlled. The basic mechanism of sterilization by this process is dehydration of microbial cell wall followed by oxidation. Higher temperature and longer periods of exposure are needed in this process of sterilization, which indicates its less effectivity in killing microorganisms when compared to moist heat sterilization. Dry heat sterilization is conducted at 150°C to 170°C for not less than two hours. The individual units of articles and substances that have to be sterilized should be small so that the heated air could be freely circulated throughout the chamber. This method of sterilization is employed for substances such as fixed oils, glycerin, petrolatum, mineral oils such as paraffin and various heat stable powders such as zinc oxide and talc, which are not effectively sterilized by moist heat sterilization.

Filtration Sterilization

This method of sterilization comes under the mechanical method of sterilization, whereby the microorganisms are physically removed by adsorption or by sieving mechanism onto the filter medium. Filtration sterilization can be effectively applied on heat-sensitive solutions. Filters that are available commercially come with various pore sizes. They are made up of thin plastic membranes of cellulosic esters with millions of pores per square inch. The pore sizes of these filters range from 0.025 μm to 14 μm. Other than the pore size, the important factors that influence the pore size are electrical charge on the filter and that of the microorganism, pH of the solution, temperature and the pressure of vacuum applied to the system.

The advantages of filtration sterilization are as follows:

1. It is inexpensive.
2. Speed in the filtration of small quantities of solution.
3. Thermolabile materials can be sterilized.
4. Complete removal of living and dead microorganisms and other particulate matter from the solution.

The following are the disadvantages:

1. Filters are fragile.
2. Filtration of large volume of liquids is time consuming.

Gas Sterilization

Sterilization by gas can be effectively employed on materials, which are heat sensitive and moisture sensitive. The most frequently used gases for this purpose are ethylene oxide, propylene oxide, and formaldehyde.

The gases mentioned are highly flammable in mixture with air, so they are diluted with an inert gas such as carbon dioxide or a suitable fluorinated hydrocarbon. A special equipment resembling autoclave is used for this method of sterilization. The method of sterilization with gas is enhanced and the exposure time required is reduced by increasing the relative humidity of the system to about 60% and by increasing the exposure temperature to 50°C to 60°C.

The method of sterilization takes an exposure time of 4–16 hours. The mechanism of sterilization is by interfering with the metabolism of the bacterial cell. Ethylene oxide gas has good penetrating power, which makes it very useful for sterilization of catheters, needles and plastic disposable syringes in their final plastic packaging before the shipment. Heat-labile enzyme preparations and antibiotics can also be sterilized by this method.

Radiation Sterilization

Sterilization by radiation uses highly penetrable ionizing radiations such as gamma rays and cathode rays. The mechanism of sterilization is by alteration of the chemical components within or supporting the microorganism to form deleterious new chemicals capable of destroying the cell. These radiations also have the capability to destroy or disorient the cell's vital structure such as the chromosomal nucleus. The applications of radiations for sterilization are limited because of the requirement of highly specialized equipment, precautionary handling measures and also their effects on products and their containers.

QUALITY CONTROL TESTS FOR STERILE DOSAGE FORMS

Learning Objective

- Various quality control tests used for sterile dosage forms

Leak Test

Sealing of ampoules may be done by tip sealing and pull sealing methods. During the sealing process there are chances that ampoules are incompletely sealed and cracks may occur around the seal or at the base of the ampoule as a result of improper handling. Hence, the leak test is intended to detect improperly filled and sealed ampoules so that they can be discarded.

The test is performed by immersing the sample ampoules in a deeply colored dye solution (usually 0.5% to 1.0% methylene blue) and by applying a negative pressure in a vacuum chamber with 27 inches Hg or more for 30 minutes. After the test period, the vacuum is gently released and the subsequent atmospheric pressure causes the dye to penetrate an opening if present, being visible after the ampoules have been washed externally and visually observed.

During the cycles of autoclaving the leak test can be performed by immersing the ampoules in a bath of dye. This provides an advantage of achieving both leak detection and sterilization in one process. Vials and bottles are not subjected to such a leak test because the rubber closure is not rigid.

Clarity Test

Clarity test is performed to confirm the quality and purity of sterilized parenteral solutions. Sometimes, these solutions contain visible particulate matter ranging from 30 μm to 40 μm and larger in size.

The USP states that GMP requires that all containers be visually inspected and that any contained with visible particles be discarded. In addition, for large volume infusions, the USP has established a limit of 50 particles of 10 microns and larger and 5 particles of 25 microns and larger (Table 8.5). Although particulate matter is of primary concern in products given intravenously, all parenteral products should be free from insoluble particles.

The visual inspection of a product container is usually done by individual human inspection of each externally clean container with the contents set in motion with a swirling action, under a good light, baffled against reflection into the eyes and viewed against a black and white background. A moving particle is much easier to see than a stationary one but care must be taken to avoid introducing air bubbles, which are difficult to distinguish from particulate matter. To see heavy particles, it may be necessary to invert the container as the final step during inspection.

Evaluation of particulate matter in liquids involves instrumental methods, which involves utilization of principles such as light scattering, light absorption and electrical resistance to obtain particle count and size distribution.

Table 8.5 Clarity Test Official Standards

Compendia	*LVI/SVI*	*Method*	*≥10 microns*	*≥25 microns*
USP	LVI	Light blockage microscope	25 parts/ml 12 parts/ml	3 parts/ml 2 parts/ml
USP	SVI	Light blockage microscope	6000 parts/container 3000 parts/container	600 parts/container 300 parts/container
EP	LVI SVI solution SVI powder	Light blockage Light blockage Light blockage	25 parts/ml 6000 parts/container 10,000 parts/container	3 parts/ml 600 parts/container 1000 parts/container
BP	LVI	Coulter counter	1000 parts/ml ≥ 2 μm	100 parts/ml ≥ 5 μm
JP	LVI	Light blockage microscope	500 parts/ml ≥ 2 μm 20 parts/ml	80 parts/ml ≥ 5 μm 2 parts/ml

Drug Content

Unless otherwise stated in the individual monograph, suspensions for injection that are presented in single-dose containers and that contain less than 10 mg or less than 10% of active ingredient comply with the following test.

The test is performed by randomly selecting 10 samples, which are estimated for drug content using the method given in the monograph or by any other suitable analytical method. The test passes if the result complies between 85% and 115% of the average value. The preparation under examination fails to comply with the test if more than one individual value is outside the limits 85%–115% of the average value or if any one individual value is outside the limits 75%–125% of the average value.

If one individual value is outside the limits of 85%–115% but within the limits 75%–125% of the average value, the determination is repeated using another 20 containers taken at random. The preparation under examination complies with the test if in the total sample of 30 containers, not more than one individual value is outside the limits 85%–115% and none is outside the limits 75%–125% of the average value.

Note: The test for uniformity of content is not applicable to suspensions for injection containing multivitamins and trace elements.

Pyrogen Test

The endotoxin metabolites of microorganisms that cause marked rise in the body temperature when contaminated with the parenteral preparations are called as pyrogens. The tests for pyrogens are carried out as follows:

Rabbit Test

The USP pyrogen test uses healthy rabbits that have been properly maintained in terms of environment and diet before the test. Normal or control temperatures are taken for each animal to be used in the test. These temperatures are used as the base for the determination of any temperature increase resulting from injection of the test solution. A given test uses three rabbits whose temperatures do not differ by more than 1°C from each other and whose body temperatures are considered not to be elevated. The product to be tested is warmed to 37°C ± 2°C and injected into the marginal ear vein of each of rabbits, completing each injection within 10 minutes of the start of administration. Temperature should be recorded at 30-minute intervals up to 1–3 hours subsequent to the injection. If no rabbit shows an individual rise in temperature of 0.5°C or more, the product meets the requirements for the absence of pyrogens. If any rabbit shows an individual temperature rise of 0.5°C or more, the test should be continued using five other rabbits. If not more than three of the eight rabbits show individual rises in temperature of the material under examination, it meets the requirements for the absence of pyrogens.

Limulus Amebocyte Lysate Test

The limulus amebocyte lysate (LAL) test is the *in vitro* test method for pyrogens that has been developed utilizing the gelling property of the lysate of the amebocyte of *Limulus polyphemus* (the horseshoe crab). In the presence of pyrogenic endotoxins from Gram-negative bacteria, a firm gel is formed within 60 minutes, when incubated at 37°C. The LAL test has been found to be 5 to 10 times more sensitive than the rabbit test and by the use of serial dilutions, it has been shown to be semiquantitative.

Sterility Test

This is a confirmatory test for the procedure of sterilization. Preparations and materials such as injectables, ophthalmic products and absorbent cotton that are required to be sterile are tested. The test is carried out under aseptic conditions to avoid contamination of the product during the test.

Principle

The sterility test is based on the principle that when microorganisms are supplied with nutrient medium and incubated at favorable temperature conditions, the microorganisms will grow and multiply. The presence of microorganisms can be identified by the turbidity in the clear medium.

Preparation of Culture Media

The culture media used for the sterility test must be capable of promoting the growth of a wide range of microorganisms such as aerobic and anaerobic bacteria and fungi. Two types of media are available:

Fluid Thioglycolate Medium: This medium is used primarily to support the growth of anaerobic bacteria. It also supports the growth of aerobic bacteria to some extent. Table 8.6 lists the ingredients required and their quantities for this medium.

Table 8.6 Composition of Fluid Thioglycolate Medium

Ingredients	*Quantity (for 1000 ml)*
L-cystine	0.5 g
Sodium chloride (NaCl)	2.5 g
Dextrose	5.5 g
Agar	0.75 g
Yeast extract	5.0 g
Pancreatic digest of casein	15.0 g
Sodium thioglycolate	0.5 g
Resazurin (0.1% fresh solution)	1.0 ml
Distilled water (q.s.)	1000 ml

Soybean–Casein Digest Medium: It is used to support the growth of aerobic bacteria and fungi. Table 8.7 lists the ingredients required and their quantities for this medium.

Table 8.7 Composition of Soybean–Casein Digest Medium

Ingredients	*Quantity (for 1000 ml)*
Pancreatic digest of casein	17.0 g
Peptic digest of soybean meal	3.0 g
Sodium chloride	5.0 g
Dibasic potassium phosphate (K_2HPO_4)	2.5 g
Dextrose	2.5 g
Distilled water (q.s.)	1000 ml

Sampling (Selection of the Size of Samples)

The selection of samples and the number of samples to be taken from any given batch of sterile product are important. The material must be thoroughly mixed if the sample is to be taken from the bulk. The sample is taken at random from the batch of final containers.

Test methods

The sterility test can be carried out by the following methods:

Membrane Filtration Method: This method is employed if the test substance is any of the following:

1. An oily preparation
2. An ointment that can be placed into solution
3. A soluble powder or a liquid with antimicrobial properties
4. A solid without antimicrobial properties and is not readily soluble in the culture media
5. For liquid products where the volume in a container is 100 ml or more

Procedure: Membrane filters of pore size not greater than 0.45 μm and diameter of 47 mm, which can retain microorganisms, are employed for the sterility test. The filtration system and the membrane are sterilized and the substances are filtered through the membrane under aseptic conditions.

If the substances have antimicrobial properties, the membrane is washed with three successive 100 ml quantities of sterile solvent.

The membrane is then aseptically cut into two equal halves. One half of the membrane is immersed in 100 ml of soybean–casein digest medium and incubated at 20°C–25°C. The other half of the membrane is immersed in 100 ml of fluid thioglycolate medium and incubated at 30°C–35°C for a time period not less than seven days.

Direct Inoculation Method: The quantity of the test substance to be used in each culture medium is directly transferred or inoculated into the culture media under aseptic conditions. The inoculated liquid is mixed with the medium. If the test substance contains antimicrobial properties, then it is neutralized by adding suitable inactivating substances (e.g., pencillinase in case of penicillin) to the medium. The inoculated media is incubated in soybean–casein digest medium at 20°C–25°C and also in fluid thioglycolate medium at 30°C–35°C. Both the media are incubated for not less than seven days.

Positive Control Test: A positive test is performed to ascertain that the culture media prepared and the environment conditions maintained during the test period favor the microbial growth. The causative test microorganism is streaked over the culture media under aseptic conditions and the method discussed earlier is adopted. At the end of the study, there should be growth or multiplication in the microbial load.

Negative Control Test: A negative test is performed to ascertain the sterility of the test area and the procedure adopted. The sterilized culture media is exposed to the test area and incubated. At the end of the study, there should not be any growth in the culture media, thereby proving the sterility and absence of microorganisms in the working area; an example is the laminar airflow unit.

Observation and Interpretation of Results

At intervals during the incubation period and at its conclusion, the media are examined for macroscopic evidence of microbial growth. If the material being tested renders the medium turbid so that the presence or absence of microbial growth cannot be easily determined by visual examination, 14 days after the beginning of incubation, portions (each not less than 1 ml) of the medium are transferred to fresh vessels of the same medium; then, the original and transfer vessels are incubated for not less than 4 days. If no evidence of microbial growth is found, the preparation under examination complies

with the test for sterility. If evidence of microbial growth is found, the preparation under examination does not comply with the test for sterility. Do not repeat the test unless it can be clearly shown that the test was invalid for causes unrelated to the preparation under examination. The test may be considered invalid only when one or more of the following conditions are fulfilled:

1. Microbial growth is found in the negative controls.
2. Data on microbial monitoring of the sterility testing facility show a fault.
3. A review of the testing procedure used for the test in question reveals a fault.
4. After identifying the microorganisms isolated from the containers showing microbial growth, the growth may be ascribed without any doubt to faults with respect to the materials and/or technique used in conducting the test procedure.

If the test is declared to be invalid, it is repeated with the same number of units as in the original test. If no evidence of microbial growth is found in the repeat test, the preparation under examination complies with the test for sterility. If microbial growth is found in the repeat test and confirmed microscopically, the preparation under examination does not comply with the test for sterility.

PARENTERAL CONTROLLED DRUG DELIVERY SYSTEMS

Learning Objectives

- Need for the parenteral controlled drug delivery
- Various approaches to control drug release in parenteral formulations

The administration of drugs via intravenous, subcutaneous or intramuscular injection leads to rapid drug absorption and rapid drug elimination from the body, hence the importance of sustained or controlled parenteral drug delivery system, which maintains an effective drug concentration in blood for a longer duration of time is needed.

The effective systemic drug concentration can be achieved by two strategies:

1. Controlling the rate of drug absorption
2. Controlling the rate of drug excretion

Controlling the absorption rate of a drug (modifying dosage forms) is much easier than controlling the excretion rate (modifying physiology of body) of a drug. Continuous intravenous infusion is used to maintain a constant drug level within a therapeutic concentration range for effective treatment.

Approaches for the Development of Parenteral Controlled Drug Delivery

Pharmaceutical approaches to develop a parenteral controlled drug delivery system include the following:

1. Preparation of water-insoluble drug derivatives such as complexes and esters
2. Use of water-miscible, viscous vehicles such as aqueous solution of PVP (polyvinylpyrrolidone) or gelatin
3. Utilization of water-immiscible vehicles such as vegetable oils and water-repelling agents such as aluminum monostearte

4. Coadministration of vasoconstrictors
5. Formulation of thioxtropic suspensions
6. Dispersion in polymeric microspheres or microcapsules such as lactide–glycolide homopolymers or copolymers

MODELS FOR PARENTERAL DEPOT FORMULATION

Learning Objective

- Various mechanisms for parenteral depot formulations

Based on the mechanism of drug release, depot formulations can be categorized into the following four types:

1. Dissolution controlled depot formulation
2. Adsorption type depot formulation
3. Encapsulation type depot formulation
4. Esterification type depot formulation

Dissolution Controlled Depot Formulation

The process of dissolution of drug particles from the formulation or the drug particles surrounded by tissue fluids is the rate limiting step. Based on this concept, the rate of drug absorption can be controlled by slow dissolution of drug particles.

Drug dissolution rate under sink conditions is given as

$$(Q/t)d = Sa\ Ds\ Cs/hd$$

where *Sa* is the surface area of the drug particles in contact with the medium, *Ds* is the diffusion coefficient of drug molecules in the medium, *Cs* is the saturation solubility of drug in the medium, and *hd* is the thickness of the hydrodynamic diffusion layer surrounding each drug particle.

There are two approaches that can be utilized to control the dissolution of drug particles and also to prolong the absorption of the drug.

Formation of Ester or Complexes with Low Aqueous Solubility: Examples are preparations of penicillin G procaine and penicillin G benzathine from the highly water-soluble alkali salts of penicillin G and preparations of naloxone pamoate from the water-soluble hydrochloride salt of naloxone.

Suspension of Macrocrystals: Crystals of large particle size (macrocrystals) dissolve more slowly than microcrystals. Typical example is the aqueous suspension of testosterone isobutyrate for intramuscular administration.

Adsorption Type Depot Preparation

The binding of drug molecules to adsorbents is the approach to depot preparation. The unbound drug from the preparation undergoes absorption and subsequently fractions of the bound drug molecules

are released to maintain equilibrium condition. This type of formulation is used in vaccine preparations in which the antigens are bound to highly dispersed aluminum hydroxide gel to sustain the antigen release and hence prolong the duration of stimulation of antibody formation.

Encapsulation Type Depot Preparation

Encapsulating the drug within a permeation barrier or dispensing drug particles in a diffusion matrix is the formulation process involved in the encapsulation type depot preparation. The drug release is controlled by the permeation rate across the permeation barrier and the rate of biodegradation of the barrier macromolecules. Different biodegradable or bioabsorbable macromolecules such as gelatin, dextran, polylactic acid, phospholipids, long-chain fatty acids and glycerides are used for designing the permeation barrier and diffusion matrix. The examples for this type of depot formulation are-biodegradable microcapsule containing naltrexone pamoate, liposomes and norethindrone-releasing biodegradable lactide–glycolide copolymer beads.

Esterification Type Depot Preparation

When a drug is esterified into a bioconvertible prodrug ester and then formulated into an injectable form, it gives rise to esterification type depot preparation. This chemical approach depends upon the number of enzymes (esterases) present at the injection site, and the formulation forms a drug reservoir at the site of injection. The absorption rate of the drug is controlled by the interfacial partitioning of drug esters from the reservoir to the tissue fluid and the rate of bioconversion of drug esters to active drug molecules. Examples of this type of depot preparation are oleaginous injections of fluphenazine enanthate and nandrolone decanoate.

ADVANCES IN DELAYED RELEASE PARENTERAL DRUG DELIVERY SYSTEMS

Learning Objective

- Various types of parenteral controlled drug delivery systems

Implants

Implants administered parenterally are defined as viscous liquids or semisolid formulations, which are injected with a needle, and as liquids that gel following administration, impregnated with a drug substance. Implants are used in chronic treatment such as hormone replacement therapy and prostate cancer.

Classification of Implants

1. **Solid Implants:** From the solid implants, the drug release is controlled by varying polymer composition and increase in polymer molecular weight. These implants exhibit biphasic drug release

kinetics, with initial burst of drug due to the release of drug deposited on the surface of the implant and further constant zero-order kinetics is achieved. An example is polylactic acid co-glycolic acid sclera implants containing ganciclovir for the treatment of cytomegalovirus infection.

2. ***In Situ* Forming Implants:** An attractive alternative to solid implants is represented by the biodegradable injectable *in situ* forming implant drug delivery systems. Based on the mechanism of depot formation, injectable *in situ* forming implants are classified into five categories:
   (a) **Thermoplastic Pastes:** These are semisolid polymers that injected as a melt form a depot upon cooling to body temperature. They have been used extensively in the manufacture of surgical sutures and ocular implants. The limitation associated with this system is that when injected at temperatures above 60°C, it leads to pain and necrosis at the site of drug administration.
   (b) ***In Situ* Cross-linked Polymer Systems:** These systems are formed by free radical reactions initiated by heat or ionic interactions between small cation and polymer anions. Examples are ion-mediated gelation using polymers such as alginates/calcium ions or chitosan/phosphate ions.
   (c) ***In Situ* Polymer Precipitation:** In these systems, a water-insoluble and biodegradable polymer is dissolved in a biocompatible organic solvent to which a drug is added, forming a solution or suspension. When injected into the body, the organic solvent dissipates, leading to the penetration of water into the organic phase. This results in phase separation and precipitation of the polymer depot at the site of injection.
   (d) **Thermally Induced Gelling System:** Certain polymers undergo physical changes as a function of environmental temperature. The thermoresponsive polymer poly(N-isopropylacrylamide)[poly(NIPAAM)] exhibits sharp lower critical solution temperature at about 32°C, which can be shifted to body temperature by formulating poly NIPAAM-based gels with salt and surfactant. Other polymers such as pluronics or poloxamers with high polymer strength solution when injected have shown gelation at body temperature.
   (e) ***In Situ* Solidifying Organogel:** Organogels are composed of amphiphilic lipids, which are insoluble and swell in water to form various types of lyotropic liquid crystals. Examples of lipids used for the drug delivery are glycerol monopalmitostearate, glycerol monolinoleate, and sorbitan monostearate and different gelation modifiers such as Tween 20 and 80 in various organic solvents and oils.

Suspensions

Suspensions can be a potential parenteral sustained release system. When a drug is administered as an aqueous or oil suspension subcutaneously, it results in the formation of a depot at the site of injection. Typical examples are oleaginous suspension of micronized crystal of penicillin procaine in peanut or sesame oil gelled with 2% aluminum monostearate.

Microspheres

Biodegradable microspheres for the delivery of small molecules, proteins and macromolecules have been in application. These are prepared by water/oil/water emulsion–solvent evaporation method and have shown zero-order drug release over one to three months after intramuscular or subcutaneous injection.

Liposomes

Drug into unilamellar and multilamellar vesicles and complexation of drug with lipids have been devised for intravascular administration. Semisolid phospholipid dispersion of vesicular morphology, termed as vesicular phospholipid gels, is another approach in liposomal technology. Examples for vesicular phospholipid gels formulations are erythropoietin protein and cetrorelix peptide.

Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLN) are solid colloidal particles that consist of biocompatible, biodegradable lipid matrix and exhibit size range between 100 nm and 400 nm. When administered parenterally, they showed protection of incorporated thermolabile drugs from degradation, good physical stability, controlled drug release depending on the incorporation of model, good tolerability and site-specific targeting. An example is prednisolone-loaded SLN.

Table 8.8 provides a list of USFDA-approved CR (controlled release) parenteral products.

Table 8.8 List of USFDA-approved CR parenteral products

Trade Name	*Active Ingredient*
Suspension Products	
Depo-Medrol	Methylprednisolone
Depo-Provera	Medoxyprogesterone
Celestone Soluspan	Betamethasone
Insulin	Lente ultralente NPH
Microsphere Products	
Lupron depot	Leuprolide
Sandostatin LAR	Octreotide
Nutropin depot	Somatropin
Plenaxis	Abarelix
Liposome Products	
Doxil	Doxorubicin
Daunoxome	Daunorubicin
Ambisome	Amphotericin B
Depocyt	Cytarabine
Lipid Complex Products	
Ambelcet	Amphotericin B
Amphotec	Amphotericin B

(*Continued*)

Table 8.8 Continued

Trade Name	*Active Ingredient*
Implant Products	
Norplant	Levonorgestrel
Gliadel	Carmustine
Zoladex	Goserelin

REVIEW QUESTIONS

Answer in Detail

1. What are the different vehicles used in sterile dosage forms? Explain them.
2. Discuss the manufacturing process of injectable preparations.
3. Explain the various parenteral sterilization techniques.
4. Discuss the sterility tests for parenteral products.
5. Explain in details the evaluation tests for parenteral dosage forms.
6. Explain the various mechanisms adopted in parenteral depot formulations.
7. Discuss in detail the recent advances in parenteral controlled drug delivery.

Answer in Brief

1. Explain the various routes of injectable administration.
2. Differentiate between bacterial endotoxin and exotoxin.
3. Write short notes on pyrogen test.
4. Discuss on the factors to be considered in the design of injectable preparation.
5. Write a note on clean room technology in parenterals.
6. Classify and define pharmaceutical waters with their uses.
7. Write a note on glass as a packaging material for parenterals.
8. Write a note on large volume parenterals.
9. What are pyrogens? Discuss the test method for pyrogens.
10. Discuss the various approaches to develop parenteral controlled drug delivery.
11. Explain the types of parenteral controlled drug delivery systems with suitable examples.

Answer in One or Two Sentences

1. Classify various parenteral dosage forms with examples.
2. Differentiate between water for injection and sterile water for injection.
3. Classify the types of glasses used for parenteral preparations.
4. Define BFS technology.
5. Define sterility test.
6. What are pyrogens? Why do they have to be eliminated?
7. Define LAL test.
8. Explain the need for positive and negative control tests in the process of sterility test.

9. Mention the need for parenteral controlled drug delivery.
10. Define implants. Mention their applications.

Multiple Choice Questions

1. When a drug is administered through joints, it is called as _____.
   (a) intravenous (b) intramuscular (c) intra-articular (d) intradermal
2. Intravenous medication was first given to humans by _____.
   (a) Johann Daniel
   (b) Henry Keller
   (c) Anthon van Robert
   (d) Alexander Fleming
3. The maximum amount of medication that can be comfortably injected subcutaneously is _____.
   (a) 4 ml (b) 2 ml (c) 5 ml (d) 1 ml
4. Sterile water for injection should have an allowable endotoxin level of _____.
   (a) not more than 0.3 USP endotoxin units per ml
   (b) not more than 0.5 USP endotoxin units per ml
   (c) not more than 0.35 USP endotoxin units per ml
   (d) not more than 0.25 USP endotoxin units per ml
5. Sodium chloride injection USP, has _____.
   (a) 154 mEq of sodium ions per liter
   (b) 154 mEq of chloride ions per liter
   (c) 154 mEq each of sodium and chloride ions per liter
   (d) 174 mEq each of sodium and chloride ions per liter
6. Type II glass is called as _____.
   (a) normal glass (b) treated soda lime glass
   (c) borosilicate glass (d) soda lime glass
7. Glass ampoules are single-dose containers and can range in size from _____.
   (a) 1 ml to 50 ml (b) 1 ml to 25 ml (c) 1 ml to 40 ml (d) 1 ml to 60 ml
8. Sterility test is performed by _____.
   (a) pyrogen test (b) LAL test (c) both (a) and (b) (d) none of these
9. Dry heat sterilization is usually conducted for not less than two hours at a temperature of _____.
   (a) 100°C to 200°C (b) 150°C to 270°C (c) 100°C to 170°C (d) 150°C to 170°C
10. Administration of large amounts of nutrients to a patient who is unable to take food orally for several weeks is possible by _____.
    (a) cardioplegia solutions (b) hyperalimentation solutions
    (c) peritoneal dialysis solutions (d) irrigation solutions

ANSWERS TO MULTIPLE CHOICE QUESTIONS

1. (c)	2. (a)	3. (b)	4. (d)	5. (c)
6. (b)	7. (a)	8. (d)	9. (d)	10. (b)

Incompatibilities

9

Learning Objective

- Incompatibility and its different types

Incompatibility may be defined as mixing two or more antagonistic substances resulting in an undesirable product, which may affect the safety, efficacy and appearance of the preparation.

There are three types of incompatibilities:

1. **Physical incompatibilities:** When two or more antagonistic substances are combined together, a physical change takes place and an unacceptable product is formed due to immiscibility, insolubility or liquefaction. The changes are visible and can be corrected by an application of pharmaceutical skill to obtain a product of a uniform dosage and an attractive appearance.
2. **Chemical incompatibilities:** These are caused by pH changes, complex formation, oxidation–reduction, hydrolysis or combination reactions. These reactions are noticed by precipitation, effervescence, decomposition, color change or explosion.
3. **Therapeutic incompatibilities:** These may be as a result of prescribing certain drugs to a patient with an intention to produce a specific degree of pharmacological action, but the nature or intensity of action produced is different from that intended by the prescriber.

MIXTURES WITH PHYSICAL INCOMPATIBILITIES

Learning Objective

- Types of physical incompatibility

The following are the various types of mixtures with physical incompatibilities:

1. **Immiscibility**
   Example: Castor oil 15 ml
   Water (q.s.) 100 ml
   Incompatibility: Oil and water do not mix.
   Remedy: Carry out emulsification by the addition of an emulsifying agent, by the use of primary emulsion formula.

2. **Insolubility**
   Example: Phenacetin 3.33 g
   Caffeine 1.11 g
   Orange syrup 13.3 ml
   Water (q.s.) 100 ml
   Incompatibility: Phenacetin is an indiffusible solid.
   Remedy: Compound powder of tragacanth (2 g/100 ml of finished product) or tragacanth mucilage is used as a suspending agent.
   It increases the viscosity of the preparation and helps to maintain a uniform distribution of the insoluble substances for sufficiently long time after shaking the bottle in order to facilitate removal of a uniform dose.

3. **Liquefaction**
   Example: Menthol 130 mg
   Camphor 260 mg
   Light magnesium oxide 390 mg
   Incompatibility: When two organic substances having a low melting point are brought into physical contact with each other, they liquefy due to the formation of a new substance that has a melting point below room temperature. The reason for this change is that each ingredient acts as an impurity for the other, thereby lowering their melting point. Such substances are called *eutectic substances*.

   Example: Menthol, camphor, thymol and ammonium chloride
   Remedy: Eutectic powders may be dispensed in following two ways:
   (a) They can be dispensed as a separate set of powders with directions that one set of each powder may be taken as a single dose.
   (b) They can also be dispensed by adding a high melting point inert substance such as kaolin, starch, lactose or light magnesium oxide. These substances act as adsorbents and prevent liquefaction.

CHEMICAL INCOMPATIBILITIES

Learning Objective

- Types of chemical incompatibility

Mixtures with chemical incompatibilities are as follows:

1. **Alkaloidal salts with alkaline substances:** Alkaloids are weak bases which are slightly soluble or insoluble in water but alkaloidal salts are soluble in water. If these salts are dispensed with

alkaline preparations such as strong ammonia solution or ammonium bicarbonate, the free alkaloid may be precipitated out.

Example:	Strychnine hydrochloride solution	5 ml
	Aromatic spirit of ammonia	3.332 ml
	Water (q.s.)	100 ml

Incompatibility: Strychnine hydrochloride is an alkaloidal salt, whereas aromatic spirit of ammonia is an alkaline substance. When they both react, strychnine gets precipitated because the quantity of strychnine hydrochloride prescribed is more than its solubility in water. This preparation contains negligible amount of alcohol that cannot dissolve strychnine. Hence, it gets precipitated as diffusible precipitate.

Remedy: Divide the vehicle into two portions. The reactants are dissolved in separate portions and mixed slowly by adding one to the other with rapid stirring. The formed diffusible precipitates are uniformly dispersible with mild shaking of the contents.

2. **Alkaloidal salts with salicylates**

Example:	Quinine hydrochloride	1.2 g
	Sodium salicylate	2.4 g
	Water (q.s.)	100 ml

Incompatibility: When quinine compounds are combined with salicylates, indiffusible precipitates of quinine salicylate are formed.

Remedy: Divide the vehicle into two portions. The first reactant is dissolved in the first portion.

Suitable amount of compound tragacanth powder is weighed (2 g/100 ml of the finished product) into a mortar and triturated with the second portion of the vehicle to form smooth mucilage. The second reactant is dissolved in this mucilage and adjusted to suitable volume. The first mixture is then slowly added to the second mixture with rapid stirring.

3. **Soluble salicylates with ferric salts**

Example:	Ferric chloride solution	2 ml
	Sodium salicylate	3 g
	Water (q.s.)	100 ml

Incompatibility: Ferric salts react with sodium salicylate to liberate indiffusible precipitates of ferric salicylate.

Remedy: Divide the vehicle into two portions. The first reactant is dissolved in the first portion.

Suitable amount of compound tragacanth powder is weighed (2 g/100 ml of the finished product) into a mortar and triturated with the second portion of the vehicle to form the smooth mucilage. The second reactant is dissolved in this mucilage and adjusted to suitable volume. The first mixture is then slowly added to the second mixture with rapid stirring.

(or)

Sodium bicarbonate is added to the preparation. In the presence of sodium bicarbonate, the precipitates of sodium salicylate remain soluble to form a clear mixture.

4. **Soluble salicylates with alkali bicarbonates**

Example:	Sodium salicylate	10 g
	Sodium bicarbonate	4g
	Chloroform water (q.s.)	100 ml

Incompatibility: If sodium salicylate solutions are dispensed with alkaline substances such as sodium bicarbonate, the mixture undergoes oxidation (by absorbing oxygen) and turns

reddish brown. This does not change the therapeutic efficacy of the mixture, but may lead to anxiety in the patient.

Remedy: A dark coloring agent like liquorice liquid extract may be added.

(or)

An antioxidant such as sodium metabisulfite (0.1% w/v) can be added to prevent oxidation.

5. **Soluble salicylates and benzoates with acids**

Most acids and acid syrups decompose sodium salicylate or sodium bezoate to form precipitates of salicylic acid and benzoic acid, respectively.

Example:	Sodium salicylate	5.01 g
	Lemon syrup	25 ml
	Water (q.s.)	100 ml

Incompatibility: Lemon syrup contains citric acid. When it reacts with sodium salicylate, indiffusible precipitates of salicylic acid are formed.

Remedy: Divide the vehicle into two portions. The first reactant is dissolved in the first portion.

Suitable amount of compound tragacanth powder is weighed (2 g/100 ml of the finished product) into a mortar and triturated with the second portion of the vehicle to form smooth mucilage. The second reactant is dissolved in this mucilage and adjusted to suitable volume. The first mixture is then slowly added to the second mixture with rapid stirring.

(or)

Replace lemon syrup with a mixture of plain syrup and tincture of lemon.

6. **Incompatibility leading to evolution of CO_2**

When carbonates or bicarbonates and acidic drugs are dispensed in a mixture along with water, they react together leading to the evolution of CO_2.

Remedy: To prevent container leakage or explosion, the reaction must be completed before the preparation is transferred to the container. The ingredients are mixed in an open vessel and the effervescence reaction is allowed to complete after which it is transferred.

Example:	Sodium bicarbonate	4 g
	Borax	2 g
	Glycerol	20 ml
	Water (q.s.)	100 ml

Incompatibility: When borax and glycerol are mixed together, hydrolysis of borax takes place with the formation of boric acid.

$$\underset{\text{Borax}}{Na_2B_4O_7 + 3H_2O} \longrightarrow \underset{\text{Sodium metaborate}}{Na_2B_4O_7} + \underset{\text{Boric acid}}{2H_3BO_3}$$

Boric acid reacts with glycerol to form monobasic glyceryl boric acid.

$$\underset{\text{Glycerol}}{2C_3H_5(OH)_3 + 3H_3BO_3} \longrightarrow \underset{\text{Glyceryl boric acid}}{(C_3H_5)_2(HBO_3)_3} + 6H_2O$$

The glyceryl boric acid further reacts with sodium bicarbonate to evolve CO_2.

$$(C_3H_5)_2(HBO_3)_3 + NaHCO_3 \longrightarrow CO_2 + H_2O\uparrow$$

Glyceryl boric acid

Remedy: All the ingredients are mixed effervescence is allowed to take place and if needed slightly warmed. Once it stops, it is transferred to the container.

7. **Herapathite reaction (quinine sulfate with iodides)**

Example:	Quinine sulfate	5 g
	Dilute sulfuric acid	10 ml
	Potassium iodide	1.5 g
	Water (q.s.)	100 ml

Incompatibility: Quinine sulfate is not freely soluble in water. It is made soluble in the presence of dilute sulfuric acid. The sulfuric acid liberates hydroiodic acid from the potassium iodide. The hydroiodic acid is partly oxidized by sulfuric acid, yielding iodine.

The iodine, hydroiodic acid and quinine sulfate then combine to form a compound called "herapathite or iodosulfate of quinine". The mixture formed is quite clear at first but after about three days, it may deposit bronze or olive green scales, which are due to "herapath reaction for quinine".

Herapath reaction:

Sulfuric acid + potassium iodide $\xrightarrow{\text{Oxidation}}$ Hydroiodic acid

Hydroiodic acid $\xrightarrow{\text{Partial oxidation by Sulfuric acid}}$ Iodine

Iodine + Hydroiodic acid + Quinine sulfate $\longrightarrow$ Herapathite or iodosulfate of Quinine which occurs as bronze or olive green scales.

Remedy: To avoid any problems, it should be given to the patient only for about three days.

(or)

The mixture should be divided, sending the potassium iodide in one bottle and quinine sulfate in another bottle. The patient should be advised to mix both the solutions and take the necessary dose.

8. **Soluble iodides with potassium chlorate**

Example:	Potassium chlorate	2.22 g
	Syrup of ferric iodide	27.8 ml
	Water (q.s.)	100 ml

Incompatibility: The ferric iodide is oxidized by potassium chlorate and the reaction is as follows:

$$KClO_3 + 3FeI_3 \rightarrow 3FeOI + 3I_2 + KCl$$

Remedy: The mixture is clear when freshly prepared but deposits crystals of iodine upon storage for sometime. So, the two reacting substances must be dispensed in separate bottles with a label indicating "*Mix the contents of both the bottles before use*".

9. **Potassium chlorate and oxidizable substances (Explosive mixture):**

Example:	Potassium chlorate	0.6 g
	Tannic acid	0.3 g
	Sucrose	0.3 g

Incompatibility: When potassium chlorate (oxidizing agent) is triturated or heated with readily oxidizable substances (reducing agents) such as charcoal, sulfur or tannic acid, there are chances of an explosion.
Remedy: Potassium chlorate and tannic acid are triturated individually. Then the powders are mixed separately with half the quantities of powdered sucrose and finally they are mixed together lightly using a spatula.

THERAPEUTIC INCOMPATIBILITY

Therapeutic incompatibility arises as a result of prescribing certain categories of drugs to patients with a sole intention of achieving a specific degree of pharmacological action. However, the nature or intensity of the resultant activity is quite different from that intended by the prescriber. Therapeutic incompatibility results due to the following reasons:

1. Error in dosage form
2. Wrong dose or dosage form
3. Contra indicated drugs
4. Synergistic and antagonistic drugs
5. Drug interactions
6. Prescribing drugs with wrong direction

1. **Error in dosage form:** The errors in writing or scientific interpretation of the prescription order often leads to therapeutic incompatibilities.

   Over dosing or under dosing in dispensing medication are the most serious forms leading to therapeutic incompatibility.

   It is highly essential on the part of the pharmacist to check for the scientific correctness of the prescription before dispensing.

   Example: R_x

Atropine sulfate	0.006 g
Phenobarbitone	0.015 g
Aspirin	0.300 g

   Prepare 10 capsules

   In the given example, the amount of atropine sulfate prescribed for each capsule is more than its recommended dose, which is 0.25 to 2 mg. So, the prescription has to be referred back to the physician or prescriber to correct the dose of the atropine sulfate.

   Example: R_x

Codeine phosphate	0.5 g

   Prepare 10 powders

   Direction: One powder to be taken at bed time.

   In the given example, the physician is supposed to prescribe 5 mg but recommended 500 mg in the prescription, which is a clear indication of over dosage. The physician might have prescribed the high dose by over sight, so the prescription needs to be referred back to the prescriber to correct the over dosage of codeine phosphate.

2. **Wrong dose or dosage form:** There are number of drugs that are having identical names and pronunciation resulting in dispensing the wrong drug. This creates problem both to the physician as well as pharmacist.

Examples: prednisolone, prednisone and digoxin and digitoxin.

Also, we have drugs available in different dosage forms. So, clarity should be maintained while writing the prescription or during dispensing.

3. **Contra-indicated drugs:** Contra-indicated drugs are those which are not to be prescribed in certain disease condition or to a particular patient who is allergic to it.

   Example: As such corticosteroids do not cause peptic ulcer but may enhance the ulcer producing effect of NSAIDs in patients having a history of peptic ulcer.

   Care should be taken in case of patients who are allergic to penicillin and sulfa drugs.

   Example: R_x

Sulfadiazine	250 mg
Sulfamerazine	250 mg
Ammonium chloride	250 mg

   Direction: Take two capsules after six hours.

   Ammonium chloride which is a urinary acidifier causes deposition of sulfonamide crystals in the kidney. So, the prescription should be referred back to the prescriber for correction.

4. **Synergistic and antagonistic drugs:** There are drugs which show synergism and antagonism when administered in combination. Whenever two drugs are prescribed together, sometimes there will be an increase in the activity of each other showing synergistic activity. Such synergistic combinations are purposely prescribed by the physician to enhance the therapeutic activity of the drugs.

   Examples: Combination of antibiotics such as penicillin and streptomycin increases the antibacterial activity.

   In certain cases, drugs when administered in combinations lead to adverse reactions. In such conditions, the prescription should be referred back to the prescriber for correction.

   Example: R_x

Amphetamine sulfate	20 mg
Ephedrine sulfate	100 mg
Syrup up to	100 ml

   Make a mixture

   In this example, there are two sympathomimetic drugs that show additive effect. So, it is necessary to reduce the dose of each drug. Hence, the prescription has to be referred back to the prescriber.

   There are drugs which show antagonistic pharmacological effects when prescribed in combination.

   Example: R_x

Acetophenetidin	150 mg
Acetyl salicylic acid	200 mg
Caffeine	30 mg

   Prepare 10 capsules

   Acetophenetidin and acetyl salicylic acid are analgesics drugs. Acetophenetidin shows side effect such as central nervous system (CNS) depressant activity, caffeine acts as a CNS stimulant that neutralizes the side effect of acetophenetidin. This kind of incompatibility reaction is needed to get the desired action and hence such kind of prescription can be dispensed as it is without correction (positive antagonism).

Example: R_x

Tetracycline hydrochloride 250 mg

Prepare 10 capsules

Direction: Take one capsule every six hours with milk.

Calcium present in the milk inactivates the tetracycline present in the capsule. Hence, milk should be avoided during administration of tetracycline. This kind of prescription is an example for therapeutic incompatibility, which should be avoided. So, the prescription should be referred back to the prescriber to correct the direction (negative antagonism).

5. **Drug interactions:** Physicians today are prescribing drugs in combinations. These drugs may modify the response to each other by interactions between them.

   Example:
   (a) Prescribing ampicillin with allopurinol increases the incidence of skin rashes.
   (b) Furosemide with amino glycoside antibiotics enhances ototoricity.
   (c) Indomethacin and related drugs can reduce the antihypertensive effect of captopril.

6. **Prescribing drugs with wrong direction:** In certain prescriptions, the directions written by the prescriber makes it extremely difficult for the pharmacist as well as patient to understand and execute the prescription. Such prescriptions are deemed as wrong prescriptions.

   Examples:
   (a) **In case of tetracycline capsules**
   Direction: One capsule need to be taken for every six hours along with milk. Calcium present in the milk inactivates the tetracycline present in the capsule leading to therapeutic incompatibility.
   (b) **In case of ointment**
   Direction: To be applied two to three times in a day to eyes.
   Skin ointments are not sterilized, which is taken as prime consideration for eye ointments leading to therapeutic incompatibility.
   (c) **In case of non-sterile solutions**
   Direction: Inject 5 ml intra muscularly (i.m).
   Maintenance of sterility and isotonicity is taken as the foremost requirement for injectable formulations. So, the given examples show therapeutic incompatibility, which can be traced out easily by the pharmacists if they had gone through the prescription thoroughly and can avoid occurrence of therapeutic hazards.

REVIEW QUESTIONS

Answer in Detail

1. Define incompatibility. Explain the three types of incompatibilities.

Answer in Brief

1. What is physical incompatibility? Explain with examples.
2. Write a note on any four chemical incompatibilities.
3. What is herapathite reaction?
4. What are eutectic mixtures? How do you dispense them?

5. What are explosive mixtures? How do you dispense them?
6. Explain therapeutic incompatibility.

Answer in One or Two Sentences

1. Define incompatibility.
2. Mention the types of incompatibilities.
3. Define chemical incompatibility.
4. Define physical incompatibility.

Multiple Choice Questions

1. Liquefaction is a type of _____.
   (a) physical incompatibility (b) chemical incompatibility
   (c) therapeutic incompatibility
2. Menthol and camphor are examples for _____.
   (a) explosive mixtures (b) eutectic substances
   (c) potent drugs
3. Tetracycline is therapeutically incompatible with _____.
   (a) milk (b) water (c) juice
4. Immiscibility between two phases can be prevented by the addition of _____.
   (a) a stabilizer (b) a suspending agent
   (c) an emulsifying agent
5. Herapathite mixture is formed due to the combination of _____.
   (a) iodine, potassium iodide and dilute hydrochloric acid
   (b) quinine sulfate, potassium iodide and dilute sulfuric acid
   (c) potassium chlorate, quinine sulfate and potassium iodide

ANSWERS TO MULTIPLE CHOICE QUESTIONS

1. (a) 2. (b) 3. (a) 4. (c) 5. (b)

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Surgical Ligatures and Sutures

10

INTRODUCTION

Surgical ligatures and sutures are the threads or strings specially prepared and sterilized for use in surgery. The term ligatures is mainly applied for those used in tying of blood vessels, whereas the term sutures is applied for those used in sewing tissues together.

HISTORICAL BACKGROUND

Sutures and ligatures have been used by surgeons from a very early period for the closing of wounds and for the control of hemorrhage. Abucasis, a famous physician of the Arabian school, who lived and wrote in 1105 B.C., speaks of the use of ligatures. They were used by Galen in the Alexandrian school in the first century B.C. and were introduced into Rome by Euelpistus shortly before the time of Celsus. Even before 200 A.D., the rabbis were familiar with the use of sutures for the closure of wounds and ligatures for control of hemorrhage. During the early sixteenth century, hemorrhage was mainly controlled by cautery. In 1564, Ambroise Paré practiced the use of ligatures.

ABSORBABLE AND NONABSORBABLE SUTURES

Learning Objective

- Absorbable and nonabsorbable sutures and materials used in the preparation

Absorbable sutures are those that are broken down in the body after a period of time. The time of degradation of the material in the body varies from days to weeks. They are used for internal body tissues where the suture eventually dissolves after performing the function. The advantage in such type of sutures is that there is no foreign material left in the body and there is no need for getting the

suture removed. Absorbable sutures were originally made from the intestines of sheep or kangaroo tendon. However, absorbable sutures used now are mostly made up of synthetic polymer fibers. These have numerous advantages over the gut sutures, namely ease of handling, low cost, low tissue reactions, nontoxicity and uniformity in manufacturing.

Nonabsorbable sutures are those that are not metabolized in the body. Hence, they are mainly used on skin wound closure or in some internal tissues where the absorbable sutures are inadequate, such as the sternal closure after cardiac or orthopedic surgery. When used on external skin, they are usually removed after a few days. The primary nonabsorbable ligature and suture materials are silk, linen, silkworm gut, horse hair and wire (silver, gold and iron). Other nonabsorbable sutures are made of artificial fibers such as polypropylene, polyester or nylon. At the place of their use, a condition of encystation is produced as a result of the presence of a foreign body in the tissue, resulting in irritation and forming of pockets and sinuses.

ESSENTIAL PROPERTIES OF LIGATURES AND SUTURES

Learning Objective

- Desirable properties of surgical ligatures and sutures

1. They have to be sterile.
2. They should have adequate strength to serve the purpose for which they are used.
3. They should be non-irritant.
4. The gauge or diameter should be as fine as possible.
5. In case of absorbable material, the approximate time of absorption should be known.

ABSORBABLE SUTURES

Learning Objective

- Steps involved in the preparation of surgical catgut

Catgut

The word catgut is derived from the German word *kitgut*. "Kit" was an old German musical instrument on which gut was used as strings, hence came the word kitgut. This word gradually changed by use, language and age, and its spelling eventually changed to catgut.

Material for Preparation

The commercial catgut suture material is obtained from the small intestine of sheep. The intestines of freshly killed sheep are cleaned of their contents and are placed in cold storage or packaged in brine for transportation. The first 75 meters of the gut is chosen for the preparation of surgical catgut. The intestines are inspected for abnormalities and only suitable gut is chosen for further processing. The intestines or casings are cleaned thoroughly in water.

Removal of Unwanted Layers

The mucous, submucous and serous layers should be separated from the connective tissue. It can be done by placing the cleaned gut in a tub of cold water and allowing it to decompose, by which the gut splits into ribbons. The unwanted tissues can then be removed by scrapping with a blunt knife until only the connective tissue is left intact.

Another method is to split the intestine into two portions by means of a round blunt pointed piece of wood having razor-like blades attached to its periphery. The gut is drawn over the instrument. The intestine is split into a rough and smooth ribbon corresponding to the mesenteric and antimesentric parts of the intestine. The split gut is placed in a tub containing 1% solution of sodium bicarbonate. It is then taken and scraped by means of a machine consisting of a set of rollers, which draws the gut between a smooth cylinder below and a rapidly revolving paddle wheel above, the latter revolving in an opposite direction to the movement of the gut. The ends of the blades of the paddle wheel are provided with flexible leather flappers that beat and scrape the uppermost side of the gut. Then, the gut goes from the scraping machine into fresh sodium bicarbonate solution. This process of scraping and soaking in the sodium solution is repeated six or eight times until both sides of the gut are cleaned of everything but the submucous connective tissue. It is then bleached and disinfected by being placed in a solution of hydrogen peroxide one-third to water two-thirds, to which has been added sufficient sodium bicarbonate to render it neutral. The solution is heated to 900°F and is kept at this temperature for six hours, after which the gut is ready for twisting. When prepared in this way, the gut is free from muscle and mucous membrane or peritoneum.

This process arranges the gut fibers in a parallel way, thus greatly increasing their tensile strength.

Hardening or Tanning

The ribbon may be tanned or hardened by soaking in solutions of chromic salts. Greater the concentration of chromium salt, slower will be the digestion of the gut in the body. Thus, tanning causes a delay in the absorption of the gut in the body.

Terms such as plain, chromic and extra chromic are used to approximate the absorption time of the gut in the body. Plain gut is digested by enzymes at a faster rate than chromic gut. Deficient tanning may result in its premature absorption.

Spinning

On account of the adhesive quality of the prepared gut, it can be twisted into an almost homogeneous strand. The strips are placed in the twisting machine. The number of strips being twisted together varies according to the size of the strand to be produced. The twisting machine consists of a stationary hook to which one end of the gut is fastened and a hook in the center of a small wheel to which the other end is fastened, the gut being under slight tension. The wheel is rotated by means of proper machinery, until the gut is twisted to the correct amount.

Drying and Finishing

After twisting, the strand is dried under tension and is then sandpapered to remove the rough surface and rubbed down with emery paper. The dust is removed by washing with water, after which it is dried, gauged and made up into rolls.

Sterilization

Learning Objective

- Sterilization methods for surgical catgut

Sheep intestine may be normally infected with pathogenic spore-forming bacteria responsible for tetanus and gas gangrene. Hence, sterilization process is very essential and it should be thorough. The final sterilized gut should be checked by sterility testing.

The processed catgut can be sterilized by either of the following methods:

1. Dry heat sterilization
2. Chemical method
3. Irradiation sterilization

Heat process: Chemically, the gut consists of collagen, which if heated in the presence of moisture gets converted into gelatin. Hence, before the catgut is exposed to heat sterilization, it should be made free from moisture.

The guts of suitable lengths are coiled on heat-resisting fiber card and placed in glass tubes with labels made of heat-resistant material. The tubes are then placed in a drying oven, the temperature of which is slowly raised. Once the gut is dried thoroughly, it can be heat-sterilized by any one of the following two methods:

1. The tubes can be autoclaved at a temperature of 160°C for several hours. As water must be absent, the autoclave should contain an anhydrous fluid such as toluene or xylol.
2. Heating can also be done in a nonpressure vessel containing anhydrous fluid with a high boiling point. Here again, the temperature of 160°C should be maintained.

The tubes can then be filled with a sterile tubing fluid and sealed by fusion of the glass under strict aseptic conditions.

Chemical method: The chemical process makes use of iodine. However, immersion in iodine causes a variation in the absorption time of the suture in the body. Ethylene oxide provides a more effective means of chemically sterilizing the sutures.

Irradiation process: The gut is packed in aluminum foil envelopes containing 90% isopropyl alcohol as a preservative. The envelopes are then passed through an irradiation area on a conveyer system. Thus, the catgut is sterilized when sealed in its final container. As the process is a rapid one, there is no lengthy hold up of material as in other processes. Each suture receives a minimum dose of 2.5 megarads. The exterior of the packet can be sterilized before opening by immersion in a solution of 1% formaldehyde in 90% isopropyl alcohol.

Boilable and Nonboilable Catgut

Learning Objective

- Boilable and nonboilable catgut

Boilable surgical catgut is packed in glass tubes with the strands immersed in a water-free high boiling tubing fluid, usually xylene. The exterior of the tubes can be sterilized at the hospital by autoclaving. The disadvantage of the boilable variety is that the absence of moisture inside the tubes makes the strands very stiff. They have to be soaked for several minutes in sterile water before they become pliable for use.

The catgut labeled as *nonboilable* is contained in either a foil or plastic packet, immersed in a pliabilizing fluid, which generally consists of an alcohol or a mixture of an alcohol with a small percentage of water. The water in the tube keeps it pliable and ready for use. The outsides can be sterilized by washing in soapy water and steeping in a germicidal solution before opening the packet.

Synthetic Absorbable Sutures

Learning Objective

- Synthetic absorbable sutures used in surgery

The properties of tensile strength and absorbability can be incorporated into synthetic fibers such as polymers. Synthetic absorbable sutures do not undergo the enzymically mediated absorption process. Rather, the suture is broken down completely by simple hydrolysis. Tissue reaction is minimal since leukocytes are not involved in the absorption process.

Cargile Membrane

This is a thin sheet of pliable tissue obtained from the appendix of the steer or ox. It is designed primarily to cover the surfaces from which the peritoneum has been removed. The membranes are available in sterile sheets of approximately 4×6 inches and sometimes used as a packing or protective sheath.

Fascia Lata

This is obtained from ox fascia and is designed for use as a heavy suture or repair in hernia or similar cases. It is usually attached firmly to a strong structure by means of a nonabsorbable suture. It is supplied in the form of sterile strips approximately half an inch wide and eight inches long.

NONABSORBABLE SUTURES

Learning Objective

- Nonabsorbable surgical sutures

Natural Nonabsorbable Sutures

Silk

The most common nonabsorbable suture is a natural fiber, silk, which undergoes a special manufacturing process to make it adequate for its use in surgery. Natural silk surgical suture is a nonabsorbable, sterile, flexible multifilament thread composed of an organic protein called fibroin.

Silk sutures are made of raw silk spun by silkworms (an animal protein). Silk sutures are usually classified as nonabsorbable, but they are subjected to a slow (e.g., two years) process of proteolysis absorption. These sutures are typically available in sterile multifilament twisted or braided thread sections (e.g., 18, 30 inches/45, 76 cm long) attached to a single-use needle as an integral device and they are usually characterized by their excellent handling properties. Silk sutures are frequently available with beeswax or silicone coating and they are frequently colored for easy identification during surgery. Their intended use includes suturing of internal organs and tissues; noncoated silk sutures are usually intended for ophthalmic surgery.

Dermal Silk

Dermal silk sutures are braided silk threads encased in an insoluble coating of tanned gelatin or other protein. The purpose of the coating is to prevent ingrowth of tissue, which makes it difficult to remove the suture later. The coating should not undergo stripping at the time of autoclaving.

Synthetic Nonabsorbable Sutures

Nylon

Synthetic sutures consist of nylon fibers made from nonabsorbable (i.e., nonbiodegradable) aliphatic (e.g., polyamide 6) polymers. These sutures are typically available in sterile coated thread sections (e.g., 18, 30 inches/45, 76 cm long) attached to a single-use needle as an integral device and they are frequently colored for easy identification during surgery. Nylon sutures keep their tensile strength for very long periods of time and they are water resistant. Nylon is not absorbed, but hydrolysis may result in the gradual loss of tensile strength over time. The intended use of nylon nonabsorbable synthetic sutures includes general soft-tissue approximation and suturing of internal organs and tissues.

Polyester Fiber

Polyester fibers are synthetic braided nonabsorbable sutures that do not lose strength upon contact with water or other body fluids. They do not contain wax or other additives and have excellent knot-holding properties. They are available in the natural color or dyed to enhance visibility in the surgical field.

Coated polyester fibers are available, which have a smoother finish thus permitting easy and gentle passage through tissues.

Metallic Sutures

Stainless steel sutures are available in monofilament, braided or twisted forms. They are made of fully softened stainless steel wire. They are nonirritant, have high tensile strength in fine gauge and are found useful in plastic and orthopedic surgeries. They are readily sterilized.

SURGICAL DRESSINGS

Learning Objective

- Study of surgical dressings
- Desirable features of a surgical dressing

Surgical dressings are mainly applied on the skin in case of injury or wounds. During any damage to the skin, the wound gets plugged with a blood clot, which is a form of natural first aid that prevents any further loss of blood or damage to the injured part. The skin is then repaired by the formation of fibrous and vascular tissues and migration of epidermal cells from the edges of the wound to cover the granulation tissue. This natural mechanism of the skin is sometimes impeded by infection of the wound by pathogens or repeated abrasion of the new epidermis. The outermost layer of the skin is composed of dead, dehydrated and keratinized skin. For proper dehydration and keratinization, evaporation of water is essential.

Surgical dressing or *curatio* is a term applied to a wide range of materials used for the dressing of wounds. They are used as coverings, absorbents, protective or supports for injured or diseased tissues.

Keeping in mind the nature of skin and the mechanisms involved in the repair of a damaged skin, the following features are required for an ideal dressing:

1. Should be water permeable in order to allow evaporation of sweat and exudates from the injured tissue
2. Should allow easy movement of the joints
3. Should be made up of a nonirritant material and should not induce any hypersensitivity reactions
4. Should be absorbent in nature, in order to absorb any fluids or secretions
5. Should not stick to granulating surfaces and the pore size should be less than 8 μm in order to prevent penetration by capillaries
6. Should provide an effective barrier for microorganisms and should be readily sterilized
7. Should have sufficient tensile strength
8. The physical properties such as tensile strength and color should not vary upon normal conditions of storage.
9. Should not have an abrasive surface, which may damage the healing skin
10. Should permit lamination by adhesives when sealing to the skin is desired. It should also be easily removable without skin damage.

Some terms used in connection with surgical dressings

***Count*:** The count of a yarn is the number of hanks, each of a specified length, in one pound, and is therefore a measure of its fineness. A hank of cotton measures 840 yards and that of wool 560 yards.

***Crepe weave*:** This produces an elastic effect due to the fact that alternate threads in the fabric are highly twisted in opposite directions.

***Fast edge*:** The edge is woven in such a way that it prevents threads from becoming loose.

***Fillers*:** These are substances such as china clay added to the fabric in order to give it a desired finish or appearance.

***Moisture regain*:** This is the difference in moisture content between dried material and material under standard humidity conditions.

***Nap*:** This is the soft, fluffy surface on a fabric produced by mechanical brushing so that the ends of numerous fibers are exposed.

***Neps*:** These are small knots on fibers caused by uneven growth or formed mechanically in processing.

***Plain weave*:** This is a weave in which the threads pass alternatively over and under the threads running at right angles.

***Plasticizers*:** These are substances (solvents) giving plasticity or fluidity to a rubbery mass.

***Raised fabric*:** This is a fabric on which a nap has been produced.

***Selvedge*:** This is a fabric edge so woven that it is fast, that is, the threads do not become loose.

***Slubs*:** These are the thick soft parts of a yarn.

***Snarls*:** These are loops protruding from the fabric due to insufficient tension on the yarn in weaving.

***Staple*:** This is an alternative term for fiber.

***Tackifiers*:** These are resins, both natural and artificial, used to give adhesiveness to a rubbery mass.

***Tissue*:** This is a dressing composed of a layer of fibers, such as cotton wool, enclosed in gauze.

***Twist*:** This refers to the direction of twisting the fibers in spinning yarn. The effect may be intensified for special purposes. For example, in crepe bandage, twist to the right and left is described as 'Z' and 'S' twist, respectively.

***Union fabric*:** This is a fabric composed of two kinds of yarn, for example, wool and cotton.

***Warp*:** This is the yarn running the long way of the fabric.

***Weft*:** This is the yarn running across the fabric.

***Yarn*:** This is the thread spun from the fibers.

CLASSIFICATION OF SURGICAL DRESSINGS

Learning Objective

- Different classes of surgical dressings

The dressings may be classified into the following types:

1. Fibers, plain and medicated
2. Fabrics, plain and medicated

3. Bandages
4. Self-adhesive plasters
5. Compound dressings

FIBERS

The most common fiber used in surgical dressings is cotton. Regenerated cellulose, wood fibers and wool are also used. Cotton also forms the basis for most of the surgical dressings such as gauze, lint, bandages and plasters.

Absorbent Cotton Wool (*Gossypium Absorbens*; Syn. Absorbent Cotton, Absorbent Wool)

Learning Objectives

- Method of preparation of absorbent cotton wool
- Standards for surgical cotton
- Uses of surgical cotton

Cotton is obtained from the epidermal trichomes from the seeds of cultivated species of *Gossypium.* The hairs or trichomes are separated from the seed by a process called ginning. The trichomes in their natural state are covered with a waxy substance, which makes it nonabsorbable in nature. The fibers are defatted by boiling in alkali under pressure. This process saponifies the fat. The saponified fat is then washed and the fibers are bleached until they are white. It is then treated with dilute acid until it is free from all coloring matter. The fibers are now in a tangled state. They are mechanically combed, which arranges them in a more uniform manner. This process of defatting and bleaching gives a clean, white, fleecy product called "cotton wool."

Standards: The following standards are specified for cotton wool in the British Pharmaceutical Codex (BPC):

1. The fibers should be well "carded," that is, untangled by combing process.
2. It should be well bleached to obtain a white product.
3. It should be free from pieces of thread.
4. It should be reasonably free from leaves and shell from the plant or seed coat.
5. It should be reasonably free from dust, that is, particles of fiber and foreign matter.
6. The quality should be the same throughout.
7. It should offer appreciable resistance when pulled.
8. The average length of the fiber is five-eighths of an inch.
9. It should contain no more neps than the sample kept at the Manchester Testing House.
10. **Absorbency test:** 1 g of cotton compressed to a volume of about 20 ml is placed lightly by means of forceps on the surface of water at 20°C. It should sink or become saturated within 10 s.
11. The fibers should not turn brown or show appreciable signs of disintegration on heating to 110°C for 20 min.

12. **Acidity test:** A solution of bromocresol green should not become distinctly yellow when sprinkled over cotton.
13. **Oxidizing substances:** When 1 g of cotton is immersed in a solution of 0.5 g of cadmium iodide and 10 drops of glacial acetic acid in mucilage of starch, no blue color should develop.
14. Water-soluble extractive is limited to 1.5%.
15. The ash limit should not be more than 0.5%.

Uses:

1. It is used for absorbing wound exudates.
2. It is used for cleaning, swabbing and medicating wounds and for applying bactericidal solutions to the skin before surgery.
3. A thick layer of cotton wool is light in weight but provides good physical protection to the wound by providing warmth to the area and is a useful barrier to organisms.

Since cotton wool consists of loose fibers, it may stick to wounds and raw surfaces. Hence, the fibers have to be separated from the wound with the help of woven fabrics.

Learning Objective

- Other fibers used in the preparation of surgical dressings

Wool (*Lana*; Syn. Animal Wool)

Wool consists of the hairs from the fleece of the sheep *Ovis aries*. The hairs are coated with wool fat. It is removed by kneading in water, where the fat gets emulsified with water. This process also helps in washing other impurities.

It is marketed as yellowish-white, continuous, slightly twisted and coherent pieces. It is highly hygroscopic and can absorb 50% of its weight of water.

Uses: Wool is used in chiropody (treatment of the feet). Since it adheres strongly to lesions, it should not be directly applied to open wounds.

Cellulose Wadding (*Cellulosum Ligni*)

Cellulose wadding is prepared from timber (usually pine). The wood is disintegrated to separate the fibers. It is then treated to remove the lignin and bleached to obtain a white product. It is then compressed into sheets and rolled.

Uses: This is used as an absorbent and protective either alone or in combination with other materials such as gauze.

Rayon (Syn. Regenerated Cellulose)

Rayon is obtained from the wood of the spruce tree. The timber is freed from the bark. It is treated chemically to remove resins, washed and bleached. This mass of white fibers is converted into alkali

cellulose by maceration with caustic soda. This is shredded, further soaked in alkali and shredded into crumbs. It is then treated with carbon disulfide to form cellulose xanthate and further dissolved in a weak caustic soda solution, to obtain viscose rayon. The solution is filtered and sprayed into an acid bath, where the viscose solidifies in the form of filaments. These filaments are twisted to form a thread and then spun into yarn.

The fibers can be given a matte appearance by dispersing finely divided titanium dioxide throughout the material. This product is known as delustered regenerated cellulose. However, titanium dioxide may delay wound healing.

Uses: Rayon or delustered rayon can be used to replace cotton partly or entirely, in a number of dressings. Lustrous regenerated cellulose (absorbent cotton wadding) is used for cleaning, swabbing and medicating wounds and for skin disinfection.

Compared with cotton, rayon is cheaper. It is cleaner, more pliable and softer. Its absorbency is not lost on storage.

FABRICS

Learning Objective

- Different fabrics used as surgical dressings

Surgical fabrics are woven from good quality cotton, wool or silk, which are free from foreign material. They are usually of plain weave.

The BPC describes certain standards for surgical dressings, which include the determination of moisture retention, count, thread per inch, weight, tensile strength, foreign matter, water-soluble extractives, elasticity and absorbency.

Absorbent Gauze

This is a cotton fabric of plain weave. It is of open texture, soft and flimsy appearance. It is 36 inches wide with selvedge edge and is supplied in various lengths.

Uses: As it does not contain loose fibers, it can be directly applied on wounds. It is absorbent in nature but requires several layers to absorb exudates and to provide any physical protection effectively. It is used for draining exudates from wounds after surgery.

Absorbent Ribbon Gauze (Syn. Unmedicated Ribbon Gauze)

Absorbent ribbon gauze is similar to absorbent gauze but with a finer texture. The weft may be cotton, rayon or both. It is supplied in the form of ribbons, wound on spools or packaged in bottles.

Uses: It is used for absorption of exudates and removal of pus and other debris without causing excessive damage to the tissues. It is used to pack dental sockets, sinuses and infected wounds.

Absorbent gauze can be made x-ray detectable by attaching an x-ray detectable strand consisting of barium sulfate. It is used in surgery, and when accidentally left behind in the body, it can be detected radiologically.

Paraffin Gauze Dressing (Tulle Gras Dressing)

This is a sterile dressing consisting of a number of pieces of cotton, rayon or cotton and rayon cloth. It is impregnated with yellow soft paraffin or soft and hard paraffin. Tulle gras dressing consists of leno fabric impregnated with soft paraffin, balsam of Peru and olive oil. When lifted with forceps, it does not curl, but remains stiff because of a kind of special weave called leno weave used in its preparation. This weave has an interlocking effect.

The dressing is sterilized by heating at 150°C for one hour or by autoclaving at 125°C for 30 minutes. The sterilization should be done in a container that can withstand the sterilization process.

Uses: This dressing is used in skin grafting operations and for treating burn, scalds and other wounds.

Absorbent Lint

It is available in both medicated and unmedicated forms. It is made up of cotton and the warps on one side are raised by brushing to give the dressing a softer feel and look. This also increases its absorbency. Apart from the requirement of the other standards, the BPC also specifies that the fabric must be tearable in both directions.

Uses: It is popular for first aid purposes. It is used for applying topical medications and externally as an absorbent and protective dressing.

Euflavine Lint

Euflavine belongs to acridine group of antiseptics. Euflavine lint is absorbent lint medicated with euflavine by immersing it in the solution of the dye. It is pressed and dried.

Uses: It is used in the first aid treatment of burns.

Boric Acid Lint

It is a medicated absorbable lint containing 3% to 7% of boric acid.

BANDAGES

Learning Objectives

- Different types of elastic and nonelastic bandages
- Different types of adhesive and nonadhesive bandages

Bandages are used to hold dressings in place by providing pressure or support. They may be inelastic or elastic or become rigid after shaping for immobilization. Bandages are prepared in varying length. They form one continuous length without joints. Edges are cut parallel to the warp and there are no loose ends. Bandages may be nonelastic or elastic.

Nonelastic Bandages

Triangular Calico Bandage

It is made up of unbleached calico. It is shaped in the form of a right-angled isosceles triangle. The warp and weft are parallel to the two equal sides.

Uses: It is used as sling. If used in contact with broken skin, it needs to be sterile.

Open Wove Bandage

It is made up of plain weave. Here, the weft contains more threads per centimeter than the warp, and hence, it is heavier.

Uses: It is used in first aid. Because of the presence of heavy wefts, it is used to give additional protection to dressings, for support and immobilization, and to secure splints into the body.

Domette Bandage

This fabric consists of two kinds of yarn. The warp is cotton and the weft is wool. The presence of wool provides additional warmth.

Uses: It is used for orthopedic purposes and in regions that need to be kept warm.

Elastic Bandages

The elasticity in the bandage can be produced by twisting threads, by using rubber threads or by crimping. These bandages are usually tinted to a light flesh color using a suitable nontoxic dye.

1. The elastic bandages produced by twisting of threads include crepe bandage, cotton crepe bandage and cotton stretch bandage. Elastic bandage is an elastic fabric of plain weave in which the warp threads are of cotton and wool and the weft threads are of cotton. This bandage conforms well to sprains and strains. It is used for correctional purposes and as a compression bandage.

   In cotton crepe bandage, the weft is of cotton, rayon or a combination cotton and rayon yarn and is used for correctional purposes.

   In cotton stretch bandage, both the warp and weft are cotton and is used for securing and protecting the dressing.

2. Elastic bandages produced by using rubber threads include cotton and rubber elastic bandage and cotton and rubber elastic net bandage. The cotton and rubber elastic bandage contains weft made of rubber threads and is used for correctional purposes, for providing support to sprains and strains, and for compressional purpose.

   The cotton and rubber elastic net bandage is one where both the weft and warp are elastic. The weft threads are of combined cotton and rubber yarn. The weft threads are of well-mercerized cotton.

3. Cotton conforming bandage is a type of elastic bandage where the elasticity is produced by crimping. Well-mercerized cotton is used for both the warp and the weft. This gives the fabric an elastic nature, which is used for protecting and securing dressings.

Impregnated Bandages

Learning Objective

- Types of impregnated bandages

Table 10.1 provides a list of various impregnated bandages along with the impregnating substances and their uses.

Table 10.1 Impregnating Substances and Uses of Impregnated Bandages

Name of the Bandage	*Impregnating Substance*	*Use*
Plaster of Paris bandage	Dried calcium sulfate (mixture of amorphous and crystalline forms), suitable adhesives (methyl cellulose and hypromellose).	As a splint. It is moistened with water and applied to the limb or body where it sets.
Zinc paste bandage	Zinc oxide	To prevent swelling of fractured limbs after removal of the plaster, to support varicose veins and to treat ulcers, varicose eczema, phlebitis and edema of the legs
Zinc paste and coal tar bandage	Zinc oxide and coal tar or ichthammol	In eczema and leg ulcers

Adhesive Bandages

Adhesive bandages contain an elastic fabric spread with an adhesive mass. The bandage is held firmly in place by the adhesive and can be used for ambulatory patients. The elastic nature of the bandage does not restrict body movement.

Learning Objective

- Types of adhesive bandages

Various adhesive bandages and their uses are listed in Table 10.2.

Table 10.2 Types of Adhesive Bandages and their Uses

Name of the Bandage	*Type*	*Use*
Diachylon elastic adhesive bandage	Lead-based (should be warmed before use for adhesion)	For treatment of chronic leg ulcers and support of varicose veins
Zinc oxide elastic self-adhesive bandage	Self-adhesive (contains an adhesive and can adhere to the skin without warming)	To secure dressings firmly in place and to support fractures, ribs, varicose veins and sprains

SELF-ADHESIVE PLASTERS

Self-adhesive plasters consist of self-adhesive mass spread on a supporting material such as an elastic cloth or a plastic film. They are used in strips to cover a smaller restricted area. The supporting material may be tinted with flesh color. Table 10.3 lists the various types of self-adhesive plasters with examples and their uses.

Table 10.3 Self-adhesive Plasters with Examples and Uses

Support	*Example*	*Use*
Plain cloth	Belladonna self-adhesive plaster	Counterirritant in rheumatism, sprains and low back ache
	Salicylic acid self-adhesive plaster	Keratolytic
	Zinc oxide self-adhesive plaster	To secure dressings and to immobilize small areas
Elastic cloth	Extension plaster	To support light sprains and fractured ribs and to support joints and limbs after removing plaster cast
	Zinc oxide elastic self-adhesive plaster	To secure dressings
Plastic film	Perforated plastic self-adhesive plaster	To cover sites of infection and to secure dressings
	Waterproof plastic self-adhesive plaster	To provide waterproof covering for sites of infection and to secure dressings
	Waterproof microporous plastic self-adhesive plaster	To cover sites of infection when free passage of air and water vapor is required

COMPOUND DRESSINGS

Learning Objective

- Different types of compound dressings

Compound dressings include *tissues*, *wound dressings* and *standard dressings*.

1. Tissues consist of a layer of fibers enclosed in a tube of gauze. They are used as protective and absorbent pads.
   Examples are gauze and cotton tissue and gauze and cellulose wadding tissue.
2. Wound dressings are composed of an absorbent pad attached to an adhesive plaster. They are used as protective covers for wounds.
   Examples are elastic adhesive dressing and waterproof plastic wound dressing.
3. Standard dressings are sterile dressings used for first aid treatment. They are packed individually in a double wrapper. The inner wrapper is sealed before sterilization and the outer is designed to be easy to tear open.
   Examples are plain lint finger dressing and eye pad with bandage.

BLOOD AND RELATED PRODUCTS

Blood serves a vital set of physiological functions in the body. It is a unique tissue and the composition of this circulating body fluid is an important indicator of cellular ion and metabolic status. Blood can be withdrawn from the body and the different components present in the blood can be separated and used in therapy.

The discoveries of blood groups by Landsteiner in 1900 and the nontoxic anticoagulant sodium citrate by Hustin in 1945 opened the way for rapid advances.

Use of Blood and Blood Components

Learning Objective

- Use of blood and blood components

When blood has been lost by hemorrhage or during accidents, whole blood is required for replacement. In some disease conditions and in emergency situations, the administration of a single component in concentrated form results in a far better response than the administration of that component as whole blood. By using specific parts of the blood, the supply of blood can be used more economically.

The red cells are used for the treatment of anemia, albumin for the treatment of shock, immunoglobulin for the prophylaxis of certain infectious diseases, and granulocytes for the treatment of granulocytopenia. The plasma present in the blood act as a vehicle for the transport of most nutrients and drugs. Electrolytes and many small organic compounds found in the plasma are freely exchanged with both the lymph and the intestinal fluids. Some of the plasma proteins are involved in the clotting of blood. The erythrocytes present in the blood are involved in oxygen and carbon dioxide transport. Leukocytes play a major role in the defense against microbes and protect the body against infection. Platelets exert a variety of important functions in hemostasis and in response to injury.

Official Products

Learning Objectives

- Different official blood products
- Collection, storage and uses of different blood products

1. Whole human blood
2. Concentrated human red blood corpuscles
3. Dried human plasma
4. Dried human serum
5. Human plasma protein fraction
6. Human fibrinogen
7. Human thrombin
8. Human fibrin foam
9. Human normal immunoglobulin injection

Whole Human Blood

This is human blood that has been mixed with a suitable anticoagulant. The use of anticoagulant mixtures such as ACD (acid citrate dextrose) and CPD (citrate phosphate dextrose) extends the useful life

of the red cells. If stored under proper conditions, the blood can be safely used within a period of 21 days after collection.

To be accepted as a donor, a person should be in good health and should not be suffering from any disease such as AIDS, syphilis, malaria, jaundice and anemia. The hemoglobin content of the blood should not be less than 12.5 for female donors and 13.5 for male donors.

Collection: The blood is collected aseptically from the median cubical vein in front of the elbow into a sterile container containing an anticoagulant solution (acid citrate dextrose, citrate phosphate dextrose or citrate phosphate dextrose with adenine). During collection, the bottle is gently shaken to ensure that the blood and the anticoagulant are mixed well to prevent the formation of small fibrin clots. A volume of 420 ml is taken at one time. The collected whole blood is handled carefully, sealed and stored at 4°C–6°C without further processing and testing. Whole blood from which the antihemophilic factor has been removed is designated as modified whole blood.

The container used for taking blood is made of plastic and is disposable. Plastic bags or blood bottles manufactured for the purpose of collecting and storing blood are used.

Concentrated Human Red Blood Corpuscles

The product is obtained by removing the citrated plasma from the whole blood that has been allowed to stand or has been centrifuged to deposit the cells. The supernatant liquid is removed under aseptic conditions. The cells are matched with the recipient's plasma and may then be mixed with matched cells from other bottles. The hemoglobin content must not be less than 15.5. The product must be used within 12 hours since there is a risk of bacterial contamination.

Uses: The product is used when the administration of whole blood is not necessary as in treatment of diseases such as chronic anemia. Large amounts of citrate are given with whole blood transfusions, which might lead to citrate toxicity in infants. Hence, red blood corpuscles are used in such cases.

Dried Human Plasma

Preparation: Dried plasma is usually prepared from time-expired citrated blood. The supernatant fluid is separated from the blood by centrifugation process under aseptic conditions. Batches of not more than 10 bottles are pooled, choosing the correct ratio of blood groups to neutralize powerful agglutinins. The pools are kept at 4°C–6°C. Samples from the batch are tested for sterility and no pool is used unless it passes the test. Usually, 400 ml quantities are dispensed into bottles and subjected to freeze-drying.

The steps involved in the freeze-drying process are as follows:

1. **Preliminary freezing:** The bottles are sealed with bacteriologically efficient fabric pads covered by ring-type closures and then centrifuged at −18°C. The liquid snap-freezes and becomes distributed around the inside of the bottle.

2. **Primary drying:** The bottles of frozen material are mounted horizontally in the drying chamber and a high vacuum is applied. The ice sublimes on to a condensing coil kept at −50°C, and the heater provides the latent heat required for evaporation. This process takes about two days, after which the residual moisture content is about 2%.

3. **Secondary drying:** This drying operation is done in another chamber by vacuum desiccation over phosphorus pentoxide. The drying process takes about 18 to 20 hours and the product is left with about 0.5% of moisture.

The fabric seal is then replaced by a closure perforated by a plugged hypodermic needle. The bottles are returned to the secondary drying chamber and re-evacuated, and then the vacuum is broken with dry sterile nitrogen. Finally, the needles are removed and the closure is protected with a sterile viscose cap.

Storage: Dried plasma should be kept below 20°C and protected from light, moisture and oxygen. Under proper storage conditions, it has an expiry date of about five years. After reconstitution, it must be used immediately. Gel formation or incomplete solution indicates deterioration.

Uses: The following are some of the uses of dried plasma:

1. Reconstituted plasma is a satisfactory alternative to whole blood in conditions where there is no loss of red cells.
2. It is important in the treatment of severe burns and scalds.
3. Because of its long storage life at convenient temperature, dried plasma is more suitable than blood as a reserve stock.

Advantages: Dried plasma has the following advantages:

1. If properly stored, it can be used for four to five years.
2. It can be stored at temperature below 20°C if protected from light.
3. It can be given to patients of any blood group.

Dried Human Serum

This is prepared in the same method as dried plasma except that the blood is collected into dry bottles and allowed to clot. The supernatant serum is separated after the clot has retracted.

Storage and use are the same as for dried plasma.

Human Plasma Protein Fraction

Human plasma protein fraction is a solution of some of the proteins from liquid plasma. It contains albumin and certain globulins that retain their solubility on heating. It is prepared by fractionating pooled citrated plasma. Figure 10.1 shows the ether fractionation of plasma.

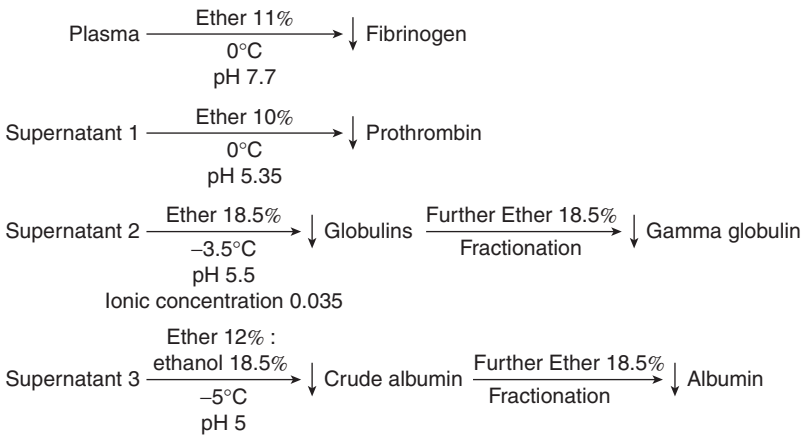

Figure 10.1 Ether Fractionation of Plasma

A stabilizer such as sodium caprylate or acetyl tryptophan is added to the human plasma protein fraction. This allows the preparation to be heated for several hours at a low temperature without significant denaturation of the proteins. Sodium chloride is added to make the preparation isotonic. The solution is sterilized by filtration aseptically, distributed into blood bottles and then heated at 60°C for 10 hours to destroy the viruses of infective hepatitis and homologous serum jaundice.

The fractionation process involves concentration of the albumin fraction. The concentration of sodium citrate is limited to 0.4%, which is not harmful. The protein content is not less than 4.3% w/v, and the product exerts a colloidal osmotic pressure approximately equivalent to that of pooled liquid plasma containing 5.25% w/v of protein.

Storage: It must be stored between 5°C and 20°C and protected from light. The preparation remains clear as the fibrinogen has been removed.

Human Fibrinogen

Fibrinogen is the soluble constituent of plasma and when thrombin is added to it, fibrinogen is converted to fibrin. After separation from plasma by fractionation, the precipitate is collected by centrifugation, dissolved in citrate saline and freeze-dried. The air in the containers is displaced by nitrogen.

The citrate prevents spontaneous clotting when the material is reconstituted. Fibrinogen dissolves slowly. However, like many of the protein solutions, it froths badly if shaken and the solid-stabilized foam is very slow to disperse. Hence, agitation should be done in a gentle manner. The solution should be used immediately or within three hours of preparation.

Uses: Fibrinogen is administered alone to treat fibrinogen deficiency, but more often it is used in conjunction with thrombin.

Human Thrombin

Thrombin is the enzyme that converts fibrinogen to fibrin. The prothrombin obtained from the fractionation of plasma is washed with distilled water and dissolved in citrate saline. It is converted to thrombin by adjusting the pH to 7 and by adding thromboplastin and calcium ions. The solution is filtered and freeze-dried, and the air in the containers is replaced with nitrogen. It is reconstituted with saline when required.

Uses: The fibrin clot produced when thrombin is mixed with fibrinogen is used in surgery to suture severed nerves and to assist adhesion of skin grafts. Since the fibrin is human, it is tolerated well by the body and new cells penetrate it rapidly.

Human Fibrin Foam

This is a sponge-like mass of human fibrin. It is prepared by whipping a solution of fibrinogen into froth by mechanical means and then adding thrombin. The product is poured into trays and freeze-dried. Then, it is cut into pieces of convenient size and sterilized by dry heat at 130°C for three hours.

Storage: Human fibrin foam should be kept below 20°C and protected from light, moisture and oxygen. It need not be kept under nitrogen.

Uses: It is used with thrombin as a hemostat in surgery. A piece is dipped into thrombin solution and applied to the bleeding area. The combination of thrombin and the large rough surface provided by the sponge causes the blood to clot. The foam can be left in situ where it will be absorbed, because it is entirely of human origin.

Human Normal Immunoglobulin Injection

Immunoglobulin or gamma globulin is obtained from the globulins fraction separated during the final stage of fractionating the plasma. Figure 10.2 shows the fractionation process.

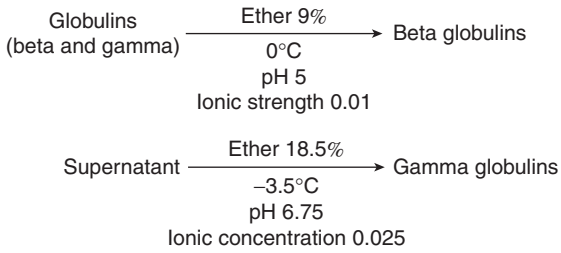

Figure 10.2 Fractionation of Immunoglobulins or Gamma Globulins

The immunoglobulins are dissolved in a suitable solvent, usually 0.8% sodium chloride solution, and a preservative, such as 0.01% of thiomersal, is added. The solution is sterilized by filtration and packed in single-dose containers.

Storage: The solution should be stored at 4°C–6°C, with protection from light.

Sterility and Pyrogens

All blood products must comply with the official tests for sterility and those preparations that are exposed to special risk of contamination with pyrogens due to lengthy processing must also pass the pyrogen test.

Plasma Substitutes

The limited supplies of plasma, the cost of producing the dried form, and the risk of transmitting serum hepatitis stimulated the attempts to find substitutes of nonhuman origin that could be used to restore the blood volume temporarily while the recipient replaced the lost protein.

Properties of an Ideal Plasma Substitute

Learning Objective

- Properties of an ideal plasma substitute

The following should be the properties of an ideal plasma:

1. It must have the same colloidal osmotic pressure as whole blood and viscosity similar to that of plasma.
2. Its molecular weight should be such that the molecules do not easily diffuse through the capillary wall.
3. It should have a fairly low rate of excretion or destruction by the body and should be nontoxic.
4. It should be free from antigenicity and pyrogenicity.

5. It should have the same isotonicity as that of blood plasma.
6. It should have stability in liquid form at normal and sterilizing temperatures and during transport and storage.

Learning Objective

- Different plasma substitutes and their uses

Dextran

Dextran is the most satisfactory plasma substitute. It is a polysaccharide produced when the bacterium *Leuconostoc mesenteroides* is grown in a sucrose-containing medium. The organism secretes an enzyme that converts to dextran according to the following equation:

$$\text{n sucrose} \xrightarrow{\text{dextran-sucrase}} \underset{\text{(Dextran)}}{\text{n(glucose}-H_2O) + \text{n fructose}}$$

Different strains produce dextrans of two main groups:

1. Long, practically unbranched chains of glucose units joined by 1:6 glucosidic linkages
2. Highly branched polymers consisting of short chains of 1:6 units joined by 1:4 and 1:3 linkages to branches

Branched chains are more likely to give rise to allergic reactions when injected, and when used for plasma substitutes in dextran, the linkages should be almost entirely of the 1:6 type. This is achieved by choosing a suitable specially developed strain of the organism that produces dextran in which about 95% of the linkages are 1:6.

Dextran 40 injection: A number of conditions, including severe burns, crush injuries and acute peritonitis are accompanied by a severe degree of sludging in the blood. This can be reduced by the administration of Dextran 40 injection, which because of the presence of polymers of low molecular weight, lowers plasma viscosity and improves capillary flow. Both these changes reduce cell aggregation, which in turn further improves the flow.

A crude dextran of low molecular weight is manufactured by including very small template molecules in the fermentation medium. Then fractionation is used to produce the clinical material, which has an average molecular weight of 40,000.

Absorbable Hemostats

These materials are used to control bleeding when it cannot be checked by more conventional means. They are gradually absorbed by the tissues; therefore, if used during surgery, they can be left in the body when the incision is closed, and if applied to a surface wound, they need not be removed when the dressing is changed. There are four important types of absorbable hemostats, namely *human fibrin foam*, *gelatin sponge*, *oxidized cellulose* and *calcium alginate*. Fibrin foam is the most acceptable one because it is of human origin and is particularly well tolerated by the tissues, but its supplies are limited.

Absorbable Gelatin Sponge

This is prepared by adding a small percentage of formaldehyde to a warm solution of gelatin, which is then whisked into a foam and freeze-dried. The porous product is cut into pieces of suitable size and sterilized by dry heat at 140°C. When pressed tightly onto a bleeding area, blood is taken up and clotting is encouraged by the large rough surface, which causes platelet disintegration. The sponge also acts as a plug by sticking to the underlying tissues and mechanically supporting the clot over the oozing vessels.

The sponge is nonantigenic and tissue reactions have been mild. The standards include a test for digestibility in acid pepsin solution. Since some microorganisms liquefy gelatin, it should not be used in septic wounds, nor is it suitable for arresting hemorrhage from large wounds. It is marketed as white or near-white, rectangular, very porous pieces that are extremely light and have a papery feel.

Oxidized Cellulose

Cellulose can be converted into polyanhydroglucuronic acid, an absorbable hemostatic material, by oxidation with nitrogen dioxide. Oxidation is carried out on the fabricated dressing and involves conversion of about 20% of the primary alcohol groups to carboxyls. Sterilization by formaldehyde is used because heat causes serious deterioration.

The material has the appearance of the original dressing, except that it may be less white in color and has a faint odor and acid taste. Its hemostatic activity may be partly due to the chemical reaction between the polyuronic acid and hemoglobin or other blood proteins. However, the fabric also acts as a scaffolding for clot formation and a plug at cut ends of the vessels. It is more effective if used dry.

Calcium Alginate

This is derived from alginic acid, a colloidal substance obtained from the sea weeds *Laminaria digitata* and *Laminaria cloustoni*. Alginic acid is a polyuronide built up from d-mannuronic acid units. Its carboxyl groups react with metallic ions to form alginates. Since the parent acid is unstable, the water-soluble sodium salt is used as the source of other alginates. If ionized calcium salt is added to sodium alginate solution, instantaneous precipitation of calcium alginate occurs, which is a sensitive reaction that can be used for preparing foams, fabrics and other physical forms. These can be sterilized by autoclaving or dry heat.

Calcium alginate dressings have a marked hemostatic effect. By including a small proportion of sodium alginate the hemostatic effect can be increased and it can be used to arrest the external bleeding, e.g., from surgical incisions, tooth sockets and sites from which grafts have been taken. A transparent protective film can be made *in situ* over a burn, wound or incision by applying a solution of sodium alginate and then spraying with calcium chloride solution. This film is impervious to water but permeable to water vapor.

REVIEW QUESTIONS

Answer in Detail

1. What are the different steps involved in the preparation of surgical catgut?
2. What is the method of preparation of absorbent cotton wool?
3. Explain the different fabrics used as surgical dressings.
4. Explain the collection, storage and uses of different blood products.
5. List the different plasma substitutes and their uses.
6. Explain the different official blood products.

Answer in Brief

1. What are absorbable and nonabsorbable sutures?
2. What are the kinds of materials used in the preparation of absorbable and nonabsorbable sutures?
3. What are the desirable properties of surgical ligatures and sutures?
4. Explain the sterilization methods for surgical catgut.
5. What is 'boilable' and 'nonboilable' catgut?
6. What are the nonabsorbable surgical sutures?
7. What are surgical dressings?
8. What are the desirable features in a surgical dressing?
9. What are the different classes of surgical dressings?
10. What are the standards for surgical cotton?
11. What are the uses of surgical cotton?
12. What are the other fibers used in the preparation of surgical dressings?
13. What are elastic and nonelastic bandages?
14. What are adhesive and nonadhesive bandages?
15. Give examples for a few impregnated bandages.
16. What are the different types of compound dressings?
17. What is the use of blood and blood components?
18. List the different official blood products.
19. What are the properties of an ideal plasma substitute?
20. What is absorbable gelatin sponge?

Answer in One or Two Sentences

1. What are absorbable sutures? Give examples.
2. What are nonabsorbable sutures? Give examples.
3. What is the raw material used in the preparation of surgical catgut?
4. How are the catgut fibers tanned or hardened?
5. Why should the gut be freed from moisture before it is exposed to heat sterilization?
6. What are the advantages of irradiation sterilization for catgut?
7. What are boilable sutures?
8. What are nonboilable sutures?
9. Give examples for synthetic absorbable sutures.
10. Give examples for synthetic nonabsorbable sutures.
11. What are 'warp' and 'weft' with respect to surgical dressings?
12. What is 'tulle gras dressing'?
13. What is the chemical composition of 'plaster of Paris' bandage?
14. Give examples for absorbable hemostats.

Multiple Choice Questions

1. Sutures that are broken in the body over a period of time are called as _____.
   (a) nonabsorbable sutures (b) nylon sutures
   (c) absorbable sutures (d) silk sutures

2. Sutures that are not metabolized in the body are called as _____.
   (a) nonabsorbable sutures (b) fascia lata
   (c) absorbable sutures (d) catgut
3. Which of the following is an example for a nonabsorbable suture?
   (a) Silk (b) Catgut
   (c) Cargile membrane (d) Fascia lata
4. Which of the following is a material for nonabsorbable suture?
   (a) Aluminum (b) Copper (c) Gold (d) Stainless steel
5. Which of the following in not an example for impregnated bandage?
   (a) Plaster of Paris bandage (b) Zinc paste bandage
   (c) Zinc paste and coal tar bandage (d) Triangular calico bandage
6. Which of the following is used as a plasma substitute?
   (a) Dextran (b) Human thrombin
   (c) Human fibrinogen (d) Dried human plasma
7. Which of the following is not an example of absorbable hemostat?
   (a) Absorbable gelatin sponge (b) Dried human serum
   (c) Oxidized cellulose (d) Calcium alginate
8. Which of the following fibers is not a material for surgical dressings?
   (a) Cotton (b) Wool (c) Cellulose (d) Nylon

ANSWERS TO MULTIPLE CHOICE QUESTIONS

1. (c) 2. (a) 3. (a) 4. (d) 5. (d)
6. (a) 7. (b) 8. (d)

Herbal Formulations

11

INTRODUCTION

Herbals are crude drugs of vegetable origin, the parts or extracts of which are used to alleviate symptoms or to treat diseased states. Herbal drugs are finished labeled products that contain active ingredients such as aerial or underground parts of plants or other plant material, or combinations thereof, whether in the crude state or as plant preparations.

Herbs are classified as both food supplements and drugs. In herbs, the active constituents are not in effective concentration, whereas in pharmaceuticals, the active ingredients are present in effective concentration.

Advantages

1. Easy availability
2. Economical
3. Fewer side effects as compared to synthetic drugs
4. Simple method of preparation
5. Provide precursor for the synthesis of many compounds

Disadvantages

1. Most of the herbal products enter the market without being tested for their safety and efficacy.
2. Standardization is required because of inconsistency in their active constituents.
3. Yield of active constituents is not constant and it varies with season.
4. Estimation of a particular constituent is difficult and sometimes tracing the active constituent is difficult.
5. Presence of other constituents in herbal formula affects therapeutic response in many ways.
6. Standardization and estimation of active constituents require modern methods.
7. Certain herbal formulations and extracts are difficult to process as they have low practical yield.

8. Herbal drug interactions are difficult to predict.
9. As compared to synthetic drugs, herbal formulations are not available in all dosage forms.

HERBAL DOSAGE FORMS

Learning Objective

- Different types of herbal dosage forms and their preparations

Herbal dosage forms include solid, liquid and semisolid preparations. The basic principles involved in the preparation of these dosage forms are similar to those of allopathic processes, but they differ in the technique and method of preparation.

Various herbal or Ayurvedic dosage forms are described as follows:

1. *Arka*—distillate
2. *Kvatha*—decoction
3. *Avaleha*—semisolid preparations
4. *Asava, Arista*—fermented preparations
5. *Ghrita*—medicated ghee and oil
6. *Taila*—herbal oils
7. *Vartti or Anjana*—eye preparations
8. *Churna*—fine powders
9. *Pisti*—very fine powders
10. *Bhasma*—calcinated residue
11. *Vati or gutika*—tablets and pills
12. *Herbal capsules*
13. *Lepa*—paste

1. ***Arka* (distillate):** This is prepared by the distillation method and is used for fresh and soft drugs, where the active constituents may get degraded by boiling. The drug to be extracted is washed thoroughly and wrapped in a muslin cloth. This cloth bag is kept in the water required for distillation, in the distillation apparatus. The apparatus is heated and the distillation process is performed. The first part of the distillate is not collected as it contains some impurities present in the condenser or unwanted volatile materials; the further obtained vapor is condensed and collected in a receiver. In general, 8 to 10 times of water is used for this distillation process. Dry and hard substances are powdered and allowed to macerate. The macerated drug along with sufficient quantity of water is subjected to distillation and the obtained distillate is collected in the receiver. Examples of *arka* include rose, fennel, sandal and peppermint.

2. ***Kvatha* (decoction):** This is a liquid preparation and is obtained by decoction. This method is used in the case of drugs that are free from volatile constituents. Hard and woody drugs are reduced to the size of coarse powder and then macerated for 12 hours. The macerated drug is boiled with a suitable solvent under constant stirring in a vessel for a specified time period. After boiling, it is allowed to cool and then filtered by passing through a muslin cloth. *Kvathas* are used for oral administration, fomentation action and cleaning the wounds. Examples are *zinger*, *apamarga* and *kantakari*.

3. ***Avaleha*:** This is a semisolid preparation obtained by evaporating *kvatha* or karra (decoction). *Kvatha* is evaporated to a semisolid consistency and then the medicine is incorporated, or it is further evaporated to get a solid product. Care must be taken to ensure that the material does not stick to the evaporating pan. *Avaleha* may also be prepared by adding the medicine to a simple syrup, which is then evaporated to get a product of desired consistency. Examples are *Chyavanprash* and *Kantakari avaleha*.

4. ***Asava* and *Arista* (fermented preparations):** These are liquid preparations that are prepared by fermentation process. The formulations prepared with the aid of heat are called *Aristas*, whereas those prepared without the aid of heat are called *Asavas*. The preparations may be either sweet or sour in taste. *Kvatha*, gur and honey are used for the preparation of *Asava* and *Arista*. Volatile substances or flavoring agents are added to impart flavor to the preparation. These formulations should be prepared and stored in wooden containers. The preparation should be at a suitable place and a particular temperature is maintained throughout the fermentation period. After fermentation, the material is filtered and stored in suitable containers. These preparations are used internally to improve digestion, to make the body active (revitalizer), for expulsion of gas (carminative), to increase the flow of urine and to treat various ailments. They are orally administered by mixing with an equal amount of water. Examples are *Madhuka asava*, *Kanakasava*, *Ashokarista* and *Dasamularista*.

5. ***Ghrita* (medicated ghee):** This is a liquid or semisolid dosage form of medicament meant for internal and external use. Medicated ghee is generally given internally for its nutritive value and to treat constipation. Examples are *Amruta ghrita* and *Panchagavya ghrita*.

6. ***Herbal oil* (*taila*):** This is a liquid dosage form of medicament meant for internal and external use. The liquid form is prepared with olive oil or any other suitable oil. The oils are applied externally for their antiseptic and fomentation action. They are extensively used for massage to a particular part or the whole body. Examples are *Kanaka taila* and *Anu taila*.

7. ***Vartti* or *Anjana* (eye preparation):** This is a solid dosage form of medicament meant for application to the eyes. *Vartti* is an elongated solid preparation, which is rubbed on a hard surface or stone with few drops of water and the contents are instilled into the eyes. *Anjana* is a very fine powder, which is meant for application into the eyes with the help of a glass stick. These preparations must be passed through a very fine sieve to remove gritty particles, which otherwise may lead to irritation and discomfort to the eyes. Examples are *Vimala Vartti* and *Muktadi Mahanjana*.

8. ***Churna* (powder):** It is a simple or compound solid dosage form of medicament meant for oral administration. Simple *churna* contains only one medicament, whereas compound *churna* contains two or more medicaments. It is administered with water, milk, fruit juices or any other suitable liquid depending on the nature of disease. In general, the dose is 2–3 grams, which may be increased or decreased according to age and severity of disease. Examples are *Eladi churna* and *Triphala churna*.

   The following are the precautions to be taken in the preparation of *churna*:

   (a) Thoroughly cleaned and dried drugs should be used for the preparation of *churna*.
   (b) The ingredients should be finely sifted or grinded.
   (c) Each substance should be powdered separately and then mixed.

(d) Equipment used for reducing the particle size and mixing the substances should be clean and dry.
(e) The *churna* must be stored in a dry container.

9. ***Pisti* (very fine powder):** It is a solid dosage form of medicament meant for internal use. It is prepared from very expensive materials such as diamonds and pearls. These materials are thoroughly cleaned to remove impurities such as dust and other foreign particles. The materials are reduced to very fine powder by prolonged grinding using suitable milling equipment. After milling, they are passed through a very fine sieve to remove the gritty particles. Examples are *Pravala pisti* and *Manikya pisti*.

10. ***Bhasma* (calcinated residue):** It is a solid dosage form of medicament meant for internal administration. In general pearl, iron, gold, silver, lead, tin, zinc and black mica are used for the preparation. The material is cleaned and reduced to a coarse powder. The powdered material is mixed with a suitable liquid and kneaded to get a wet mass. The wet mass is then converted into small cakes. These cakes are dried in sunlight or in an oven and stored in earthen pots. Two pots are used at a time, the mouths of which are joined together and the joint is sealed by a cloth dipped in mud slurry and dried in the sun. Then, these earthen pots are kept in a heap of cow dung cakes, which are burnt later. The material is heated in the burning fire for 12 hours and is then allowed to cool slowly. The obtained mass is removed and the contents are ground by means of a mill. Examples are *Tamra bhasma* and *Pravala bhasma*.

11. ***Vati* or *Gutika* (tablets and pills):** These are the solid dosage form of medicaments meant for oral administration and are prepared by hand or machine. The powdered drug materials along with the excipients are mixed together and a suitable liquid is incorporated to make the wet mass. The wet mass is further kneaded in between the fingers so as to get a uniform mass. The mass so prepared is rolled on a hard surface and then divided into desired number of pieces and each piece is rounded by fingers and dried. The tablets and pills can also be prepared with rotary tablet punching machine by compressing the dried granules. Examples are *Gandhaka vati* and *Eladi gutika*.

    The following are the precautions to be taken in the preparation of *vati* or *gutika*:

    (a) If the dose of the drugs is small, diluents may be added to increase the bulk. For potent drugs, lactose may be used as the diluent.
    (b) The material should be finely powdered.
    (c) Only substances that can dissolve in stomach should be used.
    (d) If the pill breaks, then a binding agent such as gum acacia may be added.
    (e) Cinnamon or *Glycyrrhiza* powder should be sprinkled over the pills to prevent them sticking with each other.
    (f) The pills should not be too soft or too hard.
    (g) Sugar coating should be given for volatile and bitter drugs.

12. **Herbal capsules:** Capsules are unit solid dosage form of medicament in which the dried and powdered herbs are placed into hard gelatin capsules shells. Most medicinal herbs are bitter in taste, so it is easier to mask the bitter taste by placing the drug in an inert shell made of gelatin. Most herbal capsules contain just one specific herb in them, but sometimes capsules containing combination of herbs are also available.

13. ***Lepa*:** Medicines in the form of paste used for external application are called *lepas*. These are classified into six types, namely *pralepa, pradeha, alepa, doshagna lepa, vishagna lepa* and *varnya lepa*. The drugs are made into fine powder and mixed with liquid medium such as water, cow's urine, ghee or oil to obtain a paste. This paste is applied externally on the skin surface. *Lepa* should always be applied on the opposite direction of hair follicles. It should be removed immediately after drying. It should be freshly prepared and used. It should not be applied one layer over another. Examples are *Kalaka lepa* and *Dasanga lepa*.

HERBAL EXTRACTS

Learning Objective

- Different herbal extracts and brief discussion on various extraction processes

Extracts

Extracts are concentrated herbs in liquid form. Powdered or dried herbs are added to a fluid or solvent and then stored for a suitable period of time. Alcohol-based extracts are usually preferred over other solvents. Herbal extracts can be classified as follows:

1. **Fluid extracts:** These are more concentrated hydroalcoholic preparations.
2. **Solid extracts:** These are concentrated preparations obtained by evaporating the solvent used for extraction and are available in powder form.

Tinctures

Tinctures are liquid alcoholic preparations containing the active principles of vegetable drugs or plant materials. They are usually prepared by maceration or percolation or may be prepared by dissolving the corresponding liquid extract or chemical substances in alcohol or hydroalcoholic solvent.

Examples are Belladonna tincture, Cardamom tincture and Nux vomica tincture.

Extraction Processes

1. **Infusion:** This method is used for drugs that are soft in nature such that water may penetrate easily into the tissues and the active constituents are water soluble. The drug to be extracted is placed at the bottom of an infusion pot, water is added and the contents are stirred occasionally. Another method of preparing the infusions is that the drug is enclosed in a piece of muslin cloth and suspended just below the level of water. After sufficient time period, the liquid is strained and dispensed. Infusions must be freshly prepared and consumed within 24 hours of its preparation. Examples are infusion of senna and infusion of quassia.
2. **Decoction:** In this process, water-soluble thermostable constituents of hard and woody crude drugs are extracted. Water is used as the solvent. The size reduced drug material is boiled with the solvent for a specified time, usually 15–20 minutes. After boiling, the liquid is cooled and

filtered more water is passed through the marc to produce the required volume. The decoction should be freshly prepared and consumed within 24 hours.

3. **Digestion:** This process is a modified form of maceration in which the extraction of drugs is carried out by applying gentle heat to the substances being extracted. This method is applicable to those drugs for which moderately elevated temperature can be used and the solvent action of the menstruum is increased by gentle heat.
4. **Maceration**
   (a) **Simple maceration for organized drugs:** In this process, the extraction of drugs is carried out by placing the finely subdivided solid drugs in contact with the whole of the menstruum in a closed vessel for 2–7 days, with occasional stirring. The liquid is strained and the marc is pressed, adding the expressed liquid to the strained liquid. The combined liquids are clarified by decantation or filtration and the final volume is not adjusted.
   (b) **Simple maceration for unorganized drugs:** In this method, the extraction of drugs is carried out by placing a weighed amount of drug in contact with four-fifths of the menstruum in a closed vessel for 2–7 hours, with occasional shaking. After the specified period, the clear liquid is decanted or filtered. The marc is not pressed and the volume is adjusted by passing more menstruum through the marc.
   (c) **Multiple maceration:** Repeated maceration is more effective than single maceration. Active constituents left behind after first maceration can be extracted out in the next maceration. The marc is pressed after each maceration process. The quantity of menstruum to be used is divided into equal quantities and used for each maceration process. Maximum extraction is obtained in multiple maceration process, which can be done by double or triple maceration.
5. **Percolation:** In this process, the suitably size reduced drug is moistened with sufficient quantity of menstruum, which is then packed in a percolator. The drug is allowed to remain in contact with the menstruum for 24 hours, after which more menstruum is added from the top and percolation is started. The required volume is collected, marc is pressed and expressed liquid is added to the percolate. The required volume is obtained by adding more menstruum and the mixed liquid is clarified by decantation or filtration. Preparations made by percolation process are tincture of belladonna, compound tincture of cardamom and strong tincture of ginger.

PREPARATION OF SOME HERBAL FORMULATIONS

Learning Objective

- Preparation of some herbal formulations: Antibacterial, antitussive and toothpaste formulations

Antibacterial Formulation

Antibacterial agent is an agent that interferes with the growth and reproduction of bacteria; it disinfects surfaces and eliminates potentially harmful bacteria.

Examples of herbal antibacterials are neem, garlic, turmeric, berberis and *Zanthoxyllum* species.

Formula

Echinacea pallid root extract	120 mg
Fresh osha root extract	120 mg
Fresh yerba mansa extract	60 mg
Neem extract	60 mg
Haldi extract	40 mg

Preparation

Echinacea pallid root, fresh osha root, fresh yerba mansa, neem and haldi are collected and dried in shade. The dried materials are then powdered and extracted with 50% aqueous alcohol for five days. Then the solvent is decanted and filtered if necessary to remove the plant debris. The extract is then concentrated under vacuum at a temperature less than 50°C and dried to obtain a powder form.

The weighed quantity of the obtained plants extracts are dissolved in 500 ml of 10% alcohol, filtered and further mixed with glycerin and natural orange flavor.

Antitussive Formulation

These are the drugs that act in the central nervous system (CMS) to raise the threshold of cough center or act peripherally in the respiratory tract to reduce tussal impulses or to perform both these actions.

Formula

Adhatoda vasaka	1.5%
Glycyrrhiza glabra	1.5%
Acorus calamus	0.1%
Alpinia galangal	0.1%
Zingiber officinale	0.1%
Sucrose	66.7%
Alcohol (10%)	50%
Water (q.s.)	100 ml

Preparation

Adhatoda vasaka, *Glycyrrhiza glabra*, *Acorus calamus*, *Alpinia galangal* and *Zingiber officinale* are collected and dried in shade. The dried materials are then powdered and extracted with 50% aqueous alcohol for five days. At the end of this process, the solvent is decanted and filtered if necessary to remove the plant debris. The extract is then concentrated under vacuum at temperature less than 50°C and lyophilized to obtain the extract in the powder form.

The plant extracts are dissolved in 50 ml of 10% alcohol, filtered and a specified quantity of sucrose is added. The preparation is heated gently with continuous stirring until sucrose is dissolved and then the volume is made with required amount of water.

Toothpaste Formulation

Toothpaste is a white or creamy, opaque, sweet, flavored and foaming semisolid preparation in which the abrasive is suspended in the aqueous mucilage base. It is used for cleaning and polishing the teeth and to maintain oral hygiene.

Formula

Pippali	0.775% w/w
Kalmirch	0.775% w/w
Sunthi	0.775% w/w
Tonar beez	0.775% w/w
Karpoor	0.38% w/w
Clove oil	0.32% v/v
Lavanga oil	0.32 % v/v
Menthol oil	0.32 % v/v
Pudina	0.28% w/w
Glycerin	0.40% v/v
Water (q.s.)	100 ml

Preparation

Pippali, kalmirch, sunthi, tonar beez, karpoor and pudina are triturated and mixed in a mortar. Glycerin is mixed with water in a beaker and added to the powder mixture with continuous stirring to form a paste. Care must be taken during mixing to avoid air entrapment. Finally clove oil, lavanga oil and menthol oil are added and mixed properly. The thoroughly mixed homogenous paste is packed in aluminum or plastic collapsible tubes. The tube is crimped, capped and labeled.

INTRODUCTION TO ALTERNATIVE SYSTEMS OF MEDICINE

Learning Objective

- Introduction to alternative systems of medicine in India and their method of treatment

Traditional and alternative systems of medicine with drugs prepared from plants and mineral substances play an important role in providing health care to a large section of population. The alternative systems of medicine recognized in India are Ayurveda, Siddha, Unani and homeopathy.

Ayurveda System of Medicine

Ayurveda, the ancient science of life, is believed to be prevalent in India for more than 4500 years. Its philosophical base is derived partly from *Nyaya-Vaisheshika* and *Samkhya* streams of Indian philosophy.

Ayurveda is a complete medicine system, which takes into consideration the physical, psychological, philosophical, ethical and spiritual well-being of mankind. This system of medicine gives great importance to living in harmony with nature and science and also emphasizes the importance of maintenance of proper lifestyle for maintaining positive health. It is found that the fundamental principles of Ayurveda got organized and enunciated around 1400 B.C. from the Vedas. *Atharvaveda* contains 114 formulations for the treatment of different diseases. Authentic information on Ayurveda has been compiled by ancient Indian medicine practitioners in forms called *Samhita* and other similar books. *Charaka Samhita* and *Sushruta Samhita* are well-known compilations. Around 600 drugs of plant, animal and mineral origin have been mentioned in *Charaka Samhita* for the treatment of different diseases.

Ayurveda is based on the hypothesis that everything in the universe is composed of five basic elements—space, air, energy, liquid and solid. These elements exist in the human body in combined forms such as *vata* (space and air), *pitta* (energy and liquid) and *kapha* (liquid and solid). These three forms together are called *tridoshas* (three pillars of life). These *tridoshas* govern and control the basic psychobiological functions in the body. It is believed that they are in harmony with each other, and in every human being, one or the other element may dominate, which is called the *prakruthi* of that person. In addition to these three humors, there exist seven basic tissues (*saptha dhatus*)—*Rasa* (lymph), *Rakta* (blood), *Mamsa* (flesh), *Meda* (adipose tissue), *Asthi* (bones), *Majja* (nervine tissue) and *Shukra* (reproductive tissue)—and three waste products of the body (*mala*)—faeces, urine and sweat.

Healthy condition of the body represents the state of optimum equilibrium among the *tridoshas*, *sapta dhatus* and *mala*. Whenever this equilibrium is disturbed due to any reason, it results in diseases. The tissues of the body are considered as structural entities and the humors are considered as physiological entities, derived from different permutations and combinations of the five basic elements. The growth and development of the body components depend on the nutrition provided in the form of food. The food is composed of the five basic elements mentioned earlier. Hence, it is considered to be the basic source material to replenish and nourish the different components of the body.

Treatment

Ayurvedic treatment lies in restoring the balance of the disturbed humors (*doshas*) through regulating diet and correcting life routine and behavior along with the administration of drugs. The preventive nondrug therapies known as *panchakarma* (five processes) and *rasayana* (rejuvenation) therapy are done for treating various diseases. Before starting the treatment, many factors such as the status of tissue and end products, environment, vitality, digestion and metabolic power, body constitution, age, psyche, body compatibility and type of food consumed are taken into consideration.

The treatments are of different types:

1. ***Pathya Vyavastha*:** In this type of treatment, certain indications and contraindications are suggested with respect to diet, activity, habits and emotional status.
2. ***Nidan Parivarjan*:** This type of treatment emphasizes on avoiding known causes or situations leading to the disease or disease aggravation.

3. ***Satvajaya*:** This type of treatment emphasizes on restraining the mind from the desires for unwholesome objects.
4. ***Rasayana*:** The therapy deals with the promotion of strength and vitality. Examples are antistress and rejuvenation drugs and adaptogens including immunomodulators.
5. ***Shodhana* therapy:** This therapy provides purificatory effect through which therapeutic benefits can be derived. This type of treatment is considered useful in neurological and musculoskeletal disorders, certain vascular or neurovascular status, respiratory diseases, and metabolic and degenerative disorders.
6. ***Shamana* therapy:** This therapy involves restoring normalcy in the vitiated *doshas* (humors). This is achieved without causing imbalance in other *doshas*. In this treatment, use of appetizers, digestives, exercise and exposure to sun and fresh air are employed.
7. ***Dipan* and *Pachan* therapy:** *Dipan* (digestion) and *pachan* (assimilation) enhancing drugs are considered good for pacifying the vitiated *doshas*. This therapy is supposed to dissolve the vitiated and accumulated *doshas* by improving the digestive power and restoring the deranged metabolic process. In severe conditions, this therapy has to be supplemented with purificatory processes such as *panchakarma*.
8. ***Panchakarma* therapy:** In this therapy, initially the accumulated vitiated *dosha* is liquefied by resorting to external and internal oleation of the patient followed by sudation (*Swedhana*) and elimination of the vitiated *dosha* through emesis (*Vamana*) or purgation (*Virechana*), *Basti* (enema—evacuating type) and *Nasya* (nasal insufflations).

Siddha System of Medicine

Siddha system of medicine is practiced mostly in South India. This system of medicine maintains a distinctive identity of its own but has a close affinity to Ayurveda. This system is considered to be of pre-Vedic period; it is identified with the Dravidian culture and is closely attached with the Tamil civilization. The term "Siddha" has come from *Siddhi*, which means achievement. *Siddhars* were the persons who achieved supreme knowledge in the field of medicine, through the practice of *bhakti*, yoga, or *tapas* (meditation). As the years passed, this system of medicine interacted with the other streams of medicines and developed as a separate stream of medicine. The materia medica of Siddha system of medicine depends to a large extent on the drugs of metal and mineral origin, in contrast to Ayurveda of earlier period, which was mainly dependent upon drugs of vegetable origin.

Philosophical Background

According to the Siddha concepts, there are two dominant entities, namely matter and energy, which have a great influence in shaping the nature of the universe. They are called *Siva* and *Sakthi* in the Siddha system. Matter cannot exist without energy and vice versa. Thus, both are inseparable. The concept of five proto-elements and three *gunas* in this system of medicine is quite similar to the Ayurvedic concept pertaining to them. This system also believes in the role of the three humors, namely *vatta*, *pitta* and *kapha*. According to this system, all objects in the universe are made up of five basic elements—earth, space, water, fire and air.

The diagnosis or identification of causative factors of diseases in the Siddha system is carried out by the well-known *ashtasthana pareeksha* (examination of eight sites), which encompasses examination of *nadi* (pulse), *kan* (eyes), *swara* (voice), *sparisam* (touch), *varna* (color), *na* (tongue), *mala* (faeces) and *neer* (urine). These examination procedures are provided in greater detail in classical Siddha literature.

Treatment

Similar to Ayurveda, Siddha system also follows *ashtanga* concept with regard to treatment procedures. However, the main emphasis is on *Bala vahatam* (pediatrics), *Nanjunool* (toxicology) and *Nayana vidhi* (ophthalmology). The therapeutics in both Ayurvedic and Siddha systems can be broadly categorized into *samana* and *sodhana* therapies. The Ayurvedic system consists of well-known procedures categorized under *panchakarma* therapy, but this therapy is not that well developed in the Siddha system; only the *vamana* therapy has received the attention of the Siddha physicians. The concept pertaining to drug composition, the concept of *rasapanchaka* (concept explaining drug properties), is almost similar in both the systems of medicine. One of the major characteristic features of Siddha materia medica is the utilization of mineral- and metal-based preparations to a greater extent in comparison to the drugs of vegetable origin in the Ayurvedic system.

The mineral- and metal-based drugs in the Siddha system are categorized as follows:

1. ***Ratnas* and *Uparatnas*:** Drugs based on precious and semi-precious stones
2. ***Loham*:** Metals and metal alloys that do not dissolve in water but melt when put into fire and solidify on cooling
3. ***Rasam*:** Drugs that are soft and sublime and when put into fire change into small crystals or amorphous powder
4. ***Uppu* (*lavanam*):** Drugs that dissolve in water
5. ***Pashanam*:** Drugs that are water insoluble but give off vapors when put into fire
6. ***Uparasam*:** Drugs that are chemically similar to *pashanam* but have different actions
7. ***Gandhakam*:** Drug components that are sulfur based, are insoluble in water and burn off when introduced into fire

Unani System of Medicine

This system of medicine is believed to have been established by the Greek physician and philosopher Hippocrates (460–377 B.C.). Galen, Aristotle and Dioscorides made valuable contributions for its further development. The next phase of development of the Unani system of medicine took place in Egypt and Persia (Iran). The Egyptians had well-evolved pharmacy and were efficient in the preparation of different dosage forms such as oils, powder, ointment and alcohol. The Arabian scholars also played an important role in the development of this system. The Arabs were instrumental in introducing Unani medicine in India around 1350 A.D. The first institution of Unani medicine in India was established in 1872 as Oriental College at Lahore (then a part of India). National Institute of Unani Medicine was established at Bengaluru in Karnataka in 1983 in collaboration with the government of

Karnataka, focusing on both academic and research and development requirements. Central Council for Research in Unani Medicine (CCRUM) is the premier agency involved in the research and development activities in the country.

Philosophical Background

The Unani system is based on two theories, namely the *Hippocratic theory* of four humors and the *Pythagorean theory* of four proximate qualities. The four humors are blood, phlegm, yellow bile and black bile, and the four qualities are the states of living human body, namely hot, cold, moist and dry. They are represented as earth, water, fire and air. The Greek ideas were adapted by the Arabian physicians as eight working principles (*umur-e-tabia*) and included elements, temperament, humors, organs, life, spirit, energy and actions. The body is made up of simple and complex organs, which obtain their nourishment from the four humors mentioned earlier. These humors also have their specific temperament. In the healthy state of the body, there is equilibrium among the humors and the body functions in the normal manner as per its own temperament and environment. The disease condition is considered to be due to the imbalance between the humors and the treatment is given accordingly.

In this system of medicine, prime importance is given for the preservation of health. It is stated that six essential factors are required for the maintenance of healthy state. They are (a) air, (b) food and drink, (c) bodily movements and response, (d) psychic movement and repose, (e) sleep and wakefulness and (f) evacuation and retention. The human body is considered to be made up of six components, which have direct bearing on the health status of a person. They are (a) elements (*Arkan*), (b) temperament (*Mijaz*), (c) humors (*Aklat*), (d) organs (*Aaza*), (e) faculties (*Quwa*) and (f) spirits (*Arwah*). These components are taken into consideration by the physician for diagnosis and also for deciding the line of treatment. The Unani system of medicine aims at treating the cause of disease and not its symptoms. Hence, the complete history of the patient is recorded in addition to his pulse, urine and stool examinations.

Diagnosis

Examination of the pulse occupies a very important place in the disease diagnosis in Unani. In addition to the pulse rate, examination of the urine and stool is also important in diagnosing the disease and for further treatment. The pulse is examined to record different features such as size, strength, speed, consistency, fullness, rate, temperature, constancy, regularity and rhythm. The urine sample is examined for its color, odor, quantity and so on. Stool is examined for color, consistency, froth, time required for passage and so on.

Treatment

Disease conditions are treated by employing four types of therapies in Unani system of medicine. They are as follows:

1. **Regimental therapy:** This mainly consists of drugless therapy such as exercise, massage, Turkish bath and douches.
2. **Dietotherapy:** This is based on the recommendation of patient-specific dietary regimen.
3. **Pharmacotherapy:** This involves administration of drugs to correct the cause of the disease. The drugs employed are mainly derived from plants, but some are obtained from animals and some are of mineral origin. Both single and compound preparations are used for the treatment. Examples of Unani medicines are Madar, Gilo, Fufal, Karanj, Kulthi, Lodh, Sana, Zeera and Siyah.

4. **Surgery:** This is carried out at the affected, infected or diseased part of the body for permanent cure or treatment.

Homeopathic System of Medicine

Homeopathy was developed in the eighteenth century by Samuel Hahnemann, a German physician and chemist. He proposed that the cause of a disease can be used for the treatment of that disease. Samuel Hahnemann put forth the law of similars, which says that "like cures like" (*similia similibus curentur*). Using this principle, he found that cinchona can produce the symptoms of malaria. He succeeded in getting relevant results with a large number of extracts prepared from plants, animals and minerals.

Philosophical Background

Homeopathy is based on seven principles, namely individualization, principle of similia, principle of simplex, principle of minimum dose, law of proving, law of dynamization and vital force.

The concept of individualization maintains that no two individuals in the world are alike, and therefore, the diseases affecting the two individuals cannot be similar. Although common symptoms could be possessed by a number of individuals, the response to the same disease would differ from person to person. Thus, the medicine used to cure the same disease is different for different individuals.

The principle of '*similia similibus curentur*' patronizes the treatment of a disease by a medicine, that produces similar symptoms in healthy individuals by 'drug proving'.

Note: The study of the effect of drugs on healthy human beings is called homeopathic 'Drug Proving'. This is carried out by administering a drug in various potencies to a number of healthy volunteers of both genders and various age groups and collecting the symptoms produced by that drug.

The principle of simplex emphasizes giving only one single simple medicine at a time and the practice of combining medicines is not allowed. Though the patient may have a number of symptoms, only a single medicine is selected from the materia medica, which has the capacity to produce all these symptoms in an healthy individual (as ascertained by drug proving study).

The principle of minimum dose means minimum medicine at a time, which is just sufficient to arouse the vital force of an individual. Dr. Hahnemann describes vital force as a dynamic power that preserves life force and its normal state indicates good health.

Diagnosis

Detailed information is gathered about the patient's mood and behavior, likes and dislikes, responses to stress conditions, reactions to food and personality. The study of the detailed case history helps to build up a *symptom picture* of the patient. This is matched with the *drug picture* mentioned in the homeopathic materia medica and the treatment is provided accordingly.

Treatment

In the homeopathic system, the drug treatment is not specified, but the choice of drug depends on the symptoms and the clinical condition of the patient. This is based on the concept of *proving* and *prover*. In a healthy person called prover, the symptoms created by different doses of drug extracts are noted, which is called proving, and it specifically considers physical, mental and economical changes of the prover. Consequently, these symptoms are compared with a patient with similar symptoms, and accordingly, the same type of extract is given for treatment. During the treatment, the drug extracts

are extremely diluted, which is believed to cause potentiation and enhancement of curative effect. The drugs are extracted in the form of mother tincture, which is further diluted in terms of decimal, centesimal, or millesimal potencies. The following are the various medicinal plants used in homeopathy:

1. Vegetable drugs—examples are Belladonna, Arnica, Ipecacuanha, Aconite and Ergot
2. Animal drugs—examples are honey bee, calcium carbonate and cantharis
3. Minerals and metals—examples are sulfur, copper, phosphorus and barium carbonate

REVIEW QUESTIONS

Answer in Detail

1. Explain the different types of Ayurvedic dosage forms.
2. Explain the history and development of Ayurveda system of medicine.
3. Discuss the history and development of Unani-based medicine system.

Answer in Brief

1. Write a note on antibacterial herbal formulation.
2. Discuss antitussive herbal formulation.
3. What is the formulation and preparation of herbal tooth paste?
4. Discuss the various herbal extraction processes.
5. Discuss the different treatments of Ayurveda.
6. Explain the principles of Siddha treatment.
7. Briefly describe the Siddha-based classification of metal- and mineral-based drugs.
8. Explain the "proving and prover" concept of homeopathic treatment.

Answer in One or Two Sentences

1. Define *kvatha* with examples.
2. Mention the merits and demerits of herbal formulation.
3. Differentiate between *pisti* and *bhasma*.
4. Mention the important difference in the simple maceration process between organized and unorganized drugs.
5. List the alternative systems of medicine in India.
6. Name the two dominant entities as per the concept of Siddha medicine.
7. Define *panchakarma* therapy.
8. Differentiate between *Pathya Vyavastha* and *Nidan Parivarjan*.

Multiple Choice Questions

1. Herbal formulations meant for application to the eyes are known as _____.
   (a) *churna* (b) *bhasma* (c) *arka* (d) *anjana*
2. The solvent used for extraction process is known as _____.
   (a) *marc* (b) *percolate* (c) *menstruum* (d) *distillate*

3. The residue left behind after an extraction process is _____.
   (a) *bhasma* (b) *pisti* (c) *marc* (d) *filtrate*
4. Homoeopathy system of medicine was developed by _____.
   (a) Samuel Hahnemann (b) Lowis Pasteur
   (c) Madam Curie (d) Haragobind Khurana
5. Panchakarma therapy is composed of _____.
   (a) *virechana* (b) *basti* (c) *awedhana* (d) all of these
6. Which of the following plants can be used for their antibacterial properties?
   (a) *vasaka* (b) *ginger* (c) *neem* (d) *cardamom*
7. The extraction process in which heat is employed to extract the chemical constituents is _____.
   (a) maceration (b) percolation (c) infusion (d) digestion
8. According to siddha system, drugs containing metals are _____.
   (a) *uppu* (b) *avaleha* (c) *rasam* (d) *loham*

ANSWERS TO MULTIPLE CHOICE QUESTIONS

1. (d) 2. (c) 3. (c) 4. (a) 5. (d)
6. (c) 7. (d) 8. (d)

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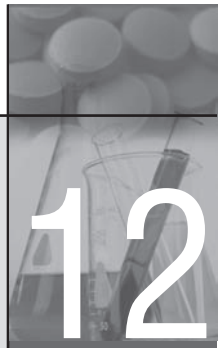
Pharmaceutical Aerosols



12

AEROSOLS AND THEIR HISTORICAL BACKGROUND

Learning Objective

- General idea regarding aerosols and its historical background

An *aerosol* is a suspension of fine solid particles or liquid droplets in a gas. In everyday life, we come across aerosols in the form of clouds and air pollution such as smog and smoke. The history of aerosols dates back to 1870, when pressurized carbonated beverages were introduced in France. Later in 1927, the first aerosol can and valve that was capable of dispensing the propellant and product was developed by Erik Rotheim of Norway. In 1953, Robert H Albanalp patented the present day aerosol valve. The first aerosol, an insecticide preparation was developed in 1942. The first pharmaceutical aerosol was developed in 1950, which was meant for topical application. Aerosol for inhalation containing the drug epinephrine was developed in 1955. Historical view of the aerosol cans is shown in Figure 12.1.

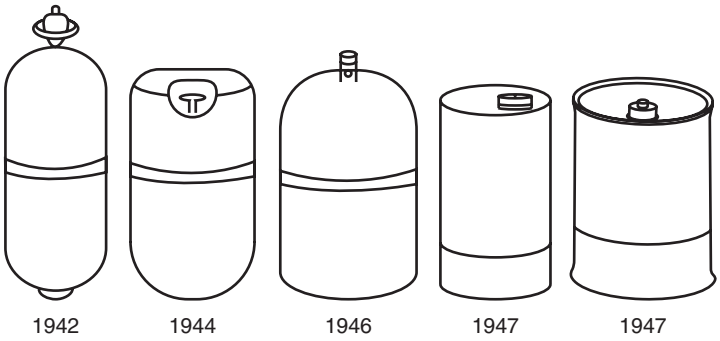


Figure 12.1 Historical View of the Aerosol Cans

PHARMACEUTICAL AEROSOLS

Learning Objective

- Definition of a pharmaceutical aerosol

Pharmaceutical aerosols are pressurized dosage forms of medicaments in which solid or liquid drugs are dissolved or suspended in a propellant. Upon activating the valve, the contents are released in the form of mist, spray or stream of foam. These products are intended for topical or local application to the nose (nasal aerosols), oral cavity (lingual aerosols) or for lungs (inhalation aerosols). They can be fitted with valves enabling metered-dose delivery such as metered topical aerosols and metered-dose inhalers (MDI). In order to achieve effective delivery with inhalation aerosols, the particle size must be carefully controlled and the average particle size must be less than 5 μm. Aerosol sprays used for other purposes may contain particles up to several hundred micrometers in diameter.

ADVANTAGES AND DISADVANTAGES OF AEROSOLS

Learning Objective

- Advantages and disadvantages of aerosols

Advantages

1. A dose can be removed without contamination of the remaining contents. This factor is especially of importance when delivering sterile dosage forms. For example, sterile saline aerosol meant for the purpose of cleaning the wound.
2. Sufficient protection is provided for the medicaments that are susceptible to oxygen and moisture, thus increasing their stability.
3. The aerosol container closure system is tamper proof.
4. The medication can be delivered directly to the affected area in a desired form such as spray, stream, quick breaking foam or stable foam. Further handling of the medicament is not needed.
5. For medications requiring accurate dosage, a metering valve can be used.
6. The required particle size of the medicament can be delivered to the desired sites such as nasal or buccal.
7. Irritation produced by the mechanical application of topical medication is reduced or eliminated since manual application of the topical medicament onto the affected area is eliminated. The medication can be applied in a thin layer.
8. A pressure package is easy and convenient to use.

Disadvantages

1. Despite the various advantages, aerosols still carry some disadvantages most of which are associated with the propellant used.
2. The propellants used in an aerosol are highly inflammable in nature.

3. Proper care is required in disposing empty aerosol containers, which may still contain residues of the propellant in them. In case of MDI, a proper coordination is necessary between valve actuation and inhalation.
4. Inaccurate use leads to increased pharyngeal deposition, and in the case of inhaled corticosteroid will result in oral candidiasis, hoarseness and increased absorption into the systemic circulation.
5. Topical application of aerosols leads to sudden cooling, which may lead to discomfort on the injured skin.

BASIC COMPONENTS OF AN AEROSOL SYSTEM

Learning Objective

- Basic components of an aerosol system

The basic components of an aerosol system are as follows:

1. Container
2. Valve and actuator
3. Concentrate containing the active ingredient(s)
4. Propellant

Characteristics such as particle size distribution, uniformity of dose (for metered valves), delivery rate, spray pattern and velocity, wetness, temperature of spray, fluid viscosity and foam density are determined by the nature of these components.

The propellant and the product concentrate will be discussed in detail in the section dealing with formulation of pharmaceutical aerosols.

Aerosol Containers

Learning Objectives

- General requirements of aerosol containers
- Various materials used in the construction of an aerosol container, their merits and demerits

The selection of container for a particular aerosol product depends on its ability to adapt to production method, compatibility with the formulation, aesthetic appeal and cost. More importantly, the aerosol container should be able to withstand pressure as high as 140 to 180 psig at 130°F. The aerosol containers are usually made of metal, glass or plastic. They are generally given a coating of plastic to improve safety characteristics of glass containers, corrosion resistance of metal containers and stability of formulations.

In most of the aerosol cans, the bottom curves inward. This helps to serve the following two purposes:

1. In containers with a flat bottom, the force of the pressurized gas might push the metal outward. A curved bottom gives the can greater structural integrity.
2. The curved shape makes it *easier to use up the entire product.*

Aerosol containers can be classified as follows:

1. Metal
   (a) Tin-plated steel
   (b) Tin-free steel
   (c) Aluminum
   (d) Stainless steel
2. Glass
   (a) Uncoated glass
   (b) Plastic-coated glass

Tin-plated Steel Containers

These are steel containers that are plated with a sheet of tin on both sides. Numbers like #25, #50 and #100 are used to denote the thickness of the tin plating. The size of the container is indicated by a measure of diameter and height of the container. These containers are lightweight and relatively inexpensive. If required, special protective coatings can be applied to the tin sheets prior to fabrication, so that the inside of the container will be protected against corrosion by the product. The coating can be of oleoresin, phenolic, vinyl or epoxy coating. The tin-plated steel containers (Figure 12.2) are generally used for topical aerosols.

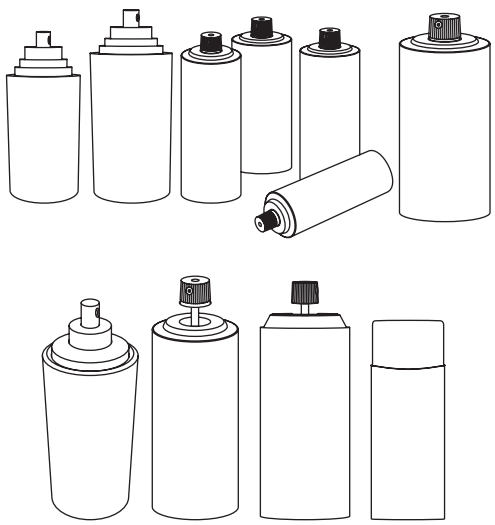


Figure 12.2 Tin-plated Steel Containers

Tin-free Steel Containers

Tin-free steel (TFS) is also called electrolytic chromium/chromium oxide coated steel. The material consists of mild steel base with a coating of chromium-chromium oxide, to protect the steel base from corrosion prior to fabrication. TFS containers need to be coated on the inside and outside with additional protective coatings like enamels and lacquers to make them corrosion resistant. Their main use in aerosol containers is to make aerosol bottoms and tops.

Aluminum Containers

These are lightweight and less reactive compared to other metal containers. Hence, these containers pose less compatibility problems and have a greater resistance to corrosion. Further coatings of phenolic, vinyl or epoxy resins confer greater protection against corrosion. Anodization of aluminum containers to form a stable coating of aluminum oxide can also be done. The impact extrusion process used in the manufacturing of these containers produces seamless containers. Hence, they have greater safety against leakage, corrosion and incompatibility. Aluminum containers (Figure 12.3) are used in MDIs, since they are made with a 20 mm neck finish that adapts to the metered valves. Containers that have neck finishes ranging from 15 to 20 mm are also available for special purposes and applications. The containers are available in sizes ranging from 10 ml to over 1,000 ml.

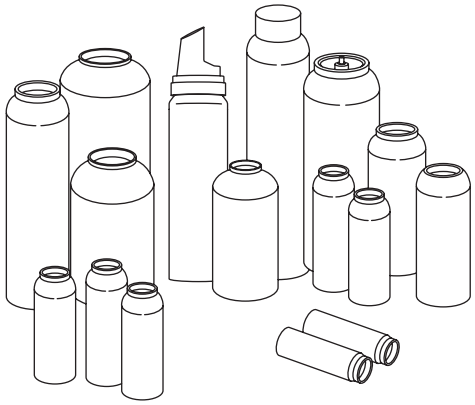


Figure 12.3 Aluminum Containers

Stainless Steel Containers

These are limited to smaller containers due to the production problems and the costs involved. They are extremely strong and resistant to most materials. They are the containers of choice for inhalation aerosols. These containers can be used as such without any internal coating. Containers that are made of stainless steel are shown in Figure 12.4.

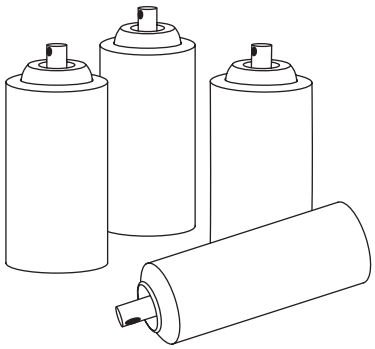


Figure 12.4 Containers made of Stainless Steel

Glass Containers

Glass containers can also be used for aerosol packaging. They are available with or without plastic coating. The plastic coating may be totally adhered or non-adhered and vented. These containers pose less compatibility problems, and hence corrosion problems are eliminated. The level of the contents in the glass container can be easily visualized. Glass is used in products that have lower pressures and lower percentages of propellants. Glass also allows greater freedom in designing the container. Plastic coatings on glass containers provide greater resistance to breakage. The plastic coatings may also serve several other purposes such as identification, protection from UV light and absorbing shock from production operations like crimping. Glass containers are generally used for small volume solution aerosols, which operate at low pressures.

Valves

Learning Objective

- Function of an aerosol valve

The valve regulates the flow of the therapeutic agent and propellant from the container. The diameter, location and the number of orifices determine the spray characteristics of the aerosol. Aerosols meant for topical products provide continuous spray operations, whereas those meant for oral and nasal use utilize metered-dose valves, which deliver a uniform quantity of the product upon activation. The materials used for the valve manufacture should be compatible with the formulations. Plastic, rubber, aluminum and stainless steel valve components are generally used.

The valves are basically of the following two types:

1. Continuous spray valve
2. Metering valves

Continuous Spray Valve

Learning Objective

- Basic components in an aerosol valve and their importance

An aerosol valve is an assembly of following different components:

1. Actuator
2. Stem
3. Stem gasket
4. Spring
5. Housing (body)
6. Dip tube
7. Mounting cup (with mounting cup gasket)

The different parts in an aerosol valve (Figure 12.5) and their basic function are described in the following section.

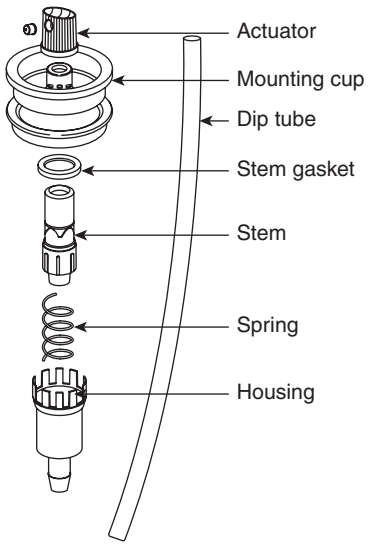


Figure 12.5 Aerosol Valve Components

Actuators

Learning Objective

- Different types of actuators

Actuators are specially designed buttons required for easy opening and closing of the valve. The type and quantity of the propellant and the design and dimension of the actuator determine the type of product discharge whether it is in spray or foam or a solid stream. Special actuators are available for use with pharmaceutical and medicinal aerosols that allow dispensing of products into the mouth, nose, throat, vagina or eye. The actuator is fitted to the valve stem. Depending upon the type of product discharge, actuators can be of the following types:

(a) Spray
(b) Foam
(c) Solid stream
(d) Special applications

Actuators can also be classified as mechanical break up actuators and non-mechanically break up actuators.

(a) *Spray actuators* are capable of dispensing the stream of product concentrate and propellant into relatively small particles. The stream is made to pass through various orifices ranging from one to three. The combination of vaporization of the propellant, orifice in the actuator and internal channels together deliver the spray in the desired particle size range. While using non-mechanical breakup actuators, the propellant concentration should be relatively high, in order to

dispense the product in the form of spray. If propellant concentration is less than 50%, mechanical breakup actuators are required that mechanically break up the stream into spray by swirling through various channels in the actuator.

(b) *Foam actuators* consist of large orifices ranging from approximately 0.070 inch to 0.125 inch and greater. The orifices allow for passage of the product into relatively large chamber, where it can be expanded and dispensed through a large orifice.

(c) *Solid stream actuators* are similar to foam actuators, where the orifice is relatively large in order to dispense semisolids like ointments.

(d) *Special actuators* are those that are specially designed to deliver the medicament to the appropriate site of action like throat, nose, eye or vaginal tract.

Different types of actuators are shown in Figure 12.6.

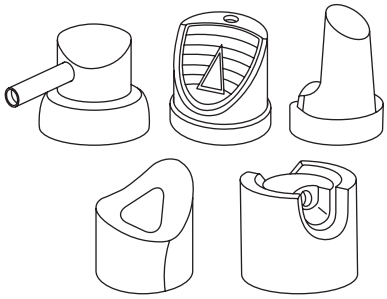


Figure 12.6 Different Types of Actuators

Stem: A stem (Figure 12.7) is a part of the valve assembly that controls the flow of the product. It may contain one to four orifices ranging in size from 1×0.010 inch to $4 \times 0.027 \times 0.045$ inch. The stems are usually made up of nylon or delrin and materials like brass and stainless steel can also be used.

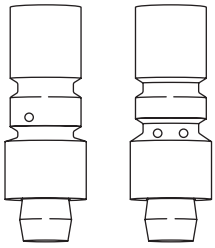


Figure 12.7 Valve Stem

Stem gasket: The stem gasket (Figure 12.8) covers the stem orifice and in other words acts as an "on-off" switch. The gasket can be made of buna-N, neoprene, butyl or viton. Testing of the stem gasket is

mandatory since the rubber may shrink or swell with different formulations. Choice of an appropriate stem gasket helps to prevent loss of the product due to leakage.

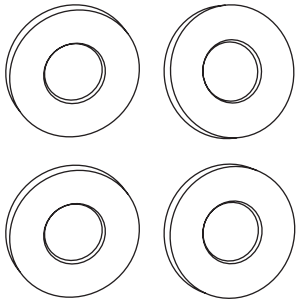


Figure 12.8 Stem Gasket

Spring: The spring (Figure 12.9) causes the valve to close after release of the actuator. It also serves to hold the actuator in place. Stainless steel valves are chosen for most of the aerosol products.

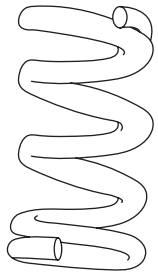


Figure 12.9 Spring

Valve body or housing: The housing encloses the stem, spring and gasket. It is generally manufactured from nylon or delrin and contains an opening at the point of the attachment of the dip tube. It acts as a secondary metering orifice. The opening may range from about 0.013 inch to 0.080 inch depending on the type of product to be dispensed. The housing may or may not contain another opening referred to as the "vapor tap" at the side or bottom of the housing. The presence of this orifice helps in expelling a dry and warmer spray, thus reducing the chilling effect of the product on the skin. Vapor tap allows the vaporized propellant along with the liquid product to escape. The vapor tap further produces fine particles, prevents valve clogging and allows the product to dispense satisfactorily in an inverted position. In the case of hydrocarbon propellants, it reduces flame extension. Different types of valve housing are shown in Figure 12.10.

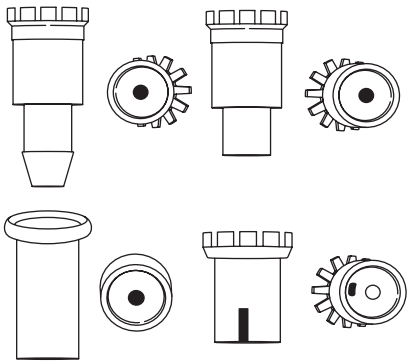


Figure 12.10 Different Types of Valve Housing

Dip tube: The dip tube (Figure 12.11) draws the product up into the valve and helps in delivering the formulation. It is made from polyethylene or polypropylene. The viscosity of the product and the delivery rate desired determine the diameter of the dip tube. The usual diameters range from:

Standard : 1/8″ (0.122″) inside diameter
Large : 3/16″ (0.190″) inside diameter
Jumbo : over 1/4″ (0.260″) inside diameter
Capillary : < 0.060″ inside diameter

The dip tubes are notched at the bottom to prevent closing off at the bottom of the can.

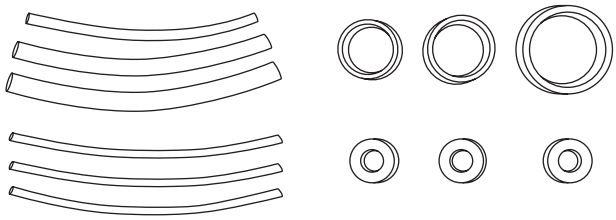


Figure 12.11 Dip Tubes

Ferrule or mounting cup: The ferrule or mounting cup (Figure 12.12) holds the valve parts together and attaches the valve properly to the container. It can be made from tin-plated steel or aluminum. The underside of the cup should be protected from corrosion by the aerosol contents. This can be achieved by a single or double epoxy or vinyl coating. Softer metals such as aluminum or brass are used for ferrules with glass containers and small aluminum tubes. The ferrule is attached to the container either by clinching the metal under the lip or by rolling the end under the lip of the bottle.

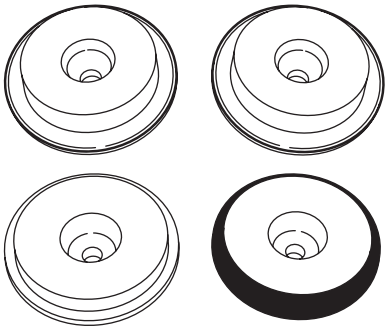


Figure 12.12 Mounting Cups

Metering Valves

The metering valves (Figure 12.13) are necessary for potent medicaments where the dose is important. These valves operate on the principle of a chamber, whose capacity determines the amount of medicament delivered per dose. Approximately 50 to 150 mg ± 10% of liquid material can be dispensed at a time.

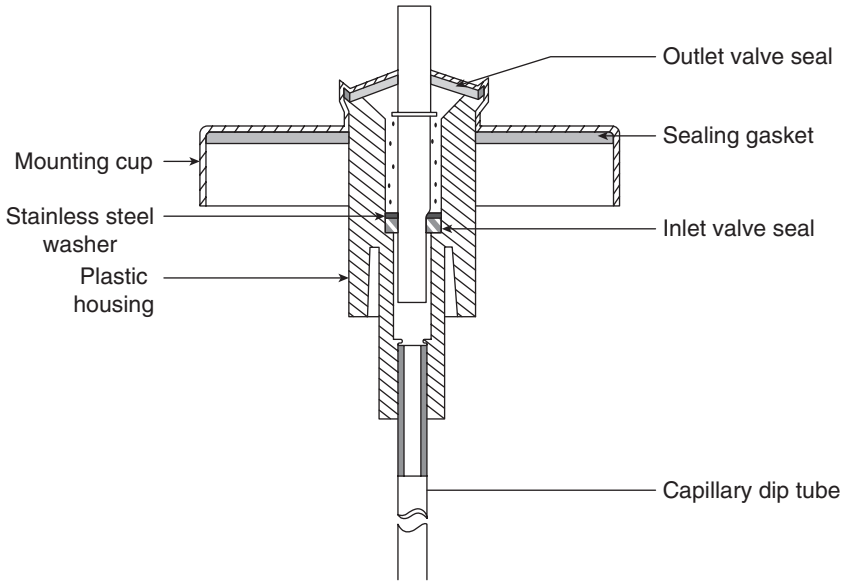


Figure 12.13 Metering Valves

Metered-dose Inhalers

Learning Objective

- Advantages and uses of MDI

A metered-dose inhaler (MDI), introduced in 1950s is a device that delivers a specific amount of medication to the lungs, in the form of a short burst of aerosolized medicine that is inhaled by the patient. It is the most commonly used delivery system for medications such as bronchodilator, corticosteroid or a combination of both for treating asthma, chronic obstructive pulmonary disease (COPD) and other respiratory diseases.

1. MDIs are pressurized aerosol containers with a metered-dose valve. The valve is placed in an oral mouth piece or adapter.
2. On activating the valve, an exact dose of the medicament is dispensed from the container and the particle size is maintained in such a way that most of the medicament gets deposited in the lungs.
3. Formulated as solution or suspension.
4. The drug in the formulation may be delivered to the patient in a micronized or solubilized form along with the excipients, propellant and/or solvent.
5. The main advantage of the MDIs is the dispensing of an accurate dose of the medicament without contamination or exposure of the remaining material.

Metered-dose inhalers are shown in Figure 12.14.

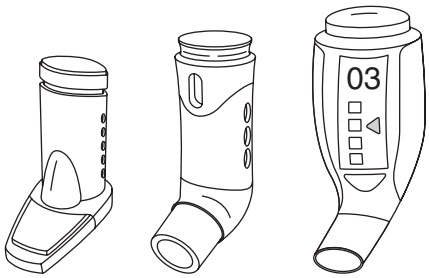


Figure 12.14 Metered-dose Inhalers

FORMULATION OF PHARMACEUTICAL AEROSOLS

The aerosol formulation consists of the following two essential components:

1. Propellant
2. Product concentrate

Propellant

Learning Objectives

- Different propellants used in aerosol preparations
- Advantages and disadvantages of the various propellants
- Nomenclature of liquefied gas propellants
- Principle of operation of aerosols with liquefied gases and compressed gases as propellants

A propellant is responsible for developing the pressure within the container and in combination with other components it expels the product in the desired physical form like spray, mist or foam.

Propellants may be broadly classified as follows:

1. Compressed gasses
2. Liquefied gases

The types of propellants used for different pharmaceutical applications are listed in Table 12.1.

Table 12.1 Types of Propellants for Different Applications

Application	*Types of propellants*
Oral and inhalation	Trichloromonofluoromethane (propellant 11), dichlorotetrafluoroethane (propellant 114) and dichlorodifluoromethane (propellant 12).
Topical	Propane, butane, isobutane and compressed gases like nitrogen and carbon dioxide.

Compressed Gases

Compressed gas propellants are widely used in pharmaceutical aerosols. The gases generally used include nitrogen, nitrous oxide and carbon dioxide. They can be used to dispense the product in the form of a solid stream, wet spray or foam. The gas is compressed in the container and occupies the head space above the liquid in the can. When the valve is pressed, the pressure of the gas on the contents acts as a piston and pushes the liquid out of the can. The pressure exerted within the container system is dependent on the concentration of the propellant. The amount of gas in the headspace remains the same, but it expands and occupies more volume, and as a result the pressure will drop during the life of the can.

The nature of the formulation and type of the compressed gas used determine the form in which the product will be dispensed, that is solid stream, wet spray or foam. In dispensing of semisolids, a substantially high initial pressure of 90 to 100 psig at 70°F is required to ensure that most of the product is dispensed from the container. The viscosity of the product should be adjusted according to the desired dispensing characteristics. The amount of residual product in the container also varies with the viscosity of the product.

In dispensing of foams, soluble compressed gases such as nitrous oxide and carbon dioxide can be used. The product concentrate is usually in an emulsion form. When the system is used, the gas dissolved in the concentrate will be evolved and causes whipping of the emulsion into foam. To facilitate the formation of foam, the system is shaken prior to use, to disperse some of the gas throughout the product concentrate. For dispensing sprays, with compressed gases as propellants, a mechanical breakup actuator is required. The product is dispensed as a wet spray and is applicable to solutions of medicinal agents in aqueous solvents. Contact lens saline aerosols are formulated with compressed nitrogen gas as propellant and sterilized using gamma radiations.

Liquefied Gases

Liquefied gases are widely used as propellants for most of the aerosol products. These are materials that exist in the gaseous or vapor state at room temperature and atmospheric pressure and are capable of being liquefied easily by lowering the temperature below its boiling point or by increasing the pressure. The compounds chosen generally have boiling points below 70°F (21°C) with vapor pressure exerting between 14 and 85 psig at 70°F (21°C). They are relatively inert and nontoxic.

Two types of liquefied gases used are the chlorofluorocarbons (CFCs) and hydrofluorocarbons. Pharmaceutical aerosols were originally developed using CFCs 11, 12 and 114. Unfortunately, these propellants have an ozone depleting effect and the current global regulations require pharmaceutical aerosols to be formulated using non-ozone depleting propellants. Their uses in pharmaceutical aerosols have been practically eliminated except in MDIs. The alternatives to CFC propellants should meet certain criteria such as they should be nontoxic and non-flammable.

Mechanism of Aerosol Operation

Liquefied gases have been used widely as propellants for most of the aerosol products. In a sealed container such as an aerosol can, the liquefied gas exists in two phases—liquid and gas, behaving as a two-phase system. The molecules in the vapor stage are responsible for exerting the pressure on the contents. As the number of molecules in the vapor phase increases, vapor pressure of the propellant also increases proportionately. The pressure attained at equilibrium is known as the vapor pressure and is unique for a given propellant at a given time. This vapor pressure is exerted equally in all directions and is independent of the quantity present.

During valve actuation, the vapor pressure exerted by the gas on the liquid phase is responsible for pushing the product up (liquid state) through the dip tube. In cases where there is no dip tube (e.g. MDIs), the container is used in the inverted position. When the valve is opened, the liquid phase is expelled with sudden volume of expansion and comes in contact with the atmospheric temperature. The propellant, whose boiling point is much less than the room temperature, vaporizes immediately. To restore the drop in pressure inside the container, more of the liquid propellant vaporizes into the head space. In comparison with compressed gases, one advantage with these propellants is that there is no drop in pressure inside the container during the usage of the product. The pressure exerted is independent of the propellant concentration within the container. Due to its large volume expansion ratio, the spray performance is maintained constant throughout the life of the aerosol until its last dose of the drug delivery.

Comparative diagram of aerosols with liquefied propellant and compressed gas propellant is shown in Figure 12.15.

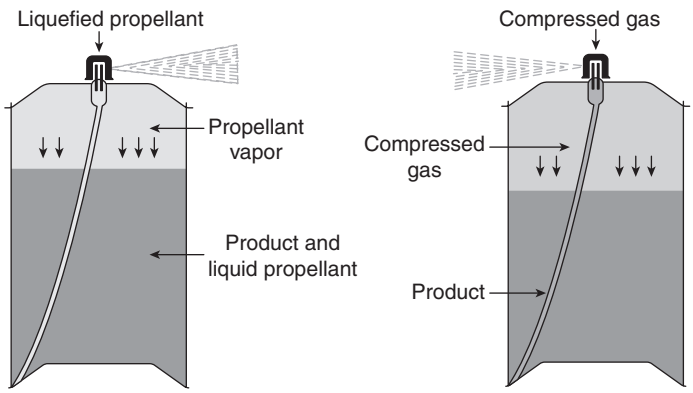


Figure 12.15 Comparative Diagram of Aerosols with Liquefied Propellant and Compressed Gas Propellant

Examples for fluorocarbon propellants used in aerosols are trichloromonofluoromethane (propellant 11), Dichlorodifluoromethane (propellant 12), and dichlorotetrafluoroethane (propellant 114). The three-digit numerical designation is used to identify each propellant. The first digit is one less than the

number of carbon atom in the compound. The second digit is one more than the number of hydrogen atoms in the compound. The last digit represents the actual number of fluorine atoms. If the value of first digit numerical designation is zero, it can be represented by only two digits. The remaining carbon valency should be satisfied by chlorine atom.

Examples: Propellant 11 is $CFCl_3$
Propellant 12 is CF_2Cl_2
Propellant 114 is $C_2F_4Cl_2$

Selection of Propellants

Blends of various fluorocarbon propellants are generally used for pharmaceutical aerosols. These mixtures help in obtaining the desirable pressure, delivery and spray characteristics. By varying the proportion of each component, any desired vapor pressure can be achieved.

The CFCs have been implicated in having ozone depleting effect, increasing the amount of UV radiations reaching the earth's surface resulting with greenhouse and global warming effect. Depletion of ozone layer is also alleged to result in increased incidence of skin cancer. After the Montreal protocol signed in 1987, which was an effort to phase out the use of ozone depleting substances, including CFCs, pharmaceutical companies have come out with alternate substances to be used as propellants in medicinal products. Hydrocarbon propellants such as butane, propane and isobutane have replaced CFCs for topical pharmaceutical aerosols. These have lower solubility but higher flammability. Their cost is also lower in comparison to CFCs.

Hydrocarbon propellants and their various blends can be used in aerosol formulations. Their density is less than one and immiscible with water, hence making them suitable for three-phase systems. They generally possess better solubility characteristics than fluorinated hydrocarbons. They are chemically stable. They are not prone to hydrolysis, hence suitable for water-based formulations. Alternative propellants such as hydrochlorofluorocarbons (HCFCs) and Hydrofluorocarbons (HFCs) can also be used as replacement for CFCs in appropriate formulations.

A comparison between liquified gases and compressed gases as propellants is given in Table 12.2.

Table 12.2 Comparison of liquefied gases and compressed gases as propellants

Liquefied gases	*Compressed gases*
The propellant is an integral part of the formula.	The propellant forms a separate phase on the surface of the product.
The spray consists of smaller and finer particles.	The spray results in large, wet particles.
The pressure is maintained throughout the life of the product.	There is a pressure drop seen during the product life.
Large temperature changes can affect pressure inside the container.	Pressure exerted by the gases is not affected by changes in temperature.
The pressure exerted is independent of propellant concentration and hence no pressure drop.	The pressure exerted is dependent on the propellant concentration and hence pressure drop.
Cost varies with the kind of propellant and generally of higher cost.	Less expensive.

Product Concentrate

It consists of active ingredient or a mixture of active ingredients with other necessary agents such as solvents, antioxidants and surfactants. Propellants can be combined with the active ingredients in many ways producing products with varying characteristics.

TYPES OF AEROSOL SYSTEMS

Learning Objective

- Different types of aerosol systems

Solution System

These are also referred to as the two-phase systems—a liquid and a vapor phase. They consist of a solution of active ingredients in pure propellant or a mixture of propellant and solvents. If the active ingredient is soluble in the propellant, no other solvent is necessary. These types of systems are easy to formulate. The propellant used depends upon the type of spray desired. Propellant 12 or A-70 produces very fine particles. A blend of propellant 12 with other propellants can also be used. If propellants having vapor pressure lower than that of propellant 12 are added in the blend, the pressure of the system decreases resulting in larger particles. Lower vapor pressure can also be achieved by addition of less volatile solvents such as ethyl alcohol, propylene glycol, ethyl acetate, glycerin and acetone. These types of sprays produce wetness and hence suitable for topical aerosols where a film of medicament will be formed on the surface. Larger particles reduce the danger of inhalation of particles by formation and subsequent inhalation of airborne particles. Diagrammatic representation of a two-phase solution system is shown in Figure 12.16.

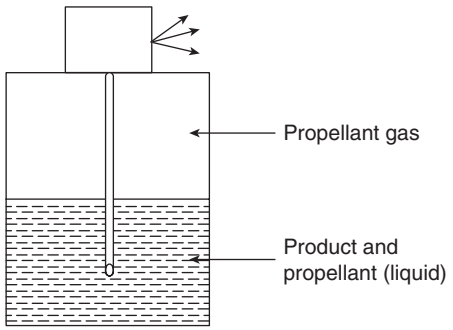


Figure 12.16 Diagrammatic Representation of a Two-phase Solution System

The system can be exemplified by the following general formula:

	Weight %
Active ingredients	10–15
Propellant 12/11 (50:50) q.s	100

The ratio of propellant 12 and 11 or propellant 12 with any other propellant such as propellant 114 can be used for other applications such as oral inhalation. As the pressure increases, the choice of container also needs to be changed.

Hydrocarbons in topical aerosol pharmaceutical preparations are used as follows:

	Weight %
Active ingredients	10–15
Solvents such as ethanol or propylene glycol	10–15
Distilled water	10–15
Hydrocarbon propellant A-46	55–70

Water-based System

These "water-based" aerosols are emitted as spray or foam depending on the formulation. The formulation consisting of an emulsion of active ingredients and other solvents produce a spray. When the product is dispensed, the propellant vaporizes and disperses the active ingredients into minute particles. Three phases are formed—liquid propellant, product concentrate and vaporized propellant. Ethanol is used as a co-solvent to solubilize some of the propellant in water.

Diagrammatic representation of a three-phase water-based system is shown in Figure 12.17.

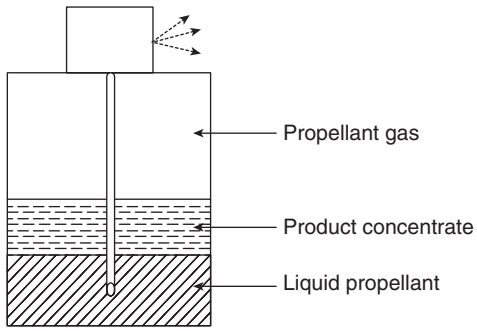


Figure 12.17 Diagrammatic Representation of a Three-phase Water-based System

Surfactants have been used to a large extent to produce a satisfactory homogenous dispersion. The surfactants having greater solubility in non-aqueous solvents have been found to be most useful. In general, about 0.5 to 2.0% of surfactant is used. The propellant content varies from about 25 to 60%, but can be as low as 5% depending on the nature of the product. When the propellant concentration is small and the water content is large, a mechanical breakup actuator along with a vapor tap is used, if a fine particle spray is desired.

The *aquasol* system is one such example where the propellant concentration is less and water content is more. The product is dispensed in a fine mist or spray and since the propellant is present only to a small extent, it does not produce any chilling effect. The aquasol system utilizes a large percentage of water in the formulation. The system is a three-phase system but unlike the other three-phase systems, aquasol permits the use of fairly large quantities of water in the formulation. Moreover, the amount of hydrocarbon propellant is relatively less, the resulting spray is non-flammable and the product is economical.

Suspension System

These systems involve the dispersion of active ingredients in the mixture of propellants. Like conventional suspensions, surfactants or suspending agents are added to the system to decrease the rate of settling of the dispersed particles. Such systems are mainly used for oral inhalation aerosols.

Stability problems associated with disperse systems such as caking, agglomeration and particle size growth can also be observed with aerosol disperse systems. In several cases, the particles may adhere to the walls of the container. Agglomeration may result in valve clogging and thus may lead to inaccurate dosing.

In order to overcome these problems, the following measures can be used:

1. Lubricants such as isopropyl myristate and oleic acid provide slippage between the particles and also lubricate the components of the valve.
2. Surfactants can be used to disperse particles.
3. Dispersing agents such as oleic acid and lecithin help in keeping the suspended particles from agglomerating.
4. The particle size of metered-dose inhalant should be between 2 μm–8 μm, while those for topical aerosols should be between 50 μm–100 μm. This is to prevent blocking of the aerosol valves.
5. The moisture content of both the propellant and the suspension should be below 300 ppm. Higher moisture levels generally result in particle agglomeration and thus strict control over the manufacturing conditions should be exercised.
6. To overcome particle size growth during the shelf life of the product, the initial particle size can be reduced to less than 5 microns.
7. The density of the propellant and the suspension are equalized.
8. To reduce valve clogging, vapor tap valves have been used with dispersion aerosols. The escaping of the propellant in the form of vapor helps in clearing the valve of solid particles.

Example for a formulation for oral inhalation containing a steroid:

Steroid compound	8.4 mg
Oleic acid	0.8 mg
Propellant 11	4.7 g
Propellant 12	12.2 g

In the above formulation, oleic acid acts as a dispersing agent for the steroid. It reduces particle growth and agglomeration. In addition, it also performs as a valve lubricant and prevents metered valves from sticking in the open position.

Emulsion System

These kinds of systems are suitable for topical aerosols. The emulsion systems may be of the following categories.

Foam systems: The active ingredient, aqueous or non-aqueous vehicle, surfactant and propellant are dispensed as stable or quick-breaking foam. The propellant generally forms the internal phase of an Oil-in-water (O/W) emulsion. The foam may be advantageous for various applications involving irritating ingredients or when the material is applied to a limited area. The type of foam systems may be aqueous stable foams, non-aqueous stable foams, quick-breaking foams and thermal foams.

MANUFACTURING OF PHARMACEUTICAL AEROSOLS

Learning Objective

- Different methods used in manufacturing aerosols

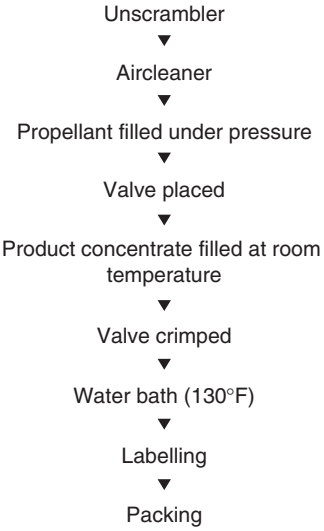
Manufacturing and packaging of aerosols requires specialized equipment and skills, special knowledge and rigid quality control. In addition to the equipment used for the compounding of liquids, suspensions, emulsions, creams and ointments, specialized equipment capable of handling and packaging materials at relatively low temperatures about −40°F or under high pressure must be available. The equipment is usually limited to packaging of aerosols.

Pressure Filling

The concentrate may be chilled slightly (15–20°C) to reduce vaporization of any volatile solvent or propellant. The concentrate is added to an open container. The valve is crimped in place. The propellant is added under pressure through the valve. The filled container is passed through the water bath maintained at 55°C to check for leakage.

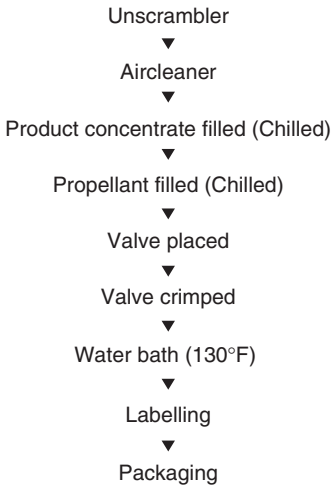
The apparatus consists of a pressure filling burette capable of metering small volumes of liquefied gas under pressure into an aerosol container. The propellant is filled into the burette through the inlet valve located at the bottom of the burette. The entrapped air is allowed to pass through the upper valve. The propellant is added into the container through the aerosol valve. The propellant flows into the container under its own vapor pressure. The flow stops when the pressure is equalized between the burette and the container. If additional propellant needs to be filled, then the burette is attached to a nitrogen gas cylinder and the pressure of the nitrogen gas pushes the propellant into the container.

Pressure filling devices can also be attached to a piston such that a positive pressure can always be maintained.



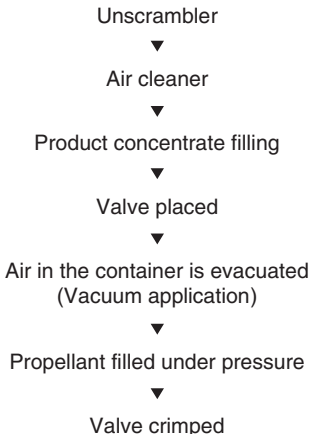
Cold Filling

The drug concentrate, which may be solution or suspension, is cooled to −30°C to −60°C. The container is also chilled and the cold concentrate is added to chilled (cooled) container. The propellant is added and the valve is crimped in place. The container is checked for leakage by passing into a water bath maintained at 55°C.



Compressed Gas Filling

Handling of compressed gases does not require any elaborate equipment. The compressed gases are under high pressure and hence a pressure reducing valve is required. The filling head is attached to a flexible hose capable of withstanding pressure of about 150 pounds per square inch and attached to a delivery gauge. The concentrate is filled in the container. The filling head is inserted into the valve opening and the valve is depressed. The gas flows into the container. When the pressure inside equals the delivery pressure, the gas stops flowing.



▼
Water bath (130°F)
▼
Labelling
▼
Packing

STABILITY TESTING OF AEROSOLS

Learning Objectives

- Stability aspects regarding the compatibility of product and container
- Stability of the valve with the product

The complete aerosol package includes both the product and the container. Hence while studying the stability aspects of aerosols, both the effect of the product on the container and the effect of the container on the product should be studied. Moreover, due to the variety of materials used in making an aerosol valve and container, it is essential to study the effect of these different materials on the product individually as well as collectively. Several container coatings as well as valves with different sub-components may be studied so that any reaction between the component and the product may be detected.

Testing of pharmaceutical aerosols is carried out based on the component namely:

- The product concentrates which includes the propellant
- The container
- The valve assembly.

The stability testing of the product concentrate includes determination of several physico-chemical parameters such as vapor pressure, spray rate of the valve, pH, density or specific gravity, refractive index, viscosity, total weight, assay of active ingredients, chromatography curves, color and odor. The compatibility of the product with the container is tested by keeping the contents in close contact with the different parts of the container.

Stability of the container is checked by chilling the container to a temperature of 0°F or less and taking out the contents. The container is examined insides for any signs of corrosion. The containers that have been lacquered on the insides are examined for softening of the lacquer. Plastic containers are checked for leaching or sorption.

The different valve components are checked for any evidence of corrosion especially the mounting cup. The other valve components are checked for softening, cracking, elongation or distortion. These problems can lead to the improper functioning of the valve during usage and hence should be corrected during the initial stage itself.

QUALITY CONTROL OF PHARMACEUTICAL AEROSOLS

Learning Objective

- Quality check of propellants, containers and valve assembly

The *propellants* meant to be used in pharmaceutical aerosols should undergo rigid quality control tests. In general, all propellants require special handling procedures and test procedures. A sample

propellant is sent to the laboratory to determine its identity by gas chromatography. When a blend of propellant is present, then the composition is estimated and the vapor pressure and density are determined. The propellant's purity is determined by estimating the moisture, halogen and non-volatile residues.

The quality control of valves is a complex process since it is not made of single component. The valves, actuators and dip tubes are subjected to both physical and chemical inspection. The different valve components are assembled in order that the valve performs its function. The examination of valves is to determine whether the valves are fit to be used. The valve is tested to determine the magnitude of valve delivery and the uniformity.

The quality control of *aerosol containers* depends on the material. Coated and uncoated metal containers are examined for defects in lining. Degree of conductivity determines the amount of exposed metal. Glass containers are examined for flaws. The dimensions of the neck and other parts must be checked to determine conformity to the specifications.

Weight checking is done on empty containers, after filling with the product concentrate and after adding the propellant. When propellant blend is used then checks are carried out to determine the proper blend.

Leak testing of the containers is carried out by passing the final filled container through water baths. The temperature of the water baths is periodically checked and recorded.

Spray testing is carried out on all pharmaceutical aerosols. This clears the dip tube of all propellants (for products filled via process of pressure filling), to clear the dip tube of pure concentrate for products filled by pressure under the cap or around the stem. The spray test helps to detect the defects in the valve. The test primes the valves of metered-dose products such that the products are ready to be used by the consumer.

EVALUATION OF PHARMACEUTICAL AEROSOLS

Learning Objective

- Physical, chemical and biological parameters for evaluating aerosols

Pharmaceutical aerosols can be evaluated by the following series of physical, chemical and biological tests:

1. Flammability and combustibility
   (a) Flame extension or projection
   (b) Flash point
2. Physicochemical characteristics
   (a) Vapor pressure
   (b) Density
   (c) Moisture content
   (d) Qualitative and quantitative tests for propellants
3. Performance characteristics
   (a) Aerosol valve discharge rate
   (b) Spray pattern
   (c) Dosage with metered valves
   (d) Net contents
   (e) Foam stability

(f) Particle size determination
(g) Leakage

4. Biological testing
   (a) Therapeutic efficiency
   (b) Toxicity

Flammability and Combustibility

Flame extension involves spraying the aerosol in an open flame for 4 seconds. The length to which the flame is extended is observed and measured. The test is to indicate the effect of an aerosol formulation on the extension of an open flame.

Flash point is determined using the *tag open-cup apparatus*. The aerosol product is chilled to a temperature of −25°F and transferred to the test apparatus. The temperature of the test liquid is increased slowly and the temperature at which the vapors ignite is taken as the flash point. This test is used to determine the amount of the flammable component in the aerosol. The flash point obtained is usually the flash point of the most flammable component.

Physicochemical Characteristics

The *vapor pressure* is determined using a pressure gauge. Excessive variations in the pressure from container to container may indicate presence of air in the head space. Can puncturing equipments are used to accurately determine the pressure. There are equipments available for both metal and glass containers.

Density is determined by hydrometer or a pycnometer. The apparatus is suitably modified to determine the density of liquefied gas propellants.

Moisture content is determined using a Karl Fischer apparatus or by gas chromatography.

Qualitative and quantitative tests for propellants is done using IR spectroscopy and gas chromatography. The methods also indicate the proportion of each propellant in the blend.

Performance Characteristics

The dosing, performance and the clinical efficacy of aerosol products especially a MDI is dependent on the design of the container and valve. The efficiency and performance of the valve is determined by the following tests.

Valve discharge rate gives the amount of contents dispensed in grams per second. The aerosol can is weighed and the contents are dispensed for a fixed time using a standard apparatus. The container is reweighed and the difference in weight divided by the time gives the valve discharge rate.

Dose uniformity test is carried out to determine whether the patient receives the same dose of the medicament, every time the value is depressed. The test can be done in two ways.

(a) Dispensing one or two doses into a solvent or onto a material that absorbs the active ingredient, and then assaying the amount of active ingredient in the solvent or sample.
(b) Weighing a filled container, dispensing several doses of the product and reweighing the container. The difference in weight, divided by the number of doses dispensed, gives the average dose.

The *spray pattern* of different products and different valves is carried out as follows. The product is sprayed on a piece of filter paper that has been treated with a dye-talc mixture. Based on the nature of

the aerosol, oil soluble or water soluble dye is used. The particles that strike the paper cause the dye to go into solution and to be absorbed onto the paper. This gives a record of the spray, which can then be used for comparison purposes.

The amount of *net contents* is determined by weighing full containers, dispensing the contents, then reweighing the container. The difference in weight gives the net weight.

Foam stability can be determined using a number of tests. The foams may be quick breaking or they may remain stable for one hour or more depending on the formulation. The stability can be determined by visual examination, by determining the time taken for a given mass to penetrate the foam, time taken for a given rod that has been inserted into the foam to fall or by using rotational viscometers.

Particle size is determined using *cascade impactor* (Figure 12.18). The test is done by carrying particles in a stream of air through a series of consecutively smaller jet openings. The bigger and higher density particles get impacted on the slide under the larger openings. As the stream proceeds, the openings get smaller and thus the smaller or the less dense particles are deposited on the progressive slides.

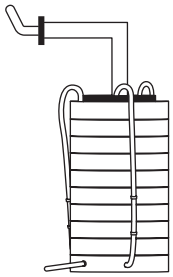


Figure 12.18 Image of a Cascade Impactor

The *leak test* determines whether the valve crimping is free from any leakage. The test can be accomplished by determining the dimensions of the crimp in metal containers and ensuring that it meets the required specifications. After filling the aerosols into the containers, a final leak test is performed by passing the filled containers through heated water baths. The containers are carried by a magnetized chain and submerged into the water bath. The container travels in the water bath such that, by the time it emerges out of the bath, the temperature of the product should reach 130°F. The container should not show any evidence of leakage or distortion.

Biological Testing

The biological tests carried out on pharmaceutical aerosols are similar to tests performed on non-aerosol preparations. Basically they are tested for their therapeutic efficacy and toxicity.

Therapeutic efficacy—the inhalation aerosols or MDIs are tested for their dose uniformity and particle size distribution along with the pharmacokinetic and pharmacodynamic studies. Topical aerosols are applied to the test area and absorption of therapeutic ingredients is determined.

Toxicity testing should include both topical and inhalation effects. Aerosols applied topically may be irritating to the affected area and/or may cause chilling effect. Thermistor probes attached to recording thermometers have been used to indicate the change in skin temperature when an aerosol is sprayed on the skin for a given period of time. Determination of inhalation toxicity is accomplished by exposing test animals to vapors sprayed from an aerosol container.

LABELLING REQUIREMENTS

Shake well.
Keep in a cool place away from heat or sunlight.
Pressurized can.
Keep out of reach of children.
Do not expose to temperatures exceeding 50°C.
Do not spray near a naked flame or any incandescent material.
Do not puncture or burn can even when it is empty.

REVIEW QUESTIONS

Answer in Detail

1. Explain with a neat labeled diagram the construction of an aerosol valve.
2. Classify propellants and mention their advantages and disadvantages.
3. Explain the different evaluation parameters for aerosols.
4. Write a note on aerosol containers.
5. Explain the methods involved in manufacturing of aerosol.
6. Write about the different aerosol systems.
7. Explain in detail the different components of an aerosol system.

Answer in Brief

1. Write the advantages and disadvantages of aerosols.
2. Explain the principle of aerosol operation.
3. Write a note on MDI.
4. Write the advantages and disadvantages of metal containers.
5. Write the advantages and disadvantages of glass containers.
6. Explain the different components of an aerosol valve.
7. Write a note on propellants.
8. Compare liquefied gases and compressed gas propellants.
9. Write a note on aquasol system.
10. Write a note on suspension aerosols.
11. Write a note on emulsion aerosols.
12. Write a note on quality control tests for aerosols.
13. Explain the different tests to determine the performance characteristics of aerosols.
14. Write a note on cold filling and pressure filling.
15. Write about the nomenclature of propellants.

Answer in One or Two Sentences

1. What is a cascade impactor?
2. What are the different materials used in the construction of aerosol containers?
3. Write a note on metering valves.

4. Give examples for liquefied gas propellant.
5. Write the disadvantages of liquefied gas propellants.
6. Which are the propellants used in topical aerosols?
7. What is the disadvantage of compressed gas propellant?
8. Mention the tests for flammability and combustibility of aerosols?
9. Explain the test used to determine dose uniformity of aerosols?
10. How do you determine leakage in aerosol containers?
11. Explain the foam stability test.

Multiple Choice Questions

1. Aerosols are suspensions of liquid globules or solid particles in _____.
   (a) gaseous vehicle (b) liquid molecules
   (c) ointment base (d) aqueous solution
2. Which of the following is not a CFC?
   (a) Dichlorofluoromethane (b) Trichlorofluoromethane
   (c) Bromochlorodifluoromethane (d) Trichloromethane
3. Which of the following propellants is used in topical aerosols?
   (a) Trichloromonofluoromethane (b) Dichloromonofluoromethane
   (c) Dichlorotetrafluoroethane (d) Propane
4. Which of the following device is used to increase the efficiency of drug delivery via aerosols?
   (a) Tube spacers (b) Metered valve (c) Actuator (d) Pressure valve
5. Which of the following component regulates the opening and closing of the valve?
   (a) Dip tube (b) Stem (c) Actuator (d) Mounting cup
6. Propellant 114 refers to which of the following?
   (a) Propane (b) Dichlorodifluoromethane
   (c) Dichlorotetrafluoroethane (d) Trichloromonofluoromethane
7. Which of the following is a disadvantage of compressed gas propellant**?**
   (a) Acts like a piston
   (b) Flammability
   (c) Temperature changes have little effect on pressure
   (d) Pressure drops during the lifetime of the product
8. Cascade impactor is used to determine which of the following parameters?
   (a) Leakage (b) Dose uniformity
   (c) Particle size distribution (d) Flammability
9. Tag open-cup apparatus is used to determine which of the following?
   (a) Flammability (b) Density
   (c) Moisture content (d) Vapor pressure

ANSWERS TO MULTIPLE CHOICE QUESTIONS

1. (a) 2. (d) 3. (d) 4. (b) 5. (c)
6. (b) 7. (d) 8. (c) 9. (a)

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