Pharmaceutical Analysis Volume - I

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CHAPTER

1

INTRODUCTION

Analysis is important in every product or service, but in Drug it is very important as it involves life. In comparison to general consumer products, in Drugs there is and there can be only quality/standard product and no other product. Quality of the product comes from series of tests from quality control, starting from raw materials, in process during manufacture, finished product etc. It is the moral obligation to the patients, and hence the manufacture and quality of drugs should be taken care off.

Quality of drugs should meet the standards related to safety, potency and efficacy. Hence, all these aspects of quality are evaluated by various quality control methods. The aim of quality control is to evaluate whether the sample of drug complies with the appropriate specifications, based on various tests. These tests may vary from single entity or combination of several potent drugs in formulation. These tests of quality control may belong to the following types :

1. Chemical methods
2. Physico-chemical methods
3. Microbiological methods
4. Biological methods

Chemical Purity :

Chemical purity as such means freedom from impurities/ foreign bodies. A state of 100% purity is very difficult, but with sufficient care in manufacturing processes the purity may be obtainable as desired. This may, many-a-times lead to the process which is economically unsound. Hence, it should be considered with the emphasis on cost of the product, desired purity and stability for pharmaceutical purposes.

The chemicals for pharmaceutical use are completely different from that to be used for general purposes. The chemicals to be used as a Drug or in Pharmaceutical formulation should be conformed to the prescribed standards and the main criterion is safety in use. Special attention is directed to impurities which may be toxic and to impurities which affect the general stability.

Although purity of the chemicals to be used in formulations is of utmost importance, the biological action of the chemical is also of equal importance when it is to be used in pharmaceuticals. This will give the acceptable level of biological response and minimum or freedom from toxicity.

Standardisation of Pharmaceutical Chemicals and Formulated Products : Official Methods of Standardisation :

Quality of pharmaceuticals is based on the pharmacopoeial specifications. These methods are designed to set the permissive limits of tolerance for the product when it reaches the patient. Official pharmacopoeia standards are designed considering all known methods of manufacture, safeguard against the varying standards of purity, impurity patterns, stability etc.

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Of course, the main stress is given to the fact that, the product is clinically satisfactory. It is also necessary that the standards so set should ensure that the reproducible products can be prepared by different operators in different laboratories and to ensure that product is of acceptable level of potency with consistent, therapeutic response and non-toxic during storage while it reaches sick human beings.

Official methods of standardization are framed taking into consideration nature and purity of chemicals, methods of manufacture, hazards of manufacture and storage conditions, etc.

Official methods of standardization i.e. monographs of Pharmaceutical chemicals and formulated products are descriptive as well as informative in addition to limits of purity, standards of the product and storage conditions.

Official monograph generally, include the following :

1. Description
2. Minimum standard of purity
3. Identification tests
4. Limit test to exclude excessive impurities
5. Physical constants
6. Storage conditions and packaging
7. Labelling
8. Dosage
9. Therapeutic category
10. Quantitative assays

Titles :

The main titles of monographs are given. Subsidiary titles or synonyms have the same significance as the main title. When the chemical composition of the substance is known, molecular formulae and molecular weight are given. The information refers to the chemically pure substances and the formulae denote the chemically pure substances. Chemical names have also been provided in monograph. These are the names sanctioned and employed by IUPAC.

Chemical formulae, molecular weight :

Molecular formulae and molecular weight are given in the monograph. This gives the chemical purity of the chemicals when the chemical composition is known.

e.g. NaCl molecular weight, Aspirin molecular weight and molecular formula and molecular weight are not given if the composition is not known correctly.

Identification :

Tests for identity are provided only as an aid to identification. They are not sufficient to establish identity in all cases. Identification tests are usually based on qualitative tests for basic and acidic radicals for inorganic chemicals. Organic substances are identified by the various characteristic reactions of one or more of the functional groups present in the molecule.

Dosage :

Doses mentioned in the monograph are intended for general guidance. Generally, if not stated, the average range of quantities which are regarded as suitable for adults when administered by mouth. They are not to be regarded as binding on prescribers. These, are included for the guidance and are not to be regarded as statements of standards.

Minimum Standard of Purity, Assay Tolerances :

Where the standard for a substance described is expressed in terms of the chemical formula for that substance an upper limit is not stated, the upper limit is not more than the equivalent of 100.5 percent. The limits of content are determined by the method prescribed therein. The limits are expressed numerically, the upper and lower limits of a range are inclusive so that the range consists of two values themselves and all intermediate values but no values outside the limits. The limits and tolerances stated in the monograph for the

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Pharmaceutical chemicals allow for analytical errors, variations in manufacture and compounding, and for deterioration to an extent considered insignificant under practical conditions. No further tolerances should be applied to the values obtained in a test assay for compliance of specifications of the monograph.

Description :

Description in relation to the chemical is relatively general in nature. It is provided to indicate the properties of the chemicals. The properties are not in themselves standards or tests for purity though they may help in the preliminary evaluation of the chemical. Statements on task are also provided only in cases, where this is a guide to the acceptability of the material. The nature of the chemicals on odour are also furnished. But such statements are not part of the official standards.

Solubility :

The statements on solubility are not standards or tests for purity but are provided primarily as information. However, where quantitative solubility test is given under standards, the drug should comply with all these requirements.

Statements of solubilities are indicated by a descriptive phrase and are intended to apply at ambient temperature. The phrases can be explained as :

	Descriptive Phrase	Approximate quantity of solvent volume for 1 part by weight of solute
1.	Very soluble	Less than 1 part
2.	Freely soluble	From 1 to 10 parts
3.	Soluble	From 10 to 30 parts
4.	Sparingly soluble	From 30 to 100 parts
5.	Slightly soluble	From 100 to 1000 parts
6.	Very slightly soluble	From 1000 to 10,000 parts
7.	Practically insoluble	More than 10,000 parts

Packaging, Storage and Labelling :

Container is the device that holds the chemical. The container should not interact physically or chemically with the chemical placed in it so as to alter the strength, quality or purity of the chemical beyond the official requirements. The container should be light sensitive container, well-closed container, tightly closed container etc.

Storage conditions do not form a part of the standards. They are defined as :

1. **Cold :** Any temperature not exceeding 8°C and usually between 2° and 8°C.
2. **Cool :** Any temperature between 8° and 25°C.
3. **Room Temperature :** Temperature prevailing in working area.
4. **Warm :** Any temperature between 20° and 40°C.
5. **Excessive Heat :** Any temperature above 40°C

Where no specific conditions are indicated, it is to be understood that storage conditions include protection from moisture, freezing and excessive heat.

In general labelling of drugs and pharmaceuticals is governed by Drugs and Cosmetics Act. In certain cases, additional information which must be stated on label is mentioned in the monograph.

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Therapeutic category :

This generally gives the use of this chemical as a pharmaceutical. The general category of the chemical is mentioned as its pharmacological activities such as analgesic antipyretic, antimalarial, antidiabetic, laxative, antacid, antibacterial, diuretic, etc.

Limit Tests

Limit tests are important to determine the permissive limits of tolerance. These tests are designed to identify and control small quantity of impurity which is likely to be present. They usually involve simple comparison of opalescence, colour or turbidity with that of standard sample prescribed in Pharmacopoeia. In these tests, concentration of impurity is expressed as ppm or as percentage.

The design of individual test is important if the errors are to be avoided in the hands of different operators. They are by considering number of factors such as :

1. Specificity of the test, 2. Sensitivity, 3. Personal error.

Physical Constants

Physical constants are the characteristic properties useful for both identification and maintenance of standards of purity and hence, they are included in monograph for the standardization of pharmaceuticals. These constants include melting point, boiling point, refractive index, optical rotation, light absorption, solubility etc.

(a) Melting point : Melting point is characteristic of sample. But, it has limitations as it is affected by various, factors such as capillary size and dimension, sample size, rate of temperature rise and so on. Reproducibility is another problem. Hence, melting range is used as criterion for purity and identity. Even traces of impurity are sufficient to cause appreciable depression in melting point and this fact is used in control of purity of Pharmaceutical chemicals.

The melting point of nicotinic acid is 234-237°C. Metronidazole 159-162°C, Benzoic acid 121-123°C, Cimetidine 139-144°, Salbutomol about 156°, Paracetamol 168-172°C.

The characteristic value of melting point can control the purity of chemical.

(b) Boiling point : It is a characteristic property of a liquid and can be used for identification.

It is the temperature at which ebullition occurs first. Even traces of impurities are sufficient to lead to increase in boiling point which can control the purity of the chemical.

The boiling point of isopropyl alcohol 81-83° acetic anhydride 136-142°, aniline 184°, chloroform 60-62°, cineole 176°, dimethyl sulfoxide 192°C.

(c) Specific gravity, relative density, Weight per millilitre : These constants are generally used for liquids and oils as standards. Weight per ml, is the weight of 1 ml of liquid at 20°C and is widely used in Pharmacopoeia. However, specific gravity, the ratio of mass of given volume of liquid to that of an equal volume of water (both at 20°C) is still used for ethanol and methylated spirits. This is not used as standard for alcoholic preparations such as tinctures and liquid extracts. Relative density is synonymous to specific gravity.

Weight per millilitre is generally used in Pharmacopoeia of India to control the purity of sample.

Weight/ml of ethyl oleate 0.869-0.874, oleic acid 0.889-0.895, castor oil 0.945-0.965.

(d) Refractive index : Refractive index is the characteristic property of liquid / solutions. Presence of impurities affect the refractive index appreciably and hence, it is used for control of purity of various liquids. Temperature measurement is also considered.

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Refractive index of castor oil should be 1.4670-1.4700, eucalyptus oil 1.457-1.469, glycerine 1.470-1.475, paraldehyde 1.403-1.406, arachis oil 1.467-1.470 as per the Pharmacopoeia.

(e) Absorption of light : Measurement of light absorption in the visible and ultra-violet range is now used as a means of identification. Absorbance at specified wavelengths is used as the basis to exclude undesired impurities.

Absorption of light in infrared range is used as the method of choice for the verification of identity of Pharmaceutical chemical because of high structural specificity of I.R. spectra. Comparison of the infrared absorption spectrum of the sample with that of authentic reference compound is widely used for identification.

The light absorption at a specific wavelength is characteristic for that chemical. e.g. Ethacrynic acid at 270 nm has E_{1cm} is 0.55-0.60, Prednisolone at 240 nm has E_{1cm} is 0.365-0.395.

Thus, it can control the purity of the chemical.

(f) Optical rotation : Optical rotation measurement helps in identification as well as the control of quality. Specific optical rotation of optically active compounds provides a valuable means in determining purity of Pharmaceutical chemicals, in which pharmacological activity is highly correlated with molecular configuration.

Specific rotation is the optical rotation produced by the solution is the angle of rotation of the plane polarized light at the wavelength of D line of sodium [589.3 nm], measured at 25°C calculated with reference to a 1 decimetre thick layer of liquid and divided by the specific gravity at 25°C.

The specific rotation of Dextrose +52.5° to 53.3°, oestradiol benzoate +57° to +63°, sorbitol +4° to +7°, Quinine sulfate –237° to 245° as per pharmacopoeia.

(g) Viscosity, swelling power : Measurement of viscosity is used as a means of distinguishing various grades of liquid paraffins. This is used to control the molecular size of dextrans.

Viscosity of PEG 1500 is 25-32 mm^2s^{-1}, PEG 4000 is 76-100 mm^2s^{-1} at 100°C. PEG 6000 470-900 mm^2s^{-1}.

The quality of Bentonite, a suspending agent which forms gels by the absorption of water, is controlled by its swelling power, a measure of its increase in volume in water.

It is also used to control the purity of Kaolin, Isaphgula Husk.

(h) Polymorphism and particle size : Solid state properties of insoluble drugs which are necessarily administered in solid form, can affect the rate of both solution and absorption of drug. Particularly, crystal form and particle size are the important factors in controlling surface area, which determines the activity of drug.

Certain products may be produced in one particularly pharmaceutically more desirable polymorphic form. Polymorphism, the ability to crystallize in alternative crystal forms, is a widespread phenomenon. Like particle size, it too can be significant in compounds of relatively low solubility in determining the level and duration of the response. Thus chloramphenicol palmitate exists in polymorphic forms of which one is biologically active.

Quantitative Assays :

The assays and tests are the standards prescribed by Pharmacopoeias. The analyst is not precluded from employing an alternative method if he is satisfied that the method which he uses will give the same results as the Pharmacopoeial method. In the event of doubt or dispute, the methods of analysis of Pharmocopoeia are alone considered official.

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Assay methods should not only be specific for the chemical but also for stability determination. Non-specific methods of assay are also frequently used; e.g. most aromatic substances show an absorption, which can form the basis of an assay, in the region 260–300 nm; this absorption is characteristic of the aromatic ring. The assay method is regarded as sufficiently specific for the purpose when it is taken in conjunction with the other requirements of the monograph.

Under quantitative assays, the procedures of quantitative analytical chemistry are applied to the analysis of materials used in pharmaceuticals. In analytical chemistry it is important to gain the information about the qualitative and quantitative composition of substances and chemical i.e. to find out what a substance is composed of and exactly how much. In qualitative analysis, the details regarding the presence or absence of one or more components are obtained, while in quantitative analysis, the details regarding how much of the pure component is present is available.

Analysis are also classified based on the sample size used for the analysis. They are as under :

(a)	Sample size of 0.1 g or more	:	macro
(b)	Sample size of 0.01 g to 0.1 g	:	semimicro
(c)	sample size of 0.001 g to 0.01 g	:	micro (meso)
(d)	sample size of 0.0001 to 0.001 g	:	submicro
(e)	sample size less than 10^{-4} g	:	ultramicro
(f)	sample size of 100-10,000 ppm	:	trace

There are various methods of Quantitative analysis. Generally, the components are related characteristically to some physical property and on the basis of that the quantity is estimated. They are classified into :

1. Chemical Methods
   (a) Volumetric, (b) Gravimetric, (c) Gasometric
2. Physico-chemical Methods or Instrumental Methods
3. Microbiological Methods
4. Biological Methods

1. Chemical Methods

(a) Volumetric methods : Volumetric or titrimetric methods are preferred to gravimetric processes specially because of speed and convenience. In volumetric methods, assay is based on the measurement of volume of solution of known strength that is required to react completely with the substance to be analysed. On the basis of this measurement of volume, quantity of pure component is estimated. In this method: criterion for the selection of reagents is that the reagent must react rapidly, reaction must be complete and there should be some method to detect the completion of reaction. This method is classified into different types depending upon the type of reactions involved in the reaction. They are :

1. Neutralisation titrations
2. Non-aqueous titrations
3. Precipitation titrations
4. Oxidation-reduction titrations
5. Complexometric titrations.

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(b) Gravimetric methods : Gravimetric analysis is a quantitative analysis by weight and is a process of isolating and weighing the compound of known composition i.e. purest form. The separation of compound is affected by number of ways like precipitation, volatilization, electroanalytical etc. In these, first two methods are important in practice. Although gravimetric analysis is time-consuming, the constituent may be examined for the presence of impurities and correction can be applied if necessary.

(c) Gasometric methods : These methods involve measurement of the volume of gases. They measure the :

(a) Volume of gas liberated in the given chemical reaction under the conditions that are described in the process [The volume measured is corrected to standard conditions of temperature and pressure] .

(b) Decrease in the volume of gas when a suitable agent is placed to absorb one of the gases present and reduced to standard conditions of temperature and pressure.

Following gases are determined by gasometric analysis in pharmacopoeia : Cyclopropane, carbon dioxide, nitrous oxide, oxygen, octyl nitrate, nitrogen, amyl nitrate, ethylene and helium etc.

The measurement of volume of gas is generally made in gas burettes or by nitrometers.

2. Instrumental Methods

They are based on the relation between the content and corresponding physicochemical and physical properties of the chemical system being analysed. The changes in the properties of the system are generally detected through the measurement of current, potential, electrical conductivity, optical density, refractive index etc. with suitable and sensitive instruments.

Physical Properties	Instrumental Methods
1. Electrical potential	Potentiometry
2. Electrical conductance	Conductometry
3. Electrical current	Polarography, voltametry
4. Absorption of radiation	Spectrophotometry
	Colorimetry,
	Atomic absorption spectroscopy
5. Emission of radiation	Emission spectroscopy
	Flame photometry
	Fluorimetry
6. Scattering of radiation	Turbidimetry, Nephelometry
7. Refraction of radiation	Refractometry
8. Rotation of plane	Polarimetry
Polarised light	Optical rotatory dispersion
9. Thermal properties	Thermal method
10 Mass to charge ratio	Mass spectrometry

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In addition to above methods, the chromatographic methods are also available. Chromatography is said to be the procedure by which active principles, excipients and impurities are separated by passage of a mixture through a fixed porous bed possessing varying but reversible affinity for individual components. Thus chromatography is a separation technique or a device by which a mixture of substances is separated into its various components. In addition to this, these methods are also used for identification as well as quality control by various pharmaceuticals.

Chromatographic methods include the column, paper, thin layer, gas, ion exchange, HPLC etc.

3. Microbiological Methods

The inhibition of microbial growth under the standardised conditions may be utilised for knowing the therapeutic efficacy of antibiotics. Any subtle change in the antibiotic molecule which may not be detected by chemical methods will be revealed by a reduction in antimicrobial activity and hence microbiological assays are very important for resolving doubts regarding possible loss of potency of antibiotics and their preparations.

The microbiological assay is based upon a comparison of the inhibition of growth of bacteria by measured concentration of antibiotics to be examined with that produced by known concentration of standard preparation of the antibiotic having a known activity. Two general methods are usually employed, the cylinder plate (or cup plate) method and the turbidimetric (or tube assay) method.

4. Biological Methods

Biological assays (bioassays) are prescribed where the potency of a drug or its preparation cannot be adequately determined by chemical or physical means, but where it may be possible to observe the biological effect of the drug on some type of living matter. The principle of such assay is to compare how much of the sample being tested produces the same biological effect as a given quantity of a standard preparation. It is also important that conditions under which the sample and the standard preparation are tested, are identical in all respects of time, environmental factors and biological media used.

However, as the problem of perfectly matching and controlling experimental conditions is very difficult, the biological responses vary to different extent and in bioassays it is necessary not only to estimate the potency of drug, but also to compute the margin of errors in estimate. The typical bioassay involves a stimulus applied to a subject. The intensity of stimulus applied to a subject is known as the dose and is measured by a weight, or preparation concentration. The observed effect of the stimulus on the subject known as response, may be measured by the total weight or weight of some organ of the subject, diameter of inhibition zone, blood sugar concentration or even a simple record of occurrence or non-occurrence and some physiological symptoms.

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CHAPTER

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IMPURITIES IN PHARMACEUTICAL SUBSTANCES AND LIMIT TESTS

The substances that are used in the pharmaceutical field, should be almost pure so that they can be used safely. It is rather difficult to obtain an almost pure substance. We find substances and chemicals, with varying degrees of purity. For example, substances like cane-sugar (sucrose), dextrose, common salt and many inorganic salts, are found with over 99 to purity while many others only contain traces of impurities. The purity of substances depends upon several factors, such as their methods of manufacture and types of crystallization or purification process. In the pharmaceutical field, one deals with a large number of drugs, chemicals and other substances which are used in formulations. All such materials need to be pure. However, it is almost impossible to get an absolutely pure material, as impurities get incorporated into them either during manufacture, purification or storage.

SOURCES OF IMPURITIES

The type and amount of impurity present in the chemicals or pharmaceutical substances, depends upon several factors. Some such factors are discussed below :

Raw Material Employed in Manufacture :

When substances or chemicals are manufactured, the raw materials from which these are prepared, often contain impurities. These impurities get incorporated into the final product. Impurities like arsenic, lead, heavy metal etc., are present in raw materials, and are hence found in substances. It is therefore, necessary to employ pure chemicals and substances as raw materials for the manufacturing process.

Method or the Process used in Manufacture :

There are a number of drugs and chemicals (especially organic), which are manufactured from different raw materials by adopting different methods or processes. Some impurities get incorporated into the materials during the manufacturing process. The type and amount of impurity present in the drugs or chemicals varies. Furthermore, for certain drugs a multiple-step-synthesis procedure is used, which produces intermediate compounds. The purification of the intermediates is also essential, otherwise impurities present in the intermediates will get into the final compound. Often, side reactions take place during the synthesis. Impurities of the side reaction product are also found in the substances.

Chemical Processes and Plant Materials employed the Process :

In the synthesis of drugs, many chemical reactions like nitration, halogenation, oxidation, reduction, hydrolysis etc., are involved. In these chemical processes, different

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solvents, chemicals etc., are used. When chemical reactions are carried out in vessels or containers, the materials of these vessels (like iron, copper, tin, aluminium etc.) are reacted upon by the solvents and chemicals, and reaction products are formed. These reaction products derived from the plant material occur as impurities in the final product. Thus, impurities of iron, lead, heavy metals, copper etc., in substances are due to the above mentioned reason.

Storage Condition :

The chemicals, substances when prepared, are stored in different types of containers, depending upon the nature of the material, batch size and the quantity. Various types of materials are used for storage purpose. These may be plastic, polythene, iron vessels, stainless steel, aluminium, copper etc. Reaction of these substances with the material of the storage vessel takes place and the products formed, occur as impurities in the stored material. The reaction may take place directly or by the leaching out effect on the storage vessel. Alkalies stored in ordinary glass containers, extract lead from it, which occurs in the final product. Similarly, strong chemicals react with iron containers, and extract iron.

Decomposition :

Some substances decompose on keeping and the decomposition is greater in the presence of light, air or oxygen. The result of decomposition causes contamination of the final product. Many substances loose water of crystallization when kept open, while deliquescent substances absorb water from the atmosphere, and get liquified. Crude vegetable drugs are especially susceptible to decomposition. A number of organic substances get spoiled, because of decomposition on exposure to the atmosphere e. g. amines, phenols, potent drugs etc. The decomposition products thus appear as impurities in the substances.

EFFECT OF IMPURITIES

It can be seen that, almost pure substances are difficult to get and that some amount of impurity is always present in the material. The impurities present in the substances may have the following effects :

1. Impurities which have a toxic effect, can be injurious when present above certain limits.
2. Impurities, even when present in traces, may show a cumulative toxic effect after a certain period.
3. Impurities are sometimes harmless, but are present in such a large proportion, that the active strength of the substance is lowered. The therapeutic effect of drug is decreased.
4. Impurities may bring about a change in the physical and chemical properties of the substance, thus making it medically useless.
5. Impurities may cause technical difficulties in the formulation and use of the substances.
6. Impurities may bring about an incompatibility with other substances.
7. Impurities may lower the shelf life of the substance.
8. Impurities, though harmless in nature, may bring about changes in odour, colour, taste etc., thus making the use of the substance unethical, as well as unhygienic.

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PERMISSIBLE IMPURITIES IN PHARMACEUTICAL SUBSTANCES

Since it is not possible to avoid impurities, it is necessary to have substances that are reasonably pure. The pharmacopoeial committee takes the following points into consideration with respect to the problem caused by impurities in substances.

1. For impurities which are of harmful type e.g. lead, arsenic etc., a low permissible limit is prescribed. This is based upon, how much of these can be tolerated ? Which itself is based upon how much of the impurity is harmful ?

2. For impurities that are harmless, the aim is to fix their limits so that, their presence does not interfere in the therapeutic usefulness of the drug. Here, again, the limits are prescribed and fixed. This is done depending upon the nature of the impurity, the type of substance, use of the substance, etc.

3. Another consideration is the practicability of obtaining substances without impurities, at reasonable costs. It may be possible to prepare substances (through a series of steps of purification) without any impurities, but this may be achieved at an exorbitant cost.

Considering this aspect, limits of various impurities are fixed.

4. Deliberate adulteration by using materials having similar qualities also accounts for the presence of impurities in the substance, e. g. adulteration of sodium salt with potassium salt, calcium salts with magnesium salts etc. Such adulteration which brings impurities into substances, need not exhibit less therapeutic activity but it is reasonable to expect unadulterated material from an ethical point of view. Pharmacopoeias guard against this type of impurity by employing tests for identification.

Test for Purity :

Pharmacopoeias of various countries prescribe *'tests for purity'*, for substances which are to be used for medical purposes. The so called *'tests for purity'*, are as a matter of fact tests for detecting impurities in the substances and pharmacopoeias fix the limits of tolerance for these impurities. The governing factor for these tests, is to determine how much impurity is likely to be harmful, or to bring about technical and other difficulties, when the substance is used. Pharmacopoeias do not aim at ensuring freedom from every possible impurity in a substance, but to test for few major impurities, which are likely to interfere in their use. Certain tests which are carried out on the substances are :

Colour, odour and taste :

Along with other tests for purity, description of taste, odour, colour etc., are given in the pharmacopoeias. Though they have limited value they are useful in determining whether the substance is reasonably pure, hygienic etc.

Physico-chemical constants :

Solubility of the substance in various solvents, determination of melting and boiling points for organic substances, optical rotation for optically active substances and refractive index for liquids, are some values which tell us about the purity of substance. Determination of the acid value, iodine value, saponification value, acetyl value, ester value etc., for vegetable oils are generally constants and a variation in their value, signifies the presence of impurities. The extent of the variation in these values, usually depends upon the nature and extent of impurities present in the substances. However, a

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very low concentration of impurities, may fail to alter these constants, and thus remain undetected, unless tested specifically, by special tests.

Acidity, Alkalinity and pH :

Substances that are prepared from chemical reactions involving acids and alkalies often contain considerable amounts of the acid or alkali, as an impurity. Thus, the tests for acidity or alkalinity are of a great help to estimate the extent of the impurity. Furthermore, solutions of certain substances have a definite pH at a given concentration. The presence of an impurity will bring about a change in the pH and thus it can be detected.

Anions and Cations :

A large number of synthetic drugs both inorganic and organic is prepared using strong acids like hydrochloric, sulphuric, nitric etc. The presence of chloride and sulphate ions are thus common impurities. Test for these ions (anions) is thus generally carried out. Similarly, tests for sodium, ammonium (cations) are often carried out to detect impurities in inorganic compounds (test for sodium in potassium salt and vice-versa, calcium in magnesium salts etc.). Tests for heavy metals, like lead, iron, copper and mercury are also carried out as these are very common impurities in substances.

Insoluble residue :

Pure substance give a clear solution in a given solvent. When insoluble impurities are present in a substance then the solution appears cloudy, or shows opalescence. The measurement of turbidity or opalescence helps to determine the amount of insoluble impurity present in the substance. If the insoluble residue is high then this can be determined by filtering and weighing the insoluble residue.

Ash, Water insoluble ash :

Determination of ash in crude vegetable drugs, organic compound, and some inorganic compounds, gives a good indication about the extent of impurities of heavy metals or minerals in nature. This determination is therefore, commonly employed for a number of substances. In certain cases, water-insoluble ash is also determined to find water-soluble heavy metals or mineral types of impurity.

It is thus clear that depending upon the type of material or substance, pharmacopoeias prescribe tests for purity of particular nature; e.g., salicylic acid in acetyl salicylic acid, phenatidine in phenacetin, acraldehyde in glycerine, p-aminophenol in paracetamol etc. In general, it could be said that, impurities of chloride, sulphate iron, heavy metals, lead and arsenic, are common in drugs and chemicals, Pharmacopoeias of various countries, therefore, prescribe limit tests for these to be carried out by a particular method.

Limit Test for Chlorides and Sulphates :

The principle of the limit test for chlorides and sulphates is based upon the measurement of opalescence or turbidity produced in the known amount of substance (by addition to reagent), and comparing it with the standard opalescence or turbidity. For comparison of turbidity for different substances with varying amount of impurity, the amount of substance to be used is varied, and not the standard turbidity. Pharmacopoeias do not give a numerical value to the limits, as it is not practicable as its content will be influenced to a great extent by large quantities of other substances present.

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The limit test for chlorides is based upon the chemical reaction between soluble chloride ions with a silver nitrate reagent in a nitric acid media. The insoluble silver chloride renders the test solution turbid (depending upon the amount of silver chloride formed and therefore, on the amount of chloride present in the substance under test.) This turbidity is compared with the standard turbidity produced by the addition of silver nitrate, to the known amount of chloride ion (sodium chloride) solution. If the test solution shows less turbidity than the standard, the sample passes the test.

In a limit test for sulphate, the solution of the substance under test is mixed with barium sulphate reagent in a hydrochloric acid medium and the turbidity so produced is compared with the standard in similar manner with a known quantity of sulphate ion (using potassium sulphate). The substance passes the limit test if it produces a turbidity that is less than the standard.

In performing these tests, it is essential to follow the directions indicated by the Pharmacopoeia.

Preparation of the Solution for Tests :

A specified amount of the substance is dissolved in distilled water, and the volume made to 50 ml in a Nessler's cylinder. Depending upon the nature of the substance, some modifications are carried out for the preparation of the solution; e.g. alkaline substances like carbonates, hydroxides, etc., are dissolved in sufficient quantity of acid so that effervescence ceases, and free acid is present. For insoluble substances like kaolin, a water extract is prepared, filtered and then the filtrate used. Salts of organic acids like sodium benzoate, sodium salicylate, etc., liberate free water insoluble organic acid, during acidification which is filtered off and the filtrate is used for the test. Coloured substances like crystal violet, malachite green etc., are carbonised and the ash so produced is extracted in water. Reducing substances like nitrite, hypophosphate etc., are oxidised with oxidising agents, and the solution is prepared and used. Substances like potassium permanganate are reduced by boiling with alcohol, and the filtrate is used.

Limit Test for Chloride

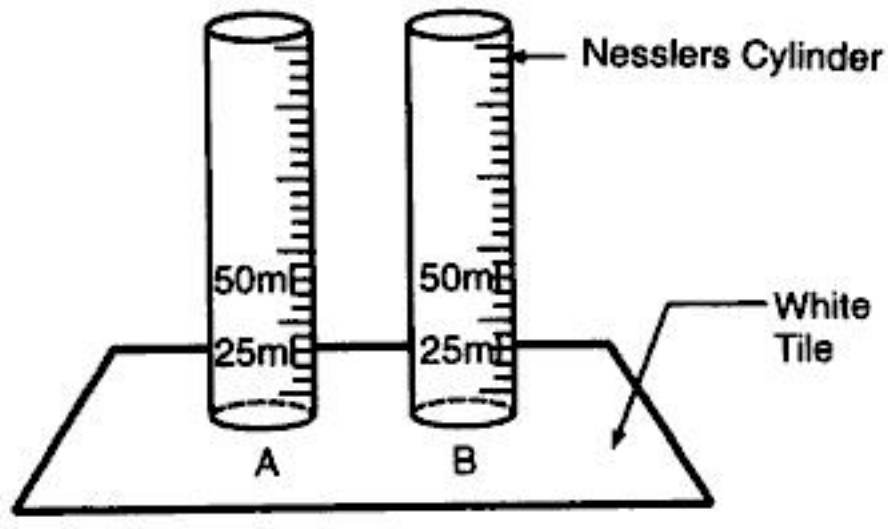

Fig. 2.1 : Nessler's Cylinder

Dissolve the specified quantity of substance in water or prepare a solution as directed in the pharmacopoeia and transfer to a Nessler's cylinder A (Figure 2.1). Add 1 ml of dilute nitric acid except when nitric acid is used in the preparation of the solution. Dilute it to 50 ml with water and add 1 ml of silver nitrate solution, stir immediately with a glass rod and set aside for 5 minutes. Simultaneously for standard opalescence, place 1 ml of

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0.05845 percent w/v solution of sodium chloride in Nessler's cylinder B and add 10 ml of dilute nitric acid, make up the volume to 50 ml with water, add 1 ml of silver nitrate solution, stir with the glass rod and set aside for 5 minutes. The opalescence produced by the sample (in cylinder A) should not be greater than standard opalescence.

Limit Test for Sulphate :

A solution of specified quantity of substance is made in water or prepared as directed in the pharmacopoeia in Nessler's cylinder and add 2 ml dilute hydrochloric acid except where hydrochloric acid is used in the preparation of solution. Dilute it to 45 ml with water, add 5 ml of barium sulphate reagent, stir immediately with the glass rod and set aside for 5 minutes. To produce standard turbidity place 1 ml of 0.1089 percent w/v solution of potassium sulphate and 2 ml of dilute hydrochloric acid in another Nessler's cylinder, dilute to 45 ml with water, add 15 ml of barium sulphate reagent, stir immediately and set aside for 5 minutes. The turbidity produced by the sample solution is not greater than the standard turbidity.

British Pharmacopeia makes use of a barium sulphate reagent, which contains barium chloride, alcohol and small amount of potassium sulphate. Alcohol prevents supersaturation, and potassium sulphate increases the sensitivity of the test by giving the ionic concentration in the reagent, which just exceeds the solubility product of barium sulphate.

Limit Test for Iron :

This test is based upon the reaction of iron in an ammoniacal solution, with thioglycollic acid which forms a pink to deep reddishpurple coloured complex of iron-thioglycollate. The colour produced from a specified amount of substance from the test, is compared by viewing vertically, with a standard (Ferritic ammonium sulphate). If the colour from test solution is less dark than the standard then the sample passes the test.

The $Fe(SCH_2COOH)_2$ formed with the ferrous form of iron, is quite stable for long period in the absence of air. The colour, however, is destroyed by oxidising agents and strong alkalies. The original state of iron is unimportant, as thioglycollic acid reduces Fe^{3+} to Fe^{2+}. This test is very sensitive. Interference of other metal cations is eliminated, by making use of 20 % citric acid, which forms complex with other metal cations.

Method :

Prepare a solution by dissolving a specified amount of substance in 40 ml water or take 10 ml of solution as directed in monograph in Nessler's cylinder. Add 2 ml of 20 % w/v solution of iron free citric acid and 0.1 ml thioglycollic acid, mix and make alkaline with iron-free ammonia solution and dilute it to 50 ml with water. Allow to stand for 5. minutes. For standard, simultaneously dilute 2 ml of standard iron solution with 40 ml of water, add same quantity of reagent as in the sample. Any colour produced by the sample is not more intense than the standard.

Earlier, ammonium thiocyanate reagent was used for the limit test of iron. Since thioglycollic acid is a more sensitive reagent for iron, it has replaced ammonium thiocyanate in the test.

Limit Test for heavy metals :

Besides the limit test for lead, the Indian Pharmacopoeia and U.S.P., include limit tests for heavy metals present in many compounds. Lead and other heavy metals are

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generally found as impurities in pharmaceutical substances. Two separate tests are therefore prescribed, by these pharmacopoeias.

The limit test for heavy metals is based upon the reaction of the metal ion with hydrogen sulphide, under the prescribed conditions of the test resulting in the formation of metal sulphides. These remain distributed in a colloidal state and produce a brownish colouration. The test solution is compared with a standard prepared using a lead solution (as the heavy metal). The metallic impurities in substances are expressed as parts of lead per million parts of the substance. The usual limit as per I. P. is 20 ppm.

Heavy metals :

The Indian Pharmacopoeia adopts three methods for the limit tests for heavy metals. The '*Method A*' is used for the substance which yields a clear colourless solution under specified conditions. '*Method B*' is used for those substances which do not yield clear colourless solution under the test conditions specified for method A. '*Method C*' is used for substances that yield clear colourless solution in sodium hydroxide medium. The reagents like acetic acid, ammonia, hydrochloric acid, nitric acid, potassium cyanide and sulphuric acid should be lead free and designated as '*Specific reagents*'.

Method A

Standard solution is prepared by taking 2 ml of standard lead solution and dilute it to 25 ml with water. Adjust the pH between 3 to 4 by using either dilute acetic acid or dilute ammonia solution. Make up the volume of 35 ml with water.

Test solution is prepared as directed in the individual monograph. Take 25 ml and adjust the pH of the solution between 3.0 to 4.0 by using dilute acetic acid or dilute ammonia and adjust the volume to 35 ml with water.

To each of the cylinders containing standard and test solution, add 10 ml of freshly prepared hydrogen sulphide solution, mix, dilute to 50 ml with water and allow it to stand for 5 minutes. The colour when viewed downwards over white surface should not be darker for test than standard solution.

Method B

The standard solution is prepared as directed under method A. Test solution is prepared in a crucible by weighing a specified quantity of substance as per monograph. Moisten the substance with sulphuric acid, ignite on a low flame till completely charred. Add few drops of nitric acid and heat to 500° C. Allow to cool, add 1 ml of hydrochloric acid and evaporate to dryness. Moisten the residue with 10 ml hydrochloric acid and digest for two minutes. Neutralize with ammonia solution and make just acidic with acetic acid. Adjust the pH between 3.0 to 4.0, filter if necessary. Adjust the volume of filtrate to 35 ml in Nessler's cylinder, add 10 ml of hydrogen sulphide solution, dilute to 50 ml with water and compare the colour with standard solution.

Method C

The standard solution is prepared by using 2 ml of standard lead solution, adding 5 ml dilute sodium hydroxide solution and making the volume to 50 ml with water. For the test solution take either 25 ml solution prepared as directed in the monograph or take specified quantity of substance, dissolve in 20 ml water, add 5 ml of dilute sodium hydroxide solution and make up the volume to 50 ml.

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To each of the above solution in Nessler's cylinder add 5 drops of sodium sulphide solution, mix and set aside for 5 minutes. The colour produced by test solution should not be darker than the standard solution.

Limit Test for volatile oils :

In 25 ml glass stoppered test tubes, 10 ml of the oil is mixed with an equal volume of water containing a drop of hydrochloric acid. Hydrogen sulphide is passed through the mixture until it is saturated. No darkening in colour should be produced either in the oil, or in the water layer, for the sample to pass the test.

Limit Test for lead :

The limit test for lead as per I. P. and U. S. P. is based upon the reaction between lead and diphenyl thio-carbozone (dithizone). Dithizone in chloroform, extracts lead from alkaline aqueous solutions as a lead Dithizone complex (red in colour).

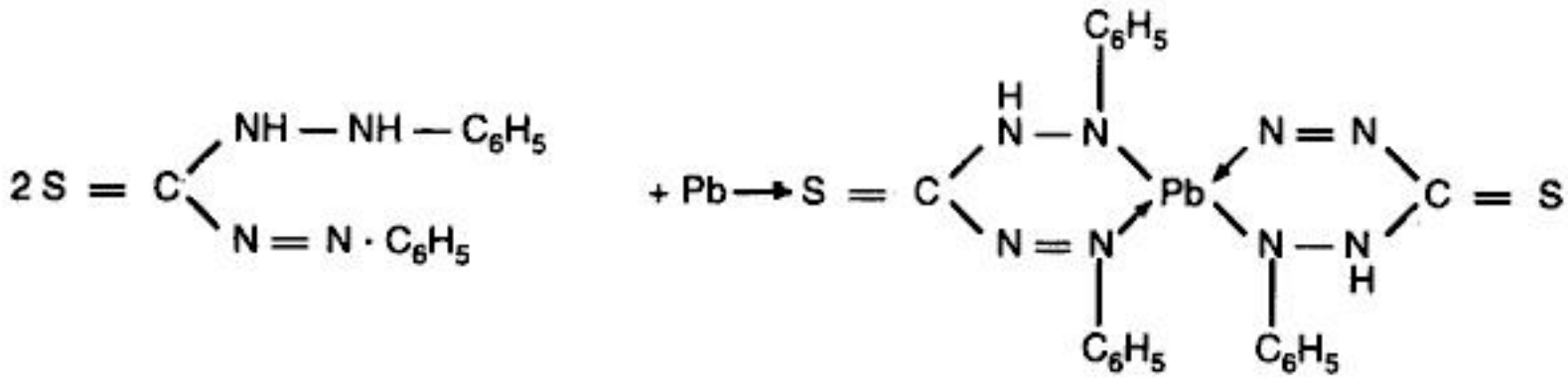

Fig. 2.2

The original dithizone has a green colour in chloroform thus the lead-dithizone shows a violet colour. The intensity of the colour of complex, depends upon the amount of lead in the solution. The colour of the lead-dithizone complex in chloroform, is compared with a standard volume of lead solution, treated in the same manner.

In this method, the lead present as an impurity in the substances, is separated by extracting an alkaline solution with a dithizone extraction solution. The interference and influence of other metal ions etc., is eliminated by adjusting the optimum pH for the extraction, by using ammonium citrate, potassium cyanide, hydroxylamine hydrochloride reagents, etc.

Method

A known quantity of the sample solution is taken in separating funnel. 6 ml of ammonium citrate, and 2 ml of hydroxylamine hydrochloride is added, followed by 2 drops of phenol red, and the solution is made alkaline by adding an ammonia solution. Add 2 ml of potassium cyanide solution and extract immediately with 5 ml portions of dithizone solution (till green). The combined dithizone extracts are shaken for 30 seconds, with 30 ml of 1 % nitric acid, and the chloroform layer discarded. To the acid solution 5 ml standard dithizone solution is added along with 4 ml of ammonium cyanide and shaken for 30 seconds. A known quantity of the standard solution of lead (equivalent to the amount of lead permitted in the sample) is treated separately. The colour (violet) of the chloroform layer of sample, should not be darker than the standard for the sample to pass the test.

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In the preparation, an appropriate preliminary treatment is given, so as to get lead in the solution, without any interfering substance or ion. All reagents employed under the test (except for standard lead solution), should be free from lead, and are designated as 'PbT' reagents in pharmacopoeias.

Limit Test for lead as per British Pharmacopeia :

British Pharmacopeia adopts another method for the limit test for lead which is based on the formation of a brownish colouration produced by the colloidal lead sulphide upon addition of sodium sulphide to the solution under test. If the lead content is more, then a brownish black precipitate of lead sulphide is obtained. The colour produced in the test solution is matched against the standard that is made from a known amount of lead in a Nessler's cylinder. In order to carry out this test two solutions, a primary and an auxiliary are prepared from the sample.

Method

Two solutions of the substance under test are prepared with hot water and acetic acid. One is the primary solution containing a definite but greater amount of substance and placed in a 50 ml Nessler's cylinder. The other is the auxiliary solution containing a known amount of the test substance in another 50 ml Nessler's cylinder. To this auxiliary solution, a definite amount of a dilute solution of lead nitrate is added. Ammonia and potassium cyanide solutions are added to both the solutions in the Nessler's cylinders. Small amounts of burnt sugar solution is added to both solutions, to correct any difference of colour and the volume is made upto 50 ml. If the solutions appear turbid, then they are filtered and the volume made upto 50 ml. Both solutions are treated with sodium sulphide solution and a colour is developed. If the colour in the auxiliary solution is darker than that in the primary, then the substance contains lead within limits.

The object of using primary and auxiliary solutions of substances is to have a comparison made under identical conditions. Interference by any unknown entity present in the solution is eliminated by this technique.

Limit Test for Arsenic :

Arsenic is an undesirable and harmful impurity in medicinal substances, and all pharmacopoeias prescribe a limit test for it. There are many qualitative and quantitative tests for arsenic. The pharmacopoeial method is based on the Gutzeit test. In this test, arsenic is converted into arsine gas, (AsH_3) which when passed over a mercuric chloride test paper, produces a yellow stain. The intensity of the stain is proportional to the amount of arsenic present. A standard stain produced from a definite amount of arsenic, is used for comparison.

The chemical reactions involved in the method are given below: When the sample is dissolved in acid, the arsenic present in the sample is converted to arsenic acid. The arsenic acid is reduced, by reducing agents (like potassium iodide, stannous chloride etc.) to arsenious acid.

$$H_2AsO_4 \rightarrow H_3AsO_3$$

The nascent hydrogen produced during the reaction, further reduces arsenious acid to arsine (gas), which reacts with mercuric chloride paper, producing a yellow stain.

$$\underset{\text{Arsenious acid}}{H_3AsO_3} + 3H_2 \rightarrow \underset{\text{Arsine (gas)}}{AsH_3} + 2H_2O$$

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To carry out the test, a specified apparatus (as described in pharmacopoeias) is used. In order to convert arsenic into arsine gas, various reducing agents like zinc and hydrochloric acid, stannous chloride, and potassium iodide are employed. The rate of evolution of gas is maintained by using a particular size of zinc, and controlling the concentration of acids and other salts of the reaction medium, besides temperature. Any impurity coming alongwith the gas (like H_2S) is trapped by placing a lead acetate soaked cotton plug in the apparatus. All the reagents employed for the test should be arsenic-free, and are designated as AsT in pharmacopoeias.

Apparatus :

An apparatus is shown in the figure 2.3 as per the specification of I. P. is used for the limit test for arsenic.

A wide mouth bottle of 120 ml capacity fitted with rubber bung carrying a glass tube 200 mm long and 6.5 mm internal diameter with a hole of 2 mm at one end is used in the test. The other end of the glass tube is cut smooth and carries rubber bungs (25 × 25 mm). Mercuric chloride paper is sandwiched between the rubber bungs. The rubber bungs are held in place by means of a clip.

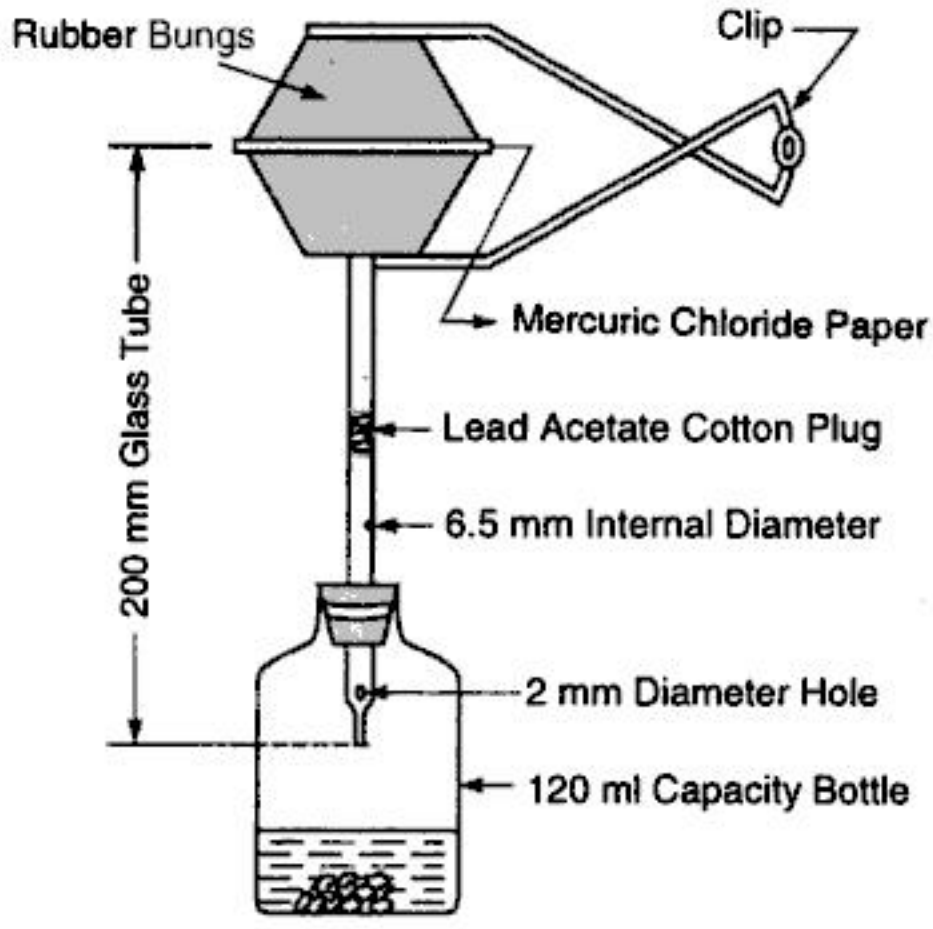

Fig. 2.3 : Apparatus used for Arsenic limit set

General Test :

A solution of the substance as specified in the monograph is placed in the generator bottle. Potassium iodide 1g and 10g of zinc AsT are added. Mercuric chloride test paper is placed in the rubber slit and the stopper is placed in the position immediately. It is set aside for 40 minutes and the stain produced on the paper is compared against standard stain. The standard stain is produced simultaneously by taking 50 ml of water, 10 ml stannated HCl and dilute arsenic solution varying from 0.02 ml to 1.0 ml. (1 ml = 0.01 mg of arsenic). If the sample shows a stain of lesser intensity than that of the standard then it passes the test.

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For example if 1 g of a substance under test is compared with 0.01 ml of dilute arsenic solution, on matching will contain 1 ppm arsenic in the sample.

The stain produced on paper fades on keeping, and therefore, comparison should be made immediately. Stained papers can be preserved by dipping in hot melted paraffin, and keeping away from light. In order to get reproducibility of the results, it is essential to follow the directions given in pharmacopoeia.

Modification of the general method of testing is carried out for certain substances. This is to have arsenic in the final solution in a readily reducible form. The interference of other substances, ions etc., is eliminated by preliminary treatment. For example, carbonates, hydroxides and oxides give effervescence, so brominated hydrochloric acid is used. Nitrates are heated with sulphuric acid, to expel nitric acid. Certain organic compounds are insoluble in acid and water, and cause frothing. Hence, organic matter is removed by igniting with calcium hydroxide. Solutions of organic acids like citric, tartaric etc., are prepared in stannated hydrochloric acid. Iron, bismuth and antimony salts are taken in 20 % HCI and distilled. Dyes and related compounds are decomposed with sulphuric acid (after preliminary treatment with nitric acid) and then used.

The British Pharmacopoeial method is similar to I.P. method. The apparatus and design is slightly different. The amounts of zinc, hydrochloric acid and other reagents employed are also different. Further B. P. adopts the use of mercuric bromide test paper. The Gutzeit test for arsenic, is very sensitive and hence, is adopted by pharmacopoeias of various countries.

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CHAPTER

3

SOME FUNDAMENTALS CONCEPTS

Some concepts are considered as fundamental with regard to the principles of quantitative analysis. These include ideas such as solution concentration, chemical equilibrium etc. The main purpose in this chapter is to discuss some of these concepts :

SOLUTION CONCENTRATION

In all the techniques of quantitative analysis the use of solutions require some basis for the expression of solution concentration. All the systems of concentration expression have a fundamentally similar basis with respect to weight relationships of solute and solvent, but actual method of expression of concentration should take on some convenient and specific form.

Normality :

The normality of a solution is given by the number of equivalents of solute per litre of solution

$$N = \frac{W}{EW \times V}$$

where,

N = Normality
W = Weight of solute
EW = Equivalent weight of solute
V = Volume of solution

Normality varies according to the reaction; as the equivalent weight of a substance may vary according to the reaction in which the solute participates. The equivalent weight is generally calculated after determining the specific changes in chemical reaction of the solute.

Percent Concentration :

Concentration is many-a-times expressed in terms of percent (parts per hundred). Percent composition of a solution can be expressed as :

1. Percent w/w $= \frac{\text{mass of solute}}{\text{mass of solution}} \times 100$
2. Percent v/v $= \frac{\text{volume of solute}}{\text{volume of solution}} \times 100$
3. Percent w/v $= \frac{\text{mass of solute}}{\text{volume of solution}} \times 100$

Percent w/w is frequently employed to express the concentration of commercial aqueous reagents, percent v/v is used to specify the concentration of a solution prepared by diluting a pure liquid with another liquid and percent w/v is employed to indicate the composition of dilute aqueous solutions of solid reagents.

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Molal Concentration :

Although rarely used in analytical practice it is worthwhile to consider it briefly. Molality of the solution is given by the number of moles of solute per 1000 g of solvent. It is represented by 'm'

$$m = \frac{\text{weight of solute}}{\text{weight of solvent} \times \text{Mol. wt. of solvent}} \times 100$$

Molality of solution is independent of temperature.

Molar Concentration :

The molar concentration of the solution is the number of moles of solute per litre of solution. It is expressed by 'M'.

$$M = \frac{\text{Number of moles of solute}}{\text{Volume of solution in litre}}$$

Molarity is also expressed in number of millimoles of a solute per millilitre of solution.

$$M = \frac{\text{Number of m moles of solute}}{\text{Number of ml of solution}}$$

Since molarity involves a basis of solution volume, it is apparent that the molarity of a solution will change as volume changes which is associated with changes in temperature.

Formal Concentration :

Some substances do not exist in molecular form, whether in solid or solution form, they remain in ionic form in solid state as well as in solution. In such cases instead of molecular weight, formula weight is used in preparation of solution and its concentration is expressed in terms of formality, for example NaCl, $FeCl_3$ can be defined very simply as number of formula weight of a solute per litre of solution. It is represented by '*F*'.

$$F = \frac{\text{Weight of solute in g}}{\text{Volume of solution in litre}} \times \text{Formula weight}$$

Formal solutions generally show changes in formality where volume changes associated with temperature.

Equivalent weight :

Equivalent weight of the substance is defined as the weight of the substance that contains or reacts with 1.0078 g of hydrogen, or 8 g of oxygen, or 35.45 g of chlorine. This generalised definition is used for calculation of equivalent weight. But depending upon the reaction involved, equivalent weight can be simplified as below.

Equivalent weight in Neutralisation Reactions :

Equivalent weight of an acid is that weight of it which contains one g atom of replaceable hydrogen e. g. 1.0078 g of hydrogen. Equivalent weight of monobasic acids is equal to its molecular weight

$$\text{Equivalent weight} = \frac{\text{Molecular weight}}{\text{Basicity}}$$

Equivalent weight of a dibasic or a tribasic acid is $\frac{1}{2}$ and $\frac{1}{3}$ respectively of its molecular weight.

Similarly, equivalent weight of a base is the weight of the substance which contains one replaceable hydroxyl group.

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$$\text{Equivalent weight} = \frac{\text{Molecular weight}}{\text{Acidity}}$$

Ex. (a) HCl $\quad \text{Eq. Wt.} = \frac{\text{Molecular weight}}{1}$

$$= \frac{36.5}{1}$$

$$= 36.5$$

(b) H_2SO_4 $\quad \text{Eq. Wt.} = \frac{\text{Molecular weight}}{\text{Basicity}}$

$$= \frac{98}{2}$$

$$= 49$$

(c) NaOH $\quad \text{Eq. Wt.} = \frac{\text{Molecular Weight}}{\text{Acidity}}$

$$= \frac{40}{1}$$

(d) Na_2CO_3 $\quad \text{Eq. Wt.} = \frac{\text{Molecular weight}}{\text{Acidity}} = \frac{106}{2} = 53$

Equivalent weight in Complexation Reactions :

The equivalent weight is the weight of the substance which contains or reacts with 1 g atom of an univalent cation M^+ (equivalent to 1.0078 g of hydrogen), $\frac{1}{2}$ g atom of a bivalent cation M^{+2}, 3 g atom of a trivalent cation M^{+3} etc. Equivalent weight of complexing agent is calculated on the basis of above definition.

For cations, equivalent weight is the atomic weight divided by the valency of atom.

Equivalent weight in Precepitation Reactions :

Equivalent weight of a salt in a precipitation reaction is the gram molecular weight of the salt divided by the valency of the reacting ions.

1. $AgNO_3$

$$AgNO_3 + \bar{C}l \rightarrow AgCl\downarrow + NO_3^-$$

$$\text{Eq. Wt.} = \frac{\text{Molecular Weight}}{\text{Valency of reacting ions}}$$

$$= \frac{\text{Mol. wt.}}{1}$$

2. NaCl

$$NaCl + Ag^+ \quad AgCl + Na^+$$

$$\text{Eq. Wt.} = \frac{\text{Molecular weight}}{1}$$

Equivalent in Oxidation-Reduction Reactions :

Equivalent weight of an oxidant or reductant can be defined as that weight of the substance which reacts or contains 1.0078 g of available hydrogen or 8.0 g of available oxygen.

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Equivalent weight can be calculated by

(a) Ion-electron balance method

(b) Oxidation number method

(a) Ion-electron balance Method : Ion electron balance method is based on following the steps :

1. Ascertain the reactants and products of the reaction.
2. Determine oxidising agent. Write down partial equation for oxidising agent
3. Determine reducing agent. Write down partial equation for reducing agent.
4. Add both partial equations and cancel out common substances after multiplying both partial equations by suitable coefficient.

Example : Reduction of potassium permanganate by ferrous sulphate in presence of dilute sulphuric acid.

The first partial (reduction) is

$$MnO_4^- \rightarrow Mn^{++}$$

To balance atomically and electrically

$$MnO_4^- + 8H^+ + 5e \rightarrow Mn^{++} + 4H_2O$$

The second partial (oxidation) is

$$Fe^{++} \rightarrow Fe^{+++}$$

To balance electrically

$$Fe^{+2} - e \rightarrow Fe^{+3}$$

$$\text{Equivalent weight} = \frac{\text{Molecular weight}}{\text{Number of electrons transferred}}$$

$$\text{Eq. Wt. } KMnO_4 = \frac{M\,W}{5} = \frac{158}{5} = \frac{158}{5} = 31.6$$

$$\text{Eq. Wt. } FeSO_4 = \frac{M\,W}{1} = 278$$

(b) Oxidation number method : Oxidation and reduction are the processes involving the changes in the valency. Oxidation number (O. N.) indicates the amount of oxidation or reduction which is required to convert one atom of the element from free state to that in the compound. If oxidation is taking place the oxidation number is positive and if, reduction is necessary oxidation number is negative.

Following general rules apply in determination of O. N.

(a) O. N. of free or uncombined element is zero.

(b) O. N. of hydrogen (except hydrides) is + 1.

(c) O. N. of oxygen except peroxides is – 2.

(d) O. N of metal in combination is generally positive.

(e) O. N. of radical or ion is equal to its electrovalency with correct sign.

(f) O. N. of compound is zero and is determined by sum of O. N. of individual atoms.

Example (i) $K^{+1}Mn^{+7}O_4^{-8} \rightarrow Mn^{+2}S^{+6}O_4^{-8}$

Change in oxidation number of manganese is from + 7 to + 2.

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$$\text{Equivalent weight} = \frac{\text{Molecular weight}}{\text{Change in O.N.}}$$

$$= \frac{\text{Mol. weight}}{5}$$

$$= \frac{158}{5} = 31.6$$

(ii) $2\,Fe^{+2}S^{-2}O_4 \rightarrow Fe_2^{+6}(SO_4^{-6})^3$

Change in O. N. per atom of iron is from +2 to +3 i.e. by 1 unit. Hence, equivalent weight of ferrous sulphate is equal to its molecular weight.

(iii) $K_2^{+2}Cr_2^{+12}O_7^{-14} \rightarrow Cr_2^{+6}(SO_4^{-6})_2$

The change in oxidation number is from +12 to + 6 i.e. by 6 units and hence equivalent is $\frac{1}{6}$ the molecular weight of potassium dichromate.

Titer :

Solution concentration is expressed in the form of titer in quantitative analysis involving volumetric methods particularly. The titer gives the weight of some particular substance with which the solute in 1 ml of solution will react.

When the normality of solution is known in relation to a specific reaction, titer of the solution can be calculated as

$$\text{Titer} = \text{Normality} \times \text{equivalent weight}$$

where equivalent weight is expressed in mg, meq. of the substance involved in the reaction and not to that of the solute.

The titer of the solution changes with volume changes associated with temperature.

Parts per Million and Parts per Billion

Parts per Million is frequently used to express the concentration of very dilute solutions and is expressed as 'ppm'.

$$C_{ppm} = \frac{\text{Mass of solute}}{\text{Mass of solution}} \times 10^6 \text{ ppm}$$

For very dilute solutions the concentration is expressed in parts per billion (ppb).

These terms are also emplcyed to express the concentration of impurities in pharmaceuticals.

VOLUMETRIC ANALYSIS

Definitions of Terms

Volumetric or titrimetric analysis : It consists of determination of volume of solution of accurately known concentration required to react completely with the solution of substance to be determined.

Standard solution : The solution of accurately known concentration is called as the *Standard Solution*.

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Titrate :

The substance being titrated is called as *Titrate.*

Titrant :

The solution of known concentration is used in *titration*. (usually added from burette or pipette).

Equivalence point or stoichiometric end point :

The point at which the reaction between titrant and titrate is just complete.

Indicator :

It is an auxiliary substance which shows clear visual change after the reaction between titrate and titrant is practically complete.

Titration error :

In practice, very small difference between theoretical end point and actual end point usually occurs. This is called as titration error.

Requirements for Volumetric Methods :

In volumetric methods, the volume of solution of known concentration (titrant) that reacts completely with the substance to be determined (titrate).

For use of chemical reaction in volumetric methods, the reaction should fulfil some of the requirements. These are as follows :

1. The reaction should be simple and expressed by a well defined chemical equation. There should not be any side reactions, so that from the reaction stoichiometry, calculation of amount of the reacting substance can be estimated.
2. The reaction should be rapid; i.e. it should be instantaneous or should proceed with great speed. Sometimes addition of catalyst increases the speed of reaction. Slower reaction rates make the reaction unsuitable with respect to time consumed in the reaction.
3. The reaction must proceed to completion when an equivalent amount of standard solution has been added. This gives satisfactory end point detection. The criterion for reaction completion may vary somewhat depending on the quantity determined.
4. There must be some sharp change in either physical or chemical properties of the solution at the equivalence point.
5. Reaction should have some simple method for the detection of end point or equivalence point of the titration. The equivalence point is that point in the titration where an equivalent amount of standard solution is added. Usually, indicator technique will signal the end point of the titration.

The requirements mentioned above are not always realized for every volumetric method. Many volumetric methods can also be applied where one or more of the above requirements are not ideally met.

CLASSIFICATION OF VOLUMETRIC METHODS OF ANALYSIS

Volumetric methods involve the chemical reactions. Depending upon the type of reaction involved, volumetric methods have been classified as :

1. **Neutralisation (Aqueous acid-base) titrations :** It involves neutralization reaction in presence of water as solvent.

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Whenever possible, standards for calibration should be made up in the same matrix as the samples to be analysed. Only gravimetric and colorimetric methods does not require calibration.

6. Calculating results : The analysis is not complete until the results have been expressed in such a way that the person can understand the significance of it. Computation of analyte from experimental data is ordinarily simple and easy task with modern calculators or computers.

7. Evaluating results and their reliability : Analytical results are incomplete without an estimate of their reliability. In recent years much attention is given for statistical techniques to confirm the reliability and accuracy of the results.

ACCURACY OF VOLUMETRIC ANALYSIS

Volumetric methods of analysis are very susceptible to high accuracy and possess several advantages. Accuracy of volumetric analysis is mainly affected by following three factors.

1. Substance of known purity for preparation of standard solution.
2. End point detection.
3. Calibrated volumetric glass wares.

1. Standardization :

Very pure reagents of high stability are used in preparation of standard solution. In such cases the accurate weight of reagent is taken, dissolved and diluted to exact known volume and concentration is calculated on theoretical basis. This method has some limitations such as all the results depend on single measurement and single weighing. The substances of high purity used in preparation of standard solution are known as *Primary Standard Substances.*

Primary standard substances :

Primary standard substance should satisfy the following requirements :

1. It must be easy to obtain, to purify, to dry and to preserve in pure state.
2. It should be 100.00 % pure although 0.01 to 0.02 % impurity is tolerable if accurately known.
3. It should be stable to atmospheric conditions. It should not decompose or be hygroscopic, or deliquescent.
4. It should show a high equivalent weight in order to reduce the effect of weighing errors. In weighing a greater amount of substance, the relative error will be smaller than that for a small amount.
5. The reaction with standard solution should be stoichiometric and practically instantaneous.
6. The reaction to be amenable to use simple indicator to determine the end point of the titration.
7. There should not be any difference between end point and theoretical equivalence point i.e. titration error should not be there.
8. It should be readily soluble under the conditions in which it is to be employed.
9. It should not have water of hydration, so that the composition of the solid does not change with variation in relative humidity.

It is not always possible to satisfy all the requirements of a primary standard but the requirements mentioned above should be met at all times as closely as possible. In practice ideal primary standard is difficult to obtain and hence, a compromise between above requirements is usually necessary.

These substances of known purity whose known accurately weighed quantity is used in the standardization of solution of unknown strength.

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- Fill the pipette to a level above the etched line using distilled water at the laboratory temperature. Remove any liquid on outside and release the pressure to allow the liquid to fall to etched line.
- Discharge the contents of pipette to a previously weighed receiver. Allow the pipette to drain completely for 20 to 30 seconds.
- Stopper the container and reweigh it. Calculate the volume of water delivered by the pipette from the weight and see the apparent volume from table .
- Calibration of pipette is repeated as a check on work and duplicate results should not differ by more than 1 mg.

The tolerances on capacity to pipettes as per Indian pharmacopoeia are given below :

	One mark Pipette		
Normal capacity ml.	10	25	50
Tolerance ± ml.	0.02	0.03	0.05
	Graduated Pipette		
Normal capacity ml.	1	5	10
Subdivision ml.	0.01	0.05	0.10
Tolerance ± ml.	0.006	0.03	0.05

Calibration of volumetric flasks :

Volumetric flasks are used in the preparation of standard solution and are available with capacities from 5 to 1000 ml. They are normally calibrated to contain a specified volume at 27°C when filled to the line etched on the neck. Volumetric flask must be thoroughly cleaned and rinsed with the pure solvent before calibration.

Calibration of a volumetric flask is necessary only for work of the highest accuracy, and it can be done by the following ways :

- Volumetric flask is cleaned, rinsed and then clamped in an inverted position to dry it.
- Stopper the flask and weigh to nearest milligram and record this weight.
- Fill the flask with distilled water at room temperature. Adjust the lower meniscus of water to the etched level mark by means of pipette or dropper.
- Stopper the flask and reweigh to the nearest milligram. Difference in weight gives the apparent volume of water contained and from the weight of water. Calculate the actual volume.
- Calibration should be checked by repeating the procedure. Duplicate results should agree within 0.3 ml for the flask.

The tolerances on capacity for volumetric flask as per Indian Pharmacopoeia are given below :

	One mark Pipette			
Normal capacity ml.	10	25	50	100
Tolerance ± ml.	0.02	0.03	0.04	0.06

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operator must walk around the cone as the shovels top of the cone is flattened out and divided into quarters. Opposites of the pile are then removed and mixed to form a smaller conical pile and again quartered. The process is repeated until the sample of suitable weight is obtained.

Tabling :

If the quantity of the material is of the order of 2 to 3 kg or less, intermixing may be accomplished by the method known as '*tabling*'. The finely divided material is spread on the centre of a large sheet of oilcloth or similar material. Each corner is pulled in succession over its diagonal partner, the lifting being reduced to a minimum. The particles are thus caused to roll over and over on themselves.

Mechanical methods also exists for dividing up particulate material into suitable sized samples. Samples obtained by these means are usually representative of the bulk material within limits of less than – 1 % and are based upon the requirements. Sample dividers exist with the different capacities and operate either by means of a series of rapidly rotating sample jars under the outlet of a loading funnel or by a rotary cascade from which samples are fed into the sets of separate compartments. Sample dividers can lead to a great deal of time saving in case of bulk quantities of powders or minerals.

Compact Solids :

In case of metals and alloys, sampling is effected by drilling holes through the material at selected points and all the material from holes is collected, mixed and a sample of suitable size is used for analysis.

It should be borne in mind that although it is possible to generalize on sampling procedures, all industries have their own established methods for obtaining samples. e.g. sampling for tobacco leaves will obviously differ from those used for bales of cotton or for coal.

PHARMACEUTICALS

Proper sampling procedure is also important for accuracy in the results depending on the individual dosage form to be analysed. The sampling procedures to obtain the analysis sample may vary. They are as :

Tablets and Pills :

The tablets or pills are available in bulk lots or containers. Equal number of tablets/pills from different locations spaced throughout mixed lot are removed to collect 20 tablets/pills. Calculate the average weight of the tablet/pills. The tablets are then reduced to fine powder and mixed thoroughly. The powder equivalent to the desired content of pure drug is then weighed and utilised for the analysis.

Capsules :

The sampling procedures are some-what similar to tablets. The equal number of capsules from different locations/containers are removed to collect 20 capsules. The counted capsules are weighed to determine gross weight per capsule. The capsules are then opened and the contents of capsule are removed. If the contents are dry then these contents are reduced to fine powder. Then the powder content equivalent to the desired content of drug is weighed and taken for the analysis.

Many times the capsules are cut into two parts and the contents are removed, washed by using alcohol and ether. Few drops of acetic acid are added to alcohol for cleaning.

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3. The precipitate should be stable to the atmospheric conditions.
4. The precipitate must be convertible to a pure compound of definite composition. This may be possible by either ignition or by simple chemical operation such as evaporation.

COLLOIDAL STATE

Colloidal suspensions are not suitable in gravimetric analysis because of its particle size. They cannot be readily filtered. The stability of these suspensions can be decreased by stirring, heating and by adding an electrolyte. This cause individual colloidal particle to bind together to give colloidal mass and is filterable. The process of converting colloidal suspension into a filterable mass is called coagulation or agglomeration. Colloidal particles are in general exhibited by substances of particle size ranging in between 0.1 μ to 1 mμ. Ordinary, quantitative filter papers will retain particles upto 10 μ and so the colloidal solution in this respect behave like true solution. Colloidal suspension are stable because all colloidal particles are either positively or negatively charged. This charge arises from the cations or anions that are adsorbed on the surface of the particles. The ions are retained on the surface by process known as adsorption. The characteristics properties of most of the colloidal particles are as under :

1. If a powerful beam of light is passed through colloidal solution and the solution is viewed at right angles to incident light, scattering of light is observed. It is called as *'Tyndal'* effect. Ultramicroscopy is based on this Tyndal effect and the limit of this ultramicroscope is about 10 mμ.
2. They can be separated from the solution by means of colladon or parchment membrane i.e. by the process of dialysis.
3. They may be regarded as they are possessing electrical charges and they migrate under the influence of suitable potential gradient.
4. Because of smallness of particles the ratio of surface area to weight is extremely large.
5. Colloidal particles have the property of adsorption which is dependant upon size of surface area.

In general colloids are classified into two groups as Lyophillic and Lyophobic colloids.

Lyophobic colloids (Suspensoids)	Lyophillic colloids (Emulsoids)
1. These are only slightly viscous.	1. They are very viscous almost jelly like known as gels.
2. Addition of water has no effect on these colloids.	2. Addition of water or solvent has effect on these colloids.
3. Comparatively small concentration of electrolyte results in flocculation of these colloids.	3. Comparatively large concentration of electrolyte is required for flocculation.
4. They possess electrical charge of definite sign which can be changed only by specific methods.	4. They change their charge easily.
5. Ultramicroscopic reveals the bright particles in vigorous motion as brownian movement. e.g. Gold solution.	5. Under ultramicroscopic only a diffused light cone is exhibited. e.g. Gelatin.

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it with hydrochloric acid. Asbestos for Gooch crucibles is available in market. They are generally used under suction.

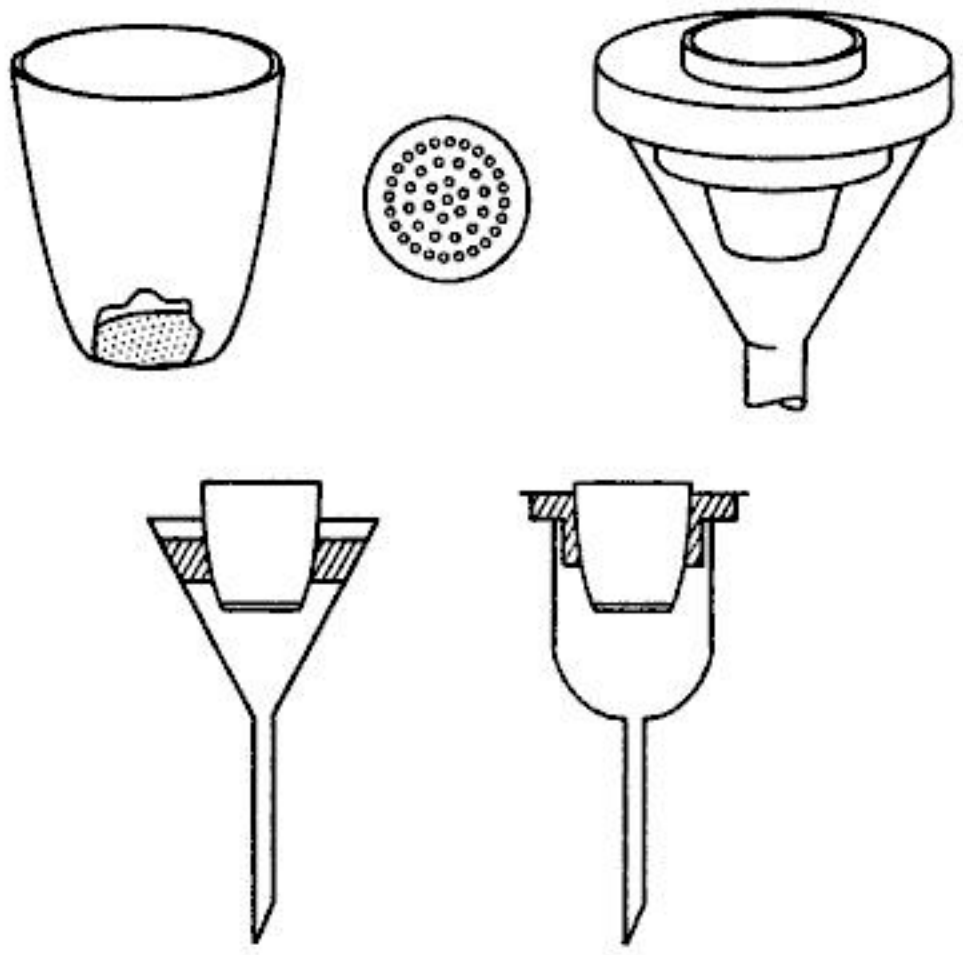

Fig. 5.1 : Gooch crucible

The crucibles can be dried to constant weight. For temperatures upto 250°C, electric oven can be used. Electrically heated muffle furnace is used for drying at higher temperature. The asbestos normally tends to loose weight above 250°C. It is generally useful for precipitates that require heating upto 250°C.

(b) Munroe Crucibles : A platinum Gooch crucible containing mat was first used by Munroe. Because of high cost of platinum, Munroe crucible are not used for routine analysis. The main advantages of these crucibles are, resistance to chemicals, filtration of finest particles, rapidity of filtration and heating to a very high temperature.

(c) Glass fibre discs : Inexpensive glass fibre discs are available for use instead of asbestos mat. A circle of glass fibre filter paper may be placed in a coarse porosity filter crucible for rapid filtration. Glass fibres are made from fine borosilicate glass fibres. They possess the main features as having excellent retention property with rapid filtration, unaffected by chemical reagents and heating upto 500° C.

4. Permanent porous filter discs : In these types, there is no preparation of filter mat as in case of Gooch crucible. Best example of this is Sintered glass crucibles.

(a) Sintered glass crucibles : These crucibles are made of resistant glass i.e. pyrex glass and have porous disc of sintered ground glass fused in the body of the crucible. These filter discs are of various porosites. They are of G_1, G_2, G_3, G_4 types. Their pore sizes (average diameter) are 100–120 microns, 40–50 microns 20–30 microns and 5–10 microns respectively. The crucible G_1 type is used for coarse particles while G_4 type for very fine particles. The crucibles are of two types tall form and the low, wide form.

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Substituting above values in this equation

$$\therefore \quad pK_a = pH - \log \frac{b + [H^+]}{a - [H^+]}$$

Practically we can consider that $[H^+]$ is much smaller as compared to 'a' or 'b'.

$$\therefore \quad \boxed{pK_a = pH - \log \frac{b}{a}}$$

This is Henderson-Hasselbalch equation which relates pH of solution containing comparable and appreciable concentration of a conjugate acid base pair to ratio of their concentrations.

This equation has application in describing solubilities of acids and bases, stability of organic compounds, measurement of dissociation constant, transport across biological membranes.

Such solutions are called *Buffer solutions*, which resist a change in pH upon addition of small amount of acid or base.

The equation can also be written as

$$pH = pK_a + \log \frac{[\text{conjugate base}]}{[\text{conjugate acid}]}$$

This equation relates 3 quantities viz pH, pK_a and ratio of b/a.

If we know two quantities we can easily find the third value.

The principle function of a buffer is to minimise changes in pH and hence, it is of practical importance to determine how this buffer capacity depends upon the buffer solution properties. To measure the buffering capacity we use the buffer index β.

If 'b' is the concentration of strong base added to a solution containing total concentration 'C' of a weak acid, the buffer index is defined by

$$\beta = \frac{db}{dpH}$$

The higher the value of β, greater is the buffer capacity of the solution.

β has maximum value when pH = pK_a of buffering acid. But for practical purposes a pH value of $pK_a \pm 1$ gives acceptable buffering capacity.

Hence, the choice of buffer solution will depend upon pH desired for the solution.

The buffering mechanism for a mixture of weak acid and its salt is governed by the following :

$$pH = \text{Constant} + \log \frac{[A^-]}{[HA]}$$

If the solution is diluted, the ratio remains constant and so the pH of the solution does not change.

If a small amount of strong acid is added, it will combine with A^- to produce HA. Thus, the change in the ratio $[A^-]/[HA]$ is small and hence the change in pH is small.

If the small amount of strong base is added, it will combine with part of HA to form the equivalent amount of A^- . Thus, again the change in ratio will be small.

Some of the common buffers in intermediate range are acetate, phosphate, carbonate, borate, citrate etc.

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(b) Azo dyes :

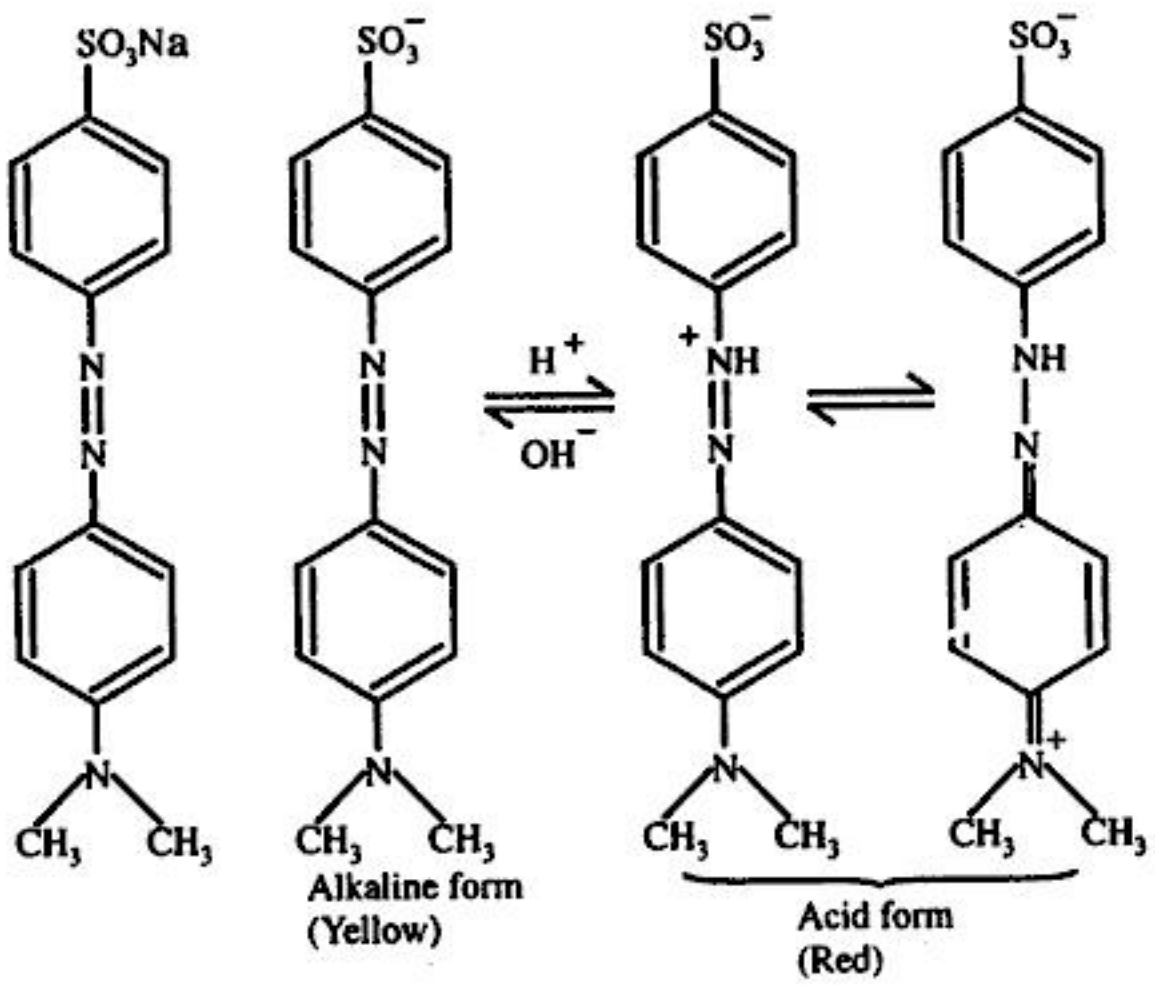

Fig. 6.2

Methyl orange is red in acid and yellow in alkaline solution. This colour change is associated with a rearrangement involving the azo link.

	pH Range	Acid	Alkaline
Methyl orange	3.1 – 4.4	Red	Orange
Thymol blue	1.2 – 2.8	Red	Yellow
Bromophenol blue	3.0 – 4.6	Yellow	Blue
Methyl red	4.2 – 6.3	Red	Yellow
Phenolpthalein	8.3 – 11.0	Colourless	Red
Phenol red	6.8 – 8.4	Yellow	Red
Bromocresol green	3.8 – 5.4	Yellow	Blue

Mixed Indicators :

In some cases, the pH range is very narrow and the colour change over this range must be very sharp. This is not easily possible with ordinary acid-base indicators. The result may be achieved by the use of the suitable mixture of indicators. These are generally selected so that their pKI_n values are close together and overlapping colours are complementary at an intermediate pH value. For example, A mixture of equal parts of neutral red (0.1 % solution in alcohol) and methylene blue (0.1 % solution in alcohol) gives a sharp colour change form violet-blue to green in passing from acid to alkaline solution at pH 7.

A mixture of phenolphthalein (3 parts of 0.1 %) and α-naphtholphthalein (1 part 0.1 %) passes from pale rose to violet at pH 8.9 (titration of phosphoric acid to dibasic stage).

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$$[\text{Acid}] = 50 \times \frac{0.1}{150}$$

$$= 3.33 \times 10^{-2}$$

$$\text{pH} = \log \frac{[\text{Salt}]}{[\text{Acid}]} + \text{pK}_a$$

$$= \log \frac{3.33 \times 10^{-2}}{3.33 \times 10^{-2}} + 4.74$$

$$= 4.74$$

Similarly, many other points are found out.

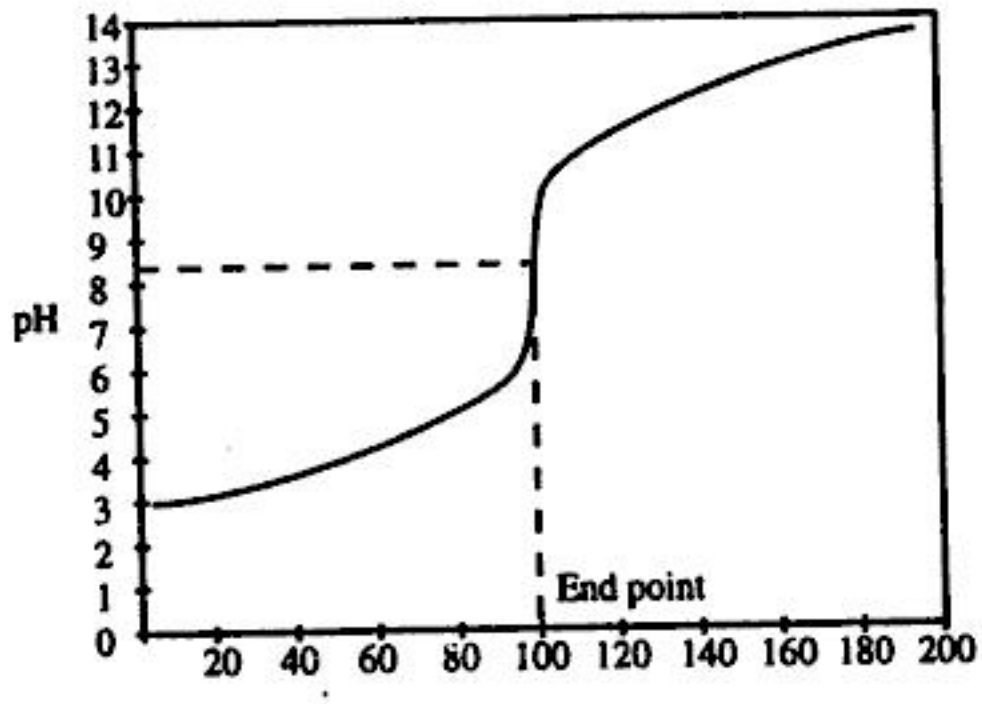

Fig. 6.4 : Titration curve for weak acid-strong base

For 0.1 N acetic acid and 0.1 N NaOH, it is evident from titration curve that neither methyl red nor methyl orange can be used as indicators. It is necessary to use indicator with range on a slightly alkaline side, such as phenolphthalein, thymolphthalein or thymol blue.

3. Weak Base-Strong Acid :

Let us consider titration of 100 ml of 0.1 N aqueous ammonia [$K_b = 1.8 \times 10^{-5}$] with 100 ml of 0.1 N hydrochloric acid. pH at equivalence point can be calculated by –

$$\text{pH} = \frac{1}{2}\,\text{pK}_w - \frac{1}{2}\,\text{pK}_b - \frac{1}{2}\log C$$

$$= 7 - \frac{1}{2}(4.74) - \frac{1}{2}\left(\bar{2}.70\right)$$

$$= 5.28$$

For other concentrations the pH may be calculated by

$$\text{pH} = \text{pK}_w - \frac{1}{2}\,\text{pK}_b - \log \frac{[\text{Salt}]}{[\text{Base}]}$$

After equivalence point has been reached the solution contains excess of H^+ ions, hydrolysis of salt will be repressed and subsequent change of pH will be due to excess of acid present.

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obtained as shown in the above figure. From this graph, the feasibility of using any equivalence point detection in titration of polyacidic bases can be interpreted. For the titration of mixture of bases against strong acid, titration curve can similarly be plotted.

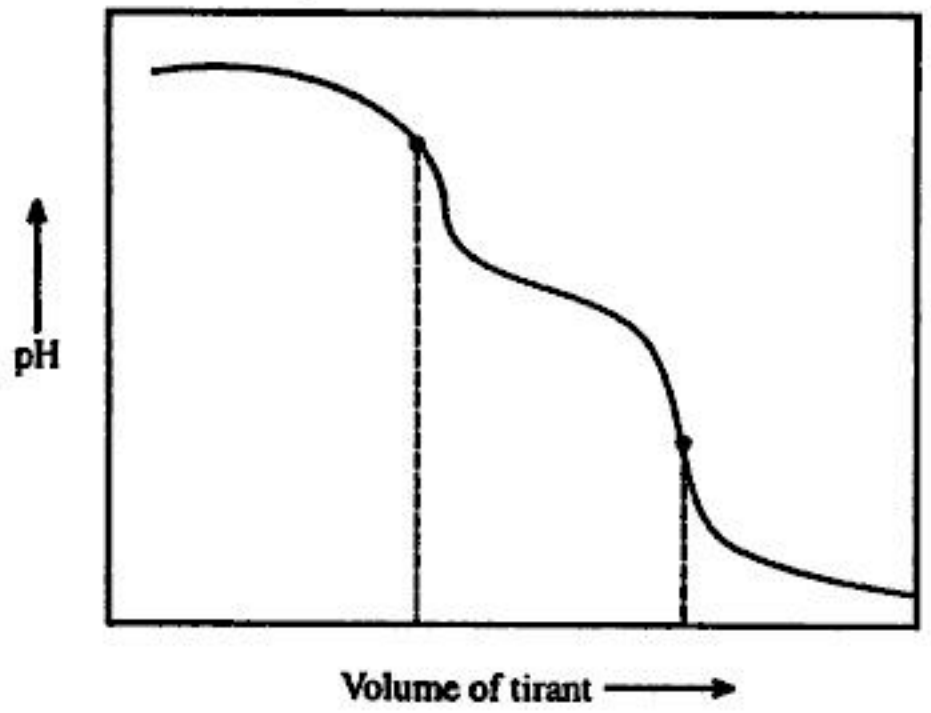

Fig. 6.8 : Titration curve for Polyacidic bases

In aqueous acid base titrations various drugs can be analysed easily.

Preparation of sodium hydroxide 1 M :

Dissolve 42 g of sodium hydroxide in sufficient carbondioxide free water to produce 1000 ml.

Standardize sodium hydroxide solution by using potassium hydogen phthalate. Weigh accurately about 5 g of potassium hydrogen phthalate previously powdered and dried at 120°C for 2 hours and dissolve in 75 ml carbondioxide free water. Add 0.1 ml of phenolphthalein solution and titrate with sodium hydroxide solution until a permanent pink colour is produced.

Each ml of 1 M sodium hydroxide is equivalent to 0.2042 g of $C_8H_5KO_4$.

Store the bottles with well fitted stoppers to avoid the contact of atmospheric carbon dioxide. The sodium hydroxide solutions must be restandardized frequently.

Sodium hydroxide solution can also be standardised using primary standards such as oxalic acid, benzoic acid, furic acid and adipic acid.

Preparation of hydrochloric acid 1 M :

Dilute 85 ml of hydrochloric acid with water to produce 1000 ml.

It is standardised by using anhydrous sodium carbonate as weighed accurately about 1.5 g of anhydrous sodium carbonate, previously heated at 270°C for 1 hour. Dissolve it in 100 ml water and add 0.1 ml of methyl red solution. Add acid slowly with constant stirring until the solution becomes faint pink. Heat the solution to boiling, cool and continue the titration. Heat again to boiling and titrate further as necessary until the faint pink colour is no longer affected by boiling.

Each ml of 1 M hydrochloric acid is equivalent to 0.05299 g of Na_2CO_3.

It also can be standardised by using thallous carbonate, borax, potassium hydrogen phthalate.

Titrations can be performed by using direct titration. If the acidic or basic solute have a sufficient strength, they can be titrated with strong base or strong acid respectively to give quantitative results.

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where,

e – Electronic charge
D – Dielectric constant of medium
r – Distance between the two ions

The work required for the separation of these two ions is,

$$w = \frac{e^2}{Dr}$$

If we assume the solvent as a homogeneous medium and the ions present as point charges, these expressions can be applied for this system also.

It can be noted from above expresion that higher the value of D for solvent, small amount of energy will separate the ions i.e. it will be easy to dissolve the ionic solute.

In a solvent of high dielectric constant, complete dissociation of polar/ionic solute occurs easily. In solvents of low dielectric constant, considerable ion pairing occurs.

Dielectric constants for solvents :

Solvents	D
Cyclohexane	2.02
Dioxane	2.21
Benzene	2.27
Chloroform	4.81
Acetic acid	6.15
Pyridine	12.5
Acetone	20.7
Ethanol	24.3
Dimethyl formamide	27.0
Methanol	32.6
Acetonitrile	37.5
Water	78.5
Sulfuric acid	100.00

3. Acid-base character :

The non-aqueous solvents can be classified based on its proton donor-acceptor properties. The solvent exert an influence on the acid-base properties of the solute. They are of four types namely protogenic protophilic, aprotic and amphiprotic solvents.

The dissociating solvent AB dissociate to give the cation A^+ [lyonium ion] and the anion B^- [Lyate ion]. The lyanium ion is considered to be the species responsible for acidic character of solvent while lyate ion is responsible for basic properties.

The generalisation of this concept can be made as acid is any substance which increases the concentration of lyonium ion when dissolved in a dissociating solvent while the substance that increases the lyate ion concentration is called a base.

Protogenic solvent : They are acidic in properties and exert levelling effect on bases. These solvents have relatively high dielectric constant. They are ionised. The ion product of liberated ions is usually greater than that of water.

Example, acetic acid, formic acid, propionic acid, etc.

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$$201.70 \text{ g } C_{10}H_{15}NO, HCl \equiv HClO_4 \equiv 1000 \text{ ml N}$$

$$0.02017 \text{ g } C_{10}H_{15}NO\,HCl \equiv 1 \text{ ml of } 0.1 \text{ N } HClO_4$$

Some hydrochloride and quaternary salts give precipitate of insoluble perchlorate in acetic acid and obscure the end point. To avoid this, solution of mercuric acetate in acetic acid is added and titration carried out in dioxane. Alternatively end point is determined by potentiometric method.

For the determination of acidic substances titrants commonly used are alkali methoxides, or tetrabutylammonium hydroxide. Lithium methoxide is preferred because less quantity of lithium metal is required to prepare solution and it does not allow gelatinous precipitate during titration. Solution is easy to prepare. Solvents employed for dissolvation of substances include dimethylformamide, n-butylamine, ethylenediamine, pyridine etc. I.P. advocates use of dimethylformamide and n-butylamine. Indicators employed in detecting end point are :

1. Quinaldine red – 0.1 percent in methanol. Colour changes from pink to colourless.
2. Thymol blue – 1.0 percent in dimethylformamide. Colour changes from yellow to blue.
3. Azoviolet – 0.2 percent in benzene. Colour changes from orange through pink to blue.

Lithium methoxide 0.1 M :

This titrant is prepared as follows : Dissolve in small portions 0.7 g of freshly cut lithium metal in 150 ml of methyl alcohol, cooling the flask during addition of the metal. When the reaction is complete add 850 ml of toluene. If cloudiness or precipitation occurs, add sufficient methyl alcohol to clarify the solution. Store in a container suitably protected from carbondioxide and moisture. Standardise as follows :

Weigh accurately about 0.25 g benzoic acid, dissolve in 25 ml of dimethylformamide and titrate with lithium methoxide solution using quinaldine red as indicator. Protect the solution during titration from carbondioxide. Perform blank using 25 ml of dimethyl-formamide. Each 0.01221 g of benzoic acid is equivalent to 1 ml of 0.1 M lithium methoxide.

$$C_6H_5COOH + CH_3OLi \rightarrow C_6H_5COOLi + CH_3OH$$

$$122.1 \text{ g of } C_7H_6O_2 \equiv LiOCH_3 \equiv 1000 \text{ ml 1 N}$$

$$0.01221 \text{ g of } C_7H_6O_2 \equiv 1 \text{ ml of } 0.1 \text{ N } LiOCH_3$$

British pharmacopoeia makes use of dry benzene in place of toluene in the preparation of titrant.

Sodium methoxide 0.1 M :

Cool 150 ml of anhydrous methanol in ice water and add in small portions 2.5 g of freshly cut sodium. When metal dissolved completely, add toluene previously dried to produce 1000 ml. Standardize this solution before use.

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33. Homatropine HBr – 0.3 g	Glacial acetic acid + mercuric acid	–	Potentiometry + Blank determination
34. Imipramine HCl – 0.3 g	Chloroform + mercuric acetate	Methanol yellow	Blank titration
35. Levodopa – 0.6 g	Glacial acetic acid + mercuric acetate	Crystal violet	Blank titration
36. Lignocaine HCl – 0.6 g	Glacial acetic acid + mercuric acetate	Crystal violet	Blank determination
37. Mebendazole – 0.25 g	Glacial acetic acid	–	Potentiometry Blank determination
38. Meclizine HCl – 0.35 g	Glacial acetic acid + Mercuric acetate	Quinaldine Red in glacial acetic acid	Blank determination
Meclizine Tab	Chloroform + Glacial acetic acid + acetic anhydride + mercuric acetate	Quinaldine Red in glacial acetic acid	Blank determination
39. Mepyramine maleate – 0.15 g	Glacial acetic acid		Blank determination, Potentiometric
40. Metformin HCl – 0.25 g	Anhydride Formic acid	Crystal Violet	Potentiometry, Blank determination
41. Methoxamine hydrochloride 0.5 g	Glacial acetic acid + mercuric acetate	Crystal Violet	Blank titration
42. Methadone HCl – 0.5 g	Glacial acetic acid + mercuric acetate	Crystal Violet	Blank titration
43. Methyldopa – 0.4 g	Glacial acetic acid + dioxan	Crystal Violet	Blank determination
44. Metronidazole – 0.15 g	Glacial acetic acid	Brilliant green	Blank determination, Potentiometric
Metronidazole Tab. – 0.2 g	Acetic anhydride		Blank determination
45. Metronidazole Benzoate – 0.25 g	Acetone + acetic anhydride		Blank determination, Potentiometric
46. Morphine HCl and sulphate – 0.5 g	Glacial acetic acid	Crystal Violet	Blank determination
47. Neostigmine Bromide – 0.75 g	Glacial acetic acid + acetic anhydride	Crystal Violet	Blank determination
48. Nicotinamide – 0.25 g	Glacial acetic acid + acetic anhydride	Crystal Violet	Blank determination
49. Nikathamide – 0.2 g	Glacial acetic acid + acetic anhydride	–	Blank determination, Potentiometric
50. Nor-adrenaline acid Tartarate – 0.6 g	Glacial acetic acid	Crystal Violet	Blank determination
51. Noscapine – 0.5 g	Glacial acetic acid	–	Blank determination, Potentiometric
52. Pentazocine HCl – 0.60 g	Acetic acid + mercuric acetate	Crystal Violet	Blank determination
53. Pethidine HCl – 0.5 g	Acetic acid + mercuric acetate	Crystal Violet	Blank determination

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MERCUROMETRIC TITRATIONS

Theory : Here, instead of silver, mercury ions are used as precipitants. Such titrations are not strictly of precipitation type. Although, these offer no advantages over the more common argentometric titration, mercurometric titrations can be regarded as an alternative method for the determination of chlorides, bromides thiocyanates and cyanides. In these titrations diphenyl carbazone or a mixture of diphenyl carbazone and bromophenol blue can be used as indicator. At equivalence point, the yellow colour of the solution becomes blue-violet due to reaction of the excess of mercury ions with diphenyl carbazone. Owing to their ability to react with diphenyl carbazone, complete absence of chromate and iron ions is a necessity, whereas other ions like Mg, Al, Mn, Zn, fluoride, sulphate, nitrate and acetate do not interfere at low concentration. The fact that, in mercurometric titrations can be applied to dilute solutions is the only possible upper edge they have over argentometric titrations. The end point obtained by mercurometry is not very sharp in aqueous solution and hence, it is advantageous to use 80 % ethanolic medium.

(i) Preparation of 0.02 M mercuric nitrate : Dissolve 6.85 g of mercuric nitrate in 20 ml 1 M nitric acid and add sufficient water to produce 1000 ml of solution.

Dissolve 15 mg of sodium chloride in 50 ml water and titrate with mercuric nitrate solution determining the end point by potentiometer.

Each ml of 0.02 M mercuric nitrate is equivalent to 0.002338 g of NaCl.

(ii) Diphenyl carbazone mixed indicator : Dissolve 0.1 g of Diphenyl carbazone in 100 ml of ethanol to get Diphenyl carbazone indicator, 1 ml of which is used during titration. Mixed indicator is prepared by dissolving 0.5 g diphenyl carbazone and 0.5 g of bromophenol blue in 100 ml of 95 % ethanol.

Precipitation titrations are useful in assay of various pharmaceuticals. The following is the list of some drugs assayed by this technique.

1.	Aminophylline (for theophylline)	Volhard's Method
2.	Aminophylline injection	Volhard's Method
3.	Aminophylline tablets	Volhard's Method
4.	Intraperitoneal Dialysis fluid (or chloride)	Mohr's Method
5.	Phenyl mercuric acetate	Volhard's Method
6.	Silver nitrate	Volhard's Method
7.	Sodium chloride	Volhard's Method
8.	Sodium chloride injection	Volhard's Method
9.	Sodium chloride hypertonic injection	Volhard's Method
10.	Sodium chloride and Dextrose injection	Mohr's Method
11.	Potassium chloride	Mohr's Method
12.	Sulphobromophthalein sodium	Volhard's Method
13.	Thiomersal	Volhard's Method

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The colours of indicator and those of complexes vary with pH. This fact and the stability of metal indicator complex should be taken into consideration while deciding selection of indicators. Indicators commonly used and official in Indian Pharmacopoeia are :

Calcon :

(Mordant Black 17, solochrome dark blue) is sodium 2-hydroxy1 (2-hydroxy-1-naphthylazo) naphthalene–4–sulphonate. It gives purple-red colour with calcium ions in alkaline solution. In absence of metal ions (when EDTA is in excess) that gives blue colour. It is employed as calcon mixture which is one part calcon and 99 parts of sodium chloride.

Catechol violet :

It forms highly coloured complexes with wide range of metals. Complexes with metals are blue in colour in acidic solutions. Thorium (Th^{4+}) complex at pH 3, bismuth at pH 1.5 are stable. Other metals like magnesium, manganese, cobalt, zinc, calcium, cadmium can be titrated in pH range of 4–7. A 0.1 percent solution in water is employed as an indicator.

Eriochrome black T (Mordant Black-II) :

Chemically it is sodium 1–(1–hydroxy – 2 – naphthylazo) – 5 – nitro – 2 – naphthol – 4 – sulphonate). A 0.2 g of dye with 2 g of hydroxylamine hydrochloride in 50 ml methylamine hydrochloride is 50 ml methyl-alcohol is employed in titration. A mixture of 0.2 percent Mordant black-II with 100 parts of sodium chloride is also employed as indicator. It has, blue colour at pH 10.0 and complex has red colour at pH 10.00. Below pH 6.3 and above pH 11.5 dye has reddish colour. Use of buffer of pH 10.0 is essential. Metals like magnesium, calcium, cadmium, zinc, etc., give excellent results when directly titrated. For barium and strontium back titration with magnesium metal solution is adopted.

Mordant Blue 3 (Solochrome cyanne R) :

It is a indicator specific for aluminum. In presence of aluminium it gives purple colour and pink colour when EDTA is in excess.

Mordant Red 7 :

It is sodium 2-hydroxyl-1-(5-hydroxy-3-methyl-1-phenyl-4-pyrazolylazo)-2-naphthalein-4-sulphonate. This indicator gives bluish-violet colour with nickel and green in presence of excess of EDTA solution. A 0.1 percent solution is employed.

Murexide (Ammonium purpurate) :

A mixture of 0.2 percent dispersed in sodium chloride is used for determination of calcium at pH 12.0. Complex of calcium murexide gives blue violet colour while indicator solution has red violet colour.

This indicator gives better results when 0.5 percent of naphthol green is incorporated in it. Calcium can be estimated in presence of magnesium (for which it forms less stable complex than calcium). This indicator was official in I. P. 1966.

Pyridylazonaphthol (PAN) :

This indicator gives red colour in presence of copper ions and yellow colour in absence of copper ions. A 0.1 percent solution in alcohol is employed in titrations.

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Dissolve 33.12 g of lead nitrate in sufficient water to make 1000 ml.

Pipette 50 ml of the solution, add 50 mg xylenol orange and sufficient hexamine to provide violent pink colour and titrate with EDTA to lemon yellow end point.

Each ml of 0.1 m disodium edetate is equivalent to 0.03312 g of $Pb(NO_3)_2$.

The pharmacopoeial drugs and chemicals assayed by complexometric (EDTA) method are given in Table 9.1, 9.2 and 9.3.

Table 9.1 : Direct titrations of Official Drugs with Disodium Edetate (0.05 M)

	Formula	Mol. Wt.	Wt. to be taken in G	Indicator used	Buffer used	Equivaient in G for 1 ml 0.05 M disodium EDTA	Remarks
Calcium carbonate	$CaCO_3$	100.09	0.1	Calcon mix.	Sod. hydro. solution	0.005004	
Dibasic calcium phosphate	$CaHPO_4\ 2H_2O$	172.09	0.3			0.01721	For calciumcontent
Tribasic calcium phosphate	$Ca_3(PO_4)_2$		1.0	Mordant black ammonium	Ammonium chloride	0.00517	
			0.5	Mordant black II	Ammonia-Ammonium Chloride		
Heavy Magnesium carbonate			0.15	Mordant black II	Amm.-Amm. Chloride	0.002015	
Heavy Magnesium oxide	MgO	40.30	0.15	Mordant black II	Amm.–Amm. Chloride	0.002015	For MgO
Magnesium sulphate	$MgSO_47H_2O$	246.47	0.3	Mordant black II	Amm.–Amm. Chloride	0.00602	
Magnesium Trisilicate	x	x	1g	Mordant black II	Amm.–Amm. Chloride	0.002015	For MgO
Zinc Chloride	$ZnCl_2$	136.29	3g	Mordant black II	Hexamine	0.001363	
Zinc Stearate	$C_{17}H_{35}COO\ Zn$	632.34	1g	Xylenol orange	Hexamine	0.00654	
Zinc Sulphate	$ZnSO_4 \cdot 7H_2O$	287.54	0.5	Xylenol orange	Hexamine	0.02875	
Zinc Undecylenate	$C_{22}H_{38}O_4Zn$	431.92	0.35	Xylenol orange	Hexamine	0.04319	
Calcium chloride	$CaCl_2.\ 2H_2O$	147.02	0.15	Calcon mix	Sodium hydroxide	0.007351	
Light magnesium carbonate	–		0.15	Mordant black II	Ammonium	0.002015	
Mag. hydroxide	$Mg(OH)_2$	58.32	0.15	Mordant black II	Ammo. chloride	0.002916	
Light magnesium oxide	MgO	40.30	0.15	Mordant black II	Ammo. chloride	0.002015	
Magnesium stearate	–	–	0.75	Mordant black II	Ammo. chloride	0.002431	
Zinc oxide	ZnO	81.38	0.15	Xylenol orange	Hexamine	0.008138	

Table 9.2 : Back Titrations of the Official Compounds with Disodium edetate

	Formula	Mol. Wt.	Wt. to be taken in G	Indicator used	Buffer used	Equivalent in G for 1 ml 0.05 M. disod. EDTA	Remarks
Aluminium hydroxide gel	–	5	5	Xylenol orange	Hexamine	0.00254 g	Black titration
Aluminium sulphate	$Al_2(SO_4)_3$	342.14	0.6	Xylenol orange	Hexamine	0.008554	with 0.05 M lead nitrate

Table 9.3 : Replacement Titrations of the Official Compounds with Disodium edetate

	Formula	Mol. Wt.	Wt. to be taken in G	Indicator used	Buffer used	Equivalent in G for 1 ml 0.05 M disod. EDTA	Remarks
Calcium gluconate	$C_{12}H_{22}CaO_{14}H_2O$	448.4	0.5	Mordant black II	Ammonia Ammonium Chloride	0.0224 g	5ml of 0.05 M Mag. Sulphate
Calcium lactate	$C_6H_{10}CaO_6 \times H_2O$	218.22 anhydrous	0.3	Mordant black II	Ammonia Ammonium Chloride	0.0109	
Calcium Levulinate	$C_{10}H_{14}CaO_62H_2O)$	306.33	0.2	Mordant black II	Ammonia Ammonium Chloride	0.01351	

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(B) Ion-Electron Balance Method :

In case of oxidation-reduction reaction, the electrons are transferred in the process. In addition to electrons, the number of ions are also balanced. This method involves the following steps.

1. Ascertain the composition and formulae of the reactants and products of the reaction.
2. Determine the oxidising agent. Write down partial equation for oxidising agent.
3. Determine the reducing agent. Write down partial equation for reducing agent.
4. Find out the coefficient required to balance the number of electrons in both reactions and multiply each partial equation by this coefficient.
5. Add both the partial equations and cancel out the common entities on both side of the equation.

It should be noted that in aqueous solutions, in addition to oxidising and reducing agents; H^+, OH^-, and H_2O molecules take part in the reaction.

Ex. : Reduction of potassium permanganate by ferrous sulfate in presence of dilute sulfuric acid.

$$KMnO_4 + FeSO_4 + H_2SO_4 \rightarrow Fe_2(SO_4)_3 + K_2SO_4 + 2\,MnSO_4 + H_2O$$

Reduction reaction is –

$$MnO_4^- \rightarrow Mn^{+2}$$

To balance the number of atoms, i.e. to take up 4 oxygen atoms, $8H^+$ are required.

$$MnO_4^- + 8H^+ \rightarrow Mn^{+2} + 4H_2O$$

To balance electrically, 5e are needed.

$$MnO_4^- + 8H^+ + 5e \rightarrow Mn^{+2} + 4H_2O$$

The second partial equation (oxidation) is

$$Fe^{++} \rightarrow Fe^{+++}$$

To balance electrically, one electron is needed.

$$Fe^{++} - e^- \rightarrow Fe^{+++}$$

Now, the loss and gain of electrons must be equal in both reactions. Hence,

$$1 \times [MnO_4^- + 8H^+ + 5e \rightarrow Mn^{+2} + 4H_2O]$$
$$5 \times [Fe^{++} - e \rightarrow Fe^{+++}]$$

To balance the equation, and number of molecules of ferric sulfate, multiply both the equations by two :

$$1 \times [MnO_4^- + 8H^+ + 5e \rightarrow Mn^{+2} + 4H_2O]$$
$$10\,[Fe^{++} - e \rightarrow Fe^{+++}]$$

$$2\,KMnO_4 + 8\,H_2SO_4 + 10\,FeSO_4 \rightarrow 5\,Fe_2(SO_4)_3 + 2\,MnSO_4 + K_2SO_4 + 8\,H_2O$$

DETECTION OF END-POINT

(A) Internal or Redox Indicator :

As seen in acid-base titrations, acid-base indicators are employed to mark the sudden change in pH during titrations. Similarly, an oxidation-reduction indicator should mark

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potassium iodide solution in the cup collar of the iodine flask and remove the stopper slowly. Rinse the stopper and sides of flask with 100 ml water and titrate the liberated iodine with 0.10 N sodium thiosulphate solution till the solution becomes faint yellow. Then add 1 ml of starch solution and continue titration till the blue colour disappears. Note the reading of thiosulphate required as (x ml). Carry out the blank using same quantities of reagents following : the same procedure simultaneously and note the reading as (y ml) of thiosulphate required.

The iodine value is calculated by using the following formula,

$$\text{Iodine value} = \frac{(y - x) \times 1.269}{\text{Weight of the substance in g}}$$

(b) Determination of iodine Value by iodine Bromide Method :

Take a 500 ml dry iodine flask, rinse with small quantity of glacial acetic acid. Transfer an accurately weighed quantity of sample and dissolve in 15 ml of chloroform. Add slowly 25.0 ml of iodine bromide solution from a burette and insert the stopper, previously moistened with potassium iodide solution. Set aside in dark for thirty minutes or as directed in monograph with frequent shaking. Add 10 ml of potassium iodide solution and 100 ml of water and titrate with 0.10 N sodium thiosulphate solution, using starch solution as indicator towards end point. Note the volume of sodium thiosulphate solution required. Perform a blank experiment with same reagents without sample and note the volume of thiosulphate required.

Calculate the iodine value by the formula given in the earlier method.

(c) Determination of iodine Value by Pyridine-bromide Method :

Place an accurately weighed quantity of the sample in a dry iodine flask and dissolve in 10 ml of carbon tetrachloride. Add 25 ml of pyridine-bromide solution, stopper and set aside for ten minutes. Then complete the determination as described in iodine monochloride method and calculate the iodine value.

4. Ester Value :

Determination of Ester value is carried on very few samples. It is defined as number of milligram of potassium hydroxide required to neutralise the acids liberated from the complete hydrolysis of 1 g of sample. It is a measure of the combined acids present in the sample.

In ester value determination, the sample is hydrolysed to alcohol and acid using excess of standard potassium hydroxide solution. The excess of alkali is back titrated. A blank determination is also carried out.

$$RCOOR' + KOH \rightarrow R\,COOK + R'\,OH$$

$$RCOOR' = KOH = H = 2000 \text{ ml of } 0.5 \text{ N}$$

For the determination, place about 2 g. accurately weighed sample in 250 ml flask, add 5 ml alcohol and neutralise the free acid present (if any) by titrating with 0.1 N alcoholic potassium hydroxide solution to pink colour of phenolphthalein indicator. Add 20 – 25 ml 0.5 N alcoholic potassium hydroxide and reflux in boiling water bath for 1 hour. Cool, add 20 ml water and back-titrate the excess of alkali with 0.5 N hydrochloric acid. Carry out a blank under similar conditions. Difference in readings gives the amount of alkali required to saponify ester.

$$\text{Ester Value} = \frac{m \times (\text{factor of acid})}{w} \times 28.5$$

where,

w = wt. in g of the sample

m = difference in burette readings

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	Acid Value	Saponification Value	Iodine Value	Peroxide Value	Hydroxyl Value	Acetyl Value	Unsaponificable matter	Ester Value
Wool Fats	≯ 1.0	90 – 105	17 – 30	> 20.0	–	–	–	–
(B.P.)	≯ 1.0	90 – 105	–	> 20.0	–	–	–	–
Hydrous Wool Fat I.P.	–	–	–	> 20.0	–	–	–	–
(B.P.)	≯ 0.8	67 – 69	–	> 15.0	–	–	–	–
Wool Alcohols I.P.	(66) 2.0	≯ 12.0	–	–	–	130 – 140	–	–
(B.P.)	≯ 2.0	≯ 12.0	–	–	–	–	–	–
White bees Wax I.P.	5 – 10	–	–	–	–	–	–	80 – 95
(B.P.)	17 – 24	87 – 104	–	–	–	–	–	70 – 80
Yellow bees Wax I.P.	5 – 10	–	–	–	–	–	–	80 – 95
(B.P.)	17 – 24	87 – 102	–	–	–	–	–	70 – 80
Emulsifying Wax I.P.	≯ 2.0	≯ 2.0	> 3.0	–	–	–	88–92%w/w	–
(anionic) (B.P.)	–	≯ 2.0	> 3.0	–	–	–	≮ 86.0%w/w	–
Polysorbate 20 I.P.	≯ 2.0	40 – 50	> 5.0	–	–	–	–	–
(B.P.)	≯ 2.0	40 – 50	> 5.0	–	96 – 108	–	–	–
Polysorbate 60 (B.P.)	≯ 2.0	45 – 55	> 5.0	–	89 – 96	–	–	–
Polysorbate 80 I.P.	≯ 2.0	45 – 55	8 – 24	–	–	–	–	–
(B.P.)	≯ 2.0	45 – 55	18 – 24	–	65 – 80	–	–	–
Cetomacrogol Emulsifying Wax (B.P.) (Nonionic)	≯ 0.5	2.0	–	–	175 – 192	–	–	–
Polyethylene glycol 1500 (I.P.)	–	–	–	–	70 – 86	–	–	–
Polyethylene glycol 4000 (I.P.)	–	–	–	–	30 – 36	–	–	–

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Perform the blank, using same quantities of the reagents, following same procedure with sample and note the reading (B ml).

The percentage of crystal violet can be calculated by the formula given below.

$$\% \text{ of crystal violet} = \frac{0.0204 \times (B - A)\, N \times 100}{0.1 \times W}$$

where 0.0204 is the factor for crystal violet + 1 ml of 0.1 N titanous chloride solution + 1 ml of 0.1 N ferric ammonium sulphate.

B = Volume of ferric ammonium sulphate required for blank.
A = Volume of ferric ammonium sulphate required for sample
N = Normality of ferric ammonium sulphate used
0.1 = Normality for factor 0.0204
w = Weight of sample in grams.

The percentage of azo group – N = N – can be calculated by using the following factors.

1 ml of 0.1 titanous salt solution + 0.007005 g of (azo)

IX. ESTIMATION OF UNSATURATION

The olefinic unsaturation or the carbon-carbon double bond/bonds can be determined by two methods.

1. Catalytic hydrogenation
2. By addition of halogen

Catalytic hydrogenation :

The compounds containing carbon-carbon double bond when treated with molecular hydrogen in presence of suitable catalyst like platinum oxide or Raney nickel undergo hydrogenation reaction under suitable conditions.

$$-C=C- + H_2 \xrightarrow{\text{Catalyst}} -\underset{|}{\overset{H}{C}}-\underset{|}{\overset{H}{C}}-$$

Volume of hydrogen absorbed at N. T. P. is calculated. From this the number of C = C bonds can be calculated by using the following formula.

$$\text{Double bond per molecule} = \frac{V \times M}{w \times 225415}$$

where,

V = Volume of hydrogen absorbed in ml. at N. T. P.
M = Molecular weight of the sample
w = Weight of the sample in grams

Catalytic hydrogenation is the most widely used method for determining the unsaturation. However, it is not easy and simple.

The platinium catalyst is very expensive, and if Raney Nickel catalyst is used it has to be prepared freshly and stored properly or stabilized Raney Nickel Catalyst prepared freshly and stored properly is used. The unstabilized Raney Nickel Catalyst is easily destroyed if not stored properly.

A special apparatus is needed to carry out the above hydrogenation. The description and use of this hydrogenation apparatus is given in standard text books.

In the second method, the unsaturation is determined by the addition of halogen to C = C, using a suitable reagent. The excess of halogen is determined by adding excess of KI

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The Counter or Back Potential :

During electrogravimetric operation a galvanic cell is formed as the products form on the electrodes. When the current is switched off the products tend to produce a current in direction opposite to the electrolysis current. This is called *back e.m.f.* Thus the voltage applied to the electrolysis cell must exceed that of back e.m.f. of cell and must also overcome the resistance of the solution to the passage of current. The amount of current that flows is given by Ohm's law -

$$I = \frac{E_{appl} - E_{back}}{R}$$

The theoretical counter or back potential is given by

$$E_{back} = E_{anode} - E_{cathode}$$

Cathode : It is the electrode at which reduction occurs. In an electrolytic cell, it is connected to negative terminal as the electrons liberated by source are accepted at this terminal while in a galvanic cell it is connected to the positive terminal, as such cell accepts electrons at this terminal.

Anode : It is the electrode at which oxidation occurs. It is the positive terminal of electrolysis cell or negative terminal of galvanic cell.

Polarisation and Overvoltage : When cell exhibits non-linear current voltage behaviour, it is said to be polarised and degree of polarisation is described by the overvoltage or overpotential.

Overvoltage or Overpotential : Polarisation requires the application of a potential to an electrolytic cell that is greater than theoretical to give a current of expected magnitude. This potential difference between the theoretical cell potential and the measured cell potential at a given level of current is called as an *overvoltage* or *overpotential*. Because of this overvoltage, a total voltage equal to the overvoltage in addition to the back e.m.f. must be supplied to the cell.

The overvoltage can be decreased by use of platinized platinum electrodes but these are rarely used in electrogravimetry because of tendency of deposit to flake off. It can also be minimised by keeping the electrode area large and the current small, so the current density (current per unit area of electrode surface) will be low.

Polarization :

Polarization is an electrode phenomenon that may affect either or both of electrodes in a cell. The degree of polarization varies widely and will be influenced by –

1. Size, shape and composition of electrodes.
2. The composition of the electrolytic solution.
3. The temperature and stirring rate.
4. The current level.
5. The physical state of the species involved in the cell.

Polarization may be of two kinds viz. concentration polarization and kinetic polarization.

Concentration Polarization :

Electron transfer between a reactive species in a solution and electrode can take place only from a thin film of solution located immediately adjacent to the electrode surface. This film contains a limited number of reactive ions hence to maintain the steady current

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In the A type a wide mouth bottle with bark cork having holes for passing two platinum wires of 1 sq. cm size is used.

In B type the electrodes are firmly fixed in the perspex lid which is provided with opening for the stirrer and the tip of the burette. The stirrer may be replaced by magnetic stirrer. This type of cell is more suitable for precipitate giving reactions since the face of electrode plates are vertical and parallel.

The C or Dip type : In a wide bore corning glass tube is fixed copper wires, the tip of which have two platinum plates of 1 sq. cm in size fixed at 1 cm apart. The terminals of copper wire are taken out for connections. The position of wire is fixed in glass tube by rosin. The two inside faces of platinum electrode of cell are plated with platinum black. This reduces polarization effect and allows absorption of ion on its surface.

For a given cell the ratio of d/A for fixed electrodes is a constant. It is called as cell constant θ. The cell constant can be determined by the following formula :

$$k = \frac{\theta}{R} \qquad \ldots (19.3)$$

where k is specific conductance and R is the resistance of solution. For accurate determination of cell constant, cell is dipped in a standard solution of known specific conductance at 18 °C or 25 °C and resistance is measured. The cell constant is found from the equation (3). Potassium Chloride solution of either 1 M. 0.1 M or 0.01 M is employed as a standard solution for cell constant determination. Specific conductance values of the above solutions are recorded in literature and can be used for the calculations.

Conductivity meter : The conductance measurements are made by using conductivity bridge. The conductivity meters are made by using wheatstone bridge circuit. (Fig. 19.2). In this cell is placed in one arm of the wheatstone bridge circuit ab and resistance R_1 constitutes the arm ac. The arms bd and dc are in the form of calibrated slide wire resister. The balance point of d is a sliding contact which shows no signal to detector D. This detector is either a galvanometer, earphone, oscilloscope, magic-eye or now-a-days calibrated digital display. A source of alternating current (V) with a frequency of 50 – 60 Hz or a mains operated oscillator giving a current with frequency upto 3000 Hz is used in the circuit by connecting b and c.

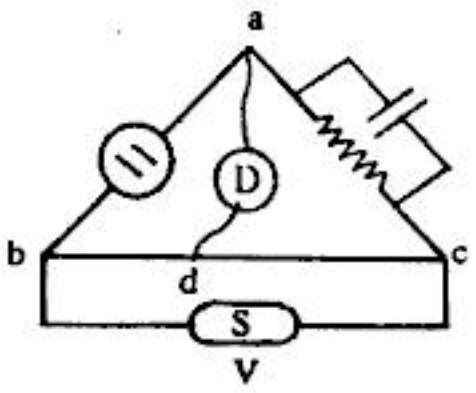

Fig. 19.2

Conductivity meters have a range switch (selector range) to select appropriate standard resistances (or standard conductances), a calibrate switch (calibrate) with which the instrument is calibrated to a desired value of conductance. A number of conductivity meters are commercially available.

To measure the conductance of electrolyte solution, conductivity cell is dipped into it and terminals connected to test terminals of conductivity bridge. The selector switch is set to the appropriate conductance range and reading is recorded from the galvanometer or read out meter.

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The conductometric cell consists of narrow bore pyrex thin walled glass tube through which solution under analysis can be drawn by syringe after addition of each volume of titrant. This tube is surrounded externally by two cylindrical metal electrodes which are separated from each other. The whole unit is enclosed in earthen metal box. Radio frequency current generated by suitable source is fed via screened cable from oscillator to one of the electrodes. The current passes across the electrode, through glass wall to solution and back across glass wall of other electrode. The current coming out of the second electrode is rectified and passed to microammeter for measurements.

Applications : The various applications of high frequency methods are :

1. It is used to measure the dielectric constants of various solvents.
2. Direct high frequency analysis of binary mixtures e.g. o and p-xylenes, acetone-water, benzene-hexane can be carried out by adopting calibration curves.
3. The technique can be used to study reaction rates for example in study of alkaline hydrolysis of esters or polymerisation reactions etc.
4. The technique is useful to follow the course of titration. Neutralisation reactions (Acid-base titrations), precipitation and complex formation reactions can be studied.
5. The other uses of high frequency titrations include determination of hardness of water by titration with standard soap solution.
6. In the oxidation-reduction reactions, oxidation of ferrous ion by permanganate and bichromate have been studied.
7. Titrations can be carried out for electrolyte or ion in presence of large excess of indifferent electrolytes e.g. chloride and sulphate have been estimated in small samples of sea bed sediments.
8. Alkaloidal assays and non-aqueous titrations are also possible by high frequency method.

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