A TEXT BOOK

PHARMACY INDIA PUBLICATION

PHARMACEUTICAL

INORGANIC AND ANALYTICAL CHEMISTRY

BP106T

As per NEP 2020

Bachelor of Pharmacy

1st Semester

Author

DR. DEBARSHI KAR MAHAPATRA,
DR. NIVEDITA BHARDWAJ, DR. KALYAN GHOSH

FULLY COLOURED BOOK

A TEXT BOOK

PHARMACEUTICAL

INORGANIC AND ANALYTICAL CHEMISTRY

BP106T

As per NEP 2020

Bachelor of Pharmacy

1st Semester

PHARMACY INDIA PUBLICATION

PUBLISHED BY
PHARMACY INDIA PUBLICATION

PHARMACY INDIA PUBLICATION

ISBN: 978-81-689235-1-5

1st Edition- 2026

PUBLISHED BY
PHARMACY INDIA PUBLICATION
STREET-4, DAYALPURAM, KHATAULI
MUZAFFARNAGAR, (U.P) 251201

Price:- **Rs. 360/-**

PHARMACY INDIA
STREET-4, DAYALPURAM, KHATAULI MUZAFFARNAGAR, 251201
8171313561, 8006781759 **pharmacyindia24@gmail.com**
pharmacyindia.co.in

PREFACE

Pharmaceutical Inorganic and Analytical Chemistry forms an essential foundation for understanding the chemical principles, analytical techniques and inorganic substances used in pharmaceutical science. The book Pharmaceutical Inorganic and Analytical Chemistry has been developed for first-semester B.Pharm students in accordance with the Pharmacy Council of India syllabus under the National Education Policy 2020. The content is presented in a simple, systematic and examination-oriented manner to help students understand both the theoretical concepts and their practical pharmaceutical applications.

The book begins with the fundamentals of pharmaceutical analysis, including different analytical techniques, methods of expressing solution strength, primary and secondary standards, sources and types of errors, accuracy, precision and significant figures. It also provides a detailed discussion of pharmaceutical impurities, their sources, regulatory significance and pharmacopoeial limit tests for chloride, sulphate, iron, arsenic, lead and heavy metals. Acid-base chemistry, buffer systems, pH calculations, isotonicity, physiological acid-base balance and the functions of major intra- and extracellular electrolytes are explained with suitable pharmaceutical examples.

The analytical chemistry section covers acid-base, non-aqueous, precipitation, complexometric and redox titrations. Theories of indicators, neutralisation curves, preparation and standardisation of titrants, gravimetric analysis, metal-ion indicators, masking and demasking agents and important assay procedures are described in a step-by-step manner. Special emphasis has been placed on the estimation of substances such as ammonium hydroxide, sodium benzoate, barium sulphate, magnesium sulphate and calcium gluconate, along with the principles of Mohr's, Volhard's, modified Volhard's and Fajans methods.

The inorganic pharmacy section includes gastrointestinal agents, acidifiers, antacids, saline cathartics, antimicrobials, expectorants, emetics, haematinics, poisons and antidotes. It also introduces radiopharmaceuticals, radioactivity, pharmaceutical applications of sodium iodide I-131, technetium-99m, cobalt-60 and phosphorus-32, together with their safe handling, storage and disposal. The book is enriched with pharmaceutical examples, chemical reactions, assay procedures, explanatory tables, flowcharts, diagrams and illustrations to make complex concepts easier to understand. It is hoped that this book will provide students with a strong foundation in pharmaceutical analysis and inorganic chemistry and support their academic, laboratory and professional development.

Authors

PHARMACEUTICAL INORGANIC AND ANALYTICAL CHEMISTRY SYLLABUS

UNIT-1 — HOURS: 07

- **Introduction to pharmaceutical analysis:** Different techniques of analysis, Methods of expressing strength of solutions, Primary and secondary standards with examples.
- **Errors:** Sources of errors, types of errors, methods of minimizing errors, accuracy, precision and significant figures.
- **Impurities:** Definition, types, contents and regulatory importance. Sources and types of impurities in Pharmaceuticals, limit tests for chloride, sulphate, iron, arsenic, lead, heavy metals, and modified limit test for chloride and sulphate.

UNIT-2 — HOURS: 08

- **Acid-Base Chemistry and Buffer Systems in Pharmacy:** Definition of acids, bases, buffers, pH Scale and its significance, Buffer equation, calculation of pH for Buffer solution. Isotonicity and its application in IV Fluids and Ophthalmic Solutions.
- **Major extra and intracellular electrolytes:** Functions of major physiological ions, Electrolytes used in the replacement therapy: Sodium chloride*, Potassium chloride, Calcium chloride and Oral Rehydration Salt (ORS), Physiological acid base balance.

UNIT-3 — HOURS: 14

- **Acid base titrations:** Theories of acid base indicators, classification of acid base titrations. Preparation and standardization of titrants viz. hydrochloric acid and sodium hydroxide. Theory involved in titrations of strong, weak, and very weak acids and bases, neutralization curves. Assay of Ammonium hydroxide.
- **Non-aqueous titrations:** Types of solvents used, acidimetric and alkalimetric titration using nonaqueous solvents. Preparation and standardization of acidic and basic titrants. Estimation of weakly acidic and basic substances using nonaqueous titrants, estimation of Sodium benzoate.
- **Precipitation titrations and gravimetry:** Principle and steps involved in gravimetric analysis, Mohr's method, Volhard's, Modified Volhard's, Fajans method. Estimation of barium sulphate by gravimetry.
- **Complexometric titrations:** Classification, metal ion indicators, masking and demasking reagents, preparation and standardization of disodium EDTA. Estimation of Magnesium sulphate and Calcium gluconate*

UNIT-4 — HOURS: 10

Gastrointestinal agents

- **Acidifiers:** Sodium acid phosphate and Dilute Hydrochloric acid.
- **Antacids:** Ideal properties of antacids, combinations of antacids, Sodium bicarbonate*, Aluminium hydroxide gel*.
- **Agents promote bowel movements:** Magnesium hydroxide, Sodium orthophosphate, Sodium Potassium tartrate and magnesium trisilicate.
- **Antimicrobials:** Mechanism, classification, Potassium permanganate, Boric acid, Hydrogen peroxide*, Chlorinated lime*, Iodine and its preparations.

Radiopharmaceuticals

Basics of radioactivity, applications of radioisotopes of Sodium Iodide I-131, Technetium-99m, Cobalt-60, Phosphorus-32 including safe handling, storage, and disposal of radiopharmaceuticals, adhering to regulatory guidelines for safety.

UNIT-5 — HOURS: 06

Miscellaneous Compounds

- **Expectorants:** Potassium iodide, Ammonium chloride*.
- **Emetics:** Copper sulphate*, Sodium potassium tartrate.
- **Haematinics:** Ferrous sulphate*, Ferrous gluconate.
- **Poison and Antidote:** Definition, classification of antidotes, Sodium thiosulphate.

INDEX

Chapter -1

Chapter -2

Chapter -3

Chapter-4

INDEX

INDEX

Chapter-9

Chapter-10

Chapter-11

Chapter-12

1 INTRODUCTION TO PHARMACEUTICAL ANALYSIS AND ERRORS

- Different techniques of analysis, methods of expressing strength of solutions, and primary and secondary standards with examples.
- Sources of errors, types of errors, methods of minimizing errors, accuracy, precision, and significant figures.

1.1 Introduction

Pharmaceutical analysis is a broad field that involves a series of systematic procedures used for the identification, determination, separation, purification, and structural elucidation of compounds employed in pharmaceutical formulations. The substances commonly subjected to pharmaceutical analysis include active pharmaceutical ingredients (APIs), pharmaceutical excipients, impurities, contaminants, and drug metabolites. Pharmaceutical excipients may include disintegrants, binders, surfactants, suspending agents, viscosity-enhancing agents, polymers, adhesives, and lubricants. The samples analyzed may consist of raw materials, intermediate products, finished pharmaceutical dosage forms, biological samples, or degradation products. Pharmaceutical analysis plays an essential role in ensuring the identity, purity, quality, safety, and efficacy of pharmaceutical products.

1.1.1 Types of Pharmaceutical Analysis

Pharmaceutical analysis is broadly classified into qualitative analysis and quantitative analysis (Figure 1.1).

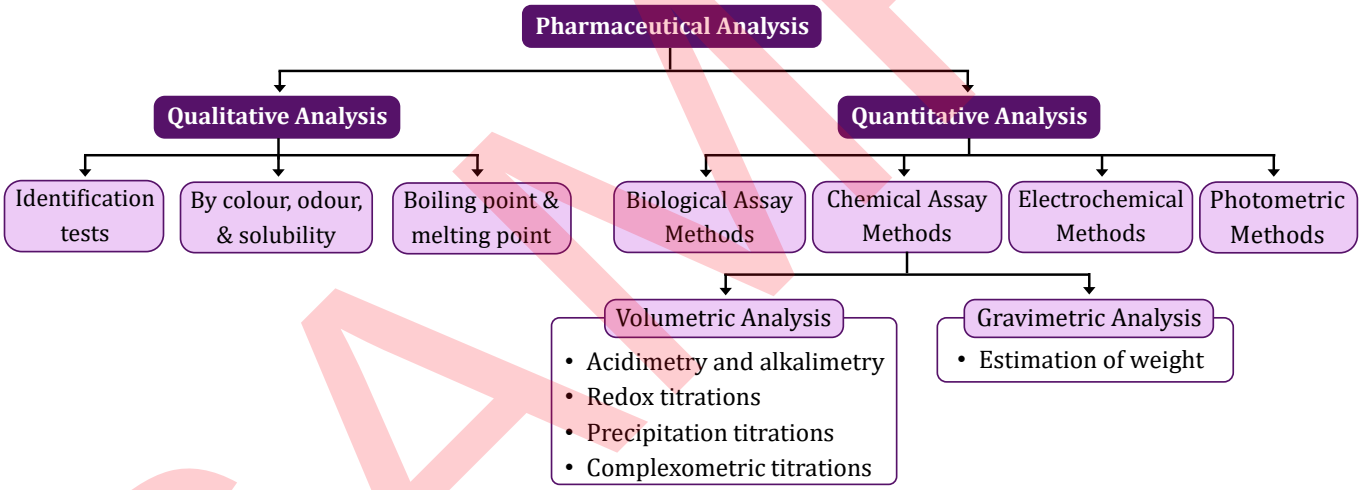


Figure 1.1: Classification of pharmaceutical analysis

1.1.1.1 Qualitative Analysis

Qualitative analysis is concerned with the identification of chemical constituents present in a natural or synthetic substance. It establishes the presence or absence of a particular element, ion, functional group, or compound in a sample. Identification is carried out by observing characteristic physical or chemical changes such as colour development, precipitate formation, gas evolution, solubility behaviour, melting point, boiling point, or specific chemical reactions. Spectroscopic and chromatographic techniques may also be used for identification. Limit tests are semi-quantitative tests used to ensure that specified impurities are present within the prescribed limits.

Colour, odour, and solubility

The preliminary examination of a pharmaceutical substance begins with the observation of its colour, odour, and solubility. Many drugs possess characteristic colours that help in their identification. For example, copper sulphate appears blue, while potassium permanganate has a deep purple colour. Similarly, certain pharmaceutical substances exhibit distinctive odours that assist in their recognition. Solubility is another important physical property because each drug has a characteristic pattern of solubility in water, alcohol, ether, acids, alkalis, and other solvents. These observations provide valuable preliminary information regarding the identity and purity of the sample.

Identification tests

Identification tests are specific chemical or instrumental tests performed to confirm the identity of a pharmaceutical substance. These tests are based on characteristic reactions that produce colour changes, precipitates, fluorescence, or other observable effects unique to the analyte. Official pharmacopoeias such as the Indian

7. Accuracy

Accuracy refers to the closeness of an observed value to the true or accepted value. A method is considered accurate when the difference between the observed and true values is minimal.

Error = Observed Value – True Value

Accuracy is commonly determined by recovery studies using a known amount of analyte.

% Recovery = (Amount Recovered)/(Amount Added)×100

8. Precision

Precision refers to the closeness of repeated measurements to one another. It indicates the consistency and reproducibility of an analytical method. Precision is commonly expressed as standard deviation or relative standard deviation (RSD).

% RSD = (Standard Deviation)/Mean×100

Wherein, a lower percentage RSD indicates better precision.

9. Repeatability

Repeatability refers to the closeness of results obtained when the same sample is analysed repeatedly by the same operator under identical conditions. The analysis should be performed using the same laboratory, analytical procedure, observer, measuring instrument, and environmental conditions. All measurements should be completed within a short interval of time.

10. Reproducibility

Reproducibility is the ability of an analytical method to produce consistent results when the experiment is repeated under changed conditions. These changes may include different analysts, laboratories, instruments, or locations.

Reproducibility is classified into the following two types:

(a) Within-laboratory reproducibility

Within-laboratory reproducibility refers to the repetition of an experiment by different analysts in the same laboratory, generally using the same equipment and analytical procedure.

(b) Between-laboratory reproducibility

Between-laboratory reproducibility refers to the repetition of an experiment in different laboratories by different analysts using different instruments and equipment.

1.2 Different Techniques used in Pharmaceutical Analysis

A wide range of analytical techniques is available for the qualitative and quantitative examination of drugs, chemicals, pharmaceutical substances, biological materials, and other samples. These techniques vary considerably in terms of sensitivity, selectivity, accuracy, precision, speed, complexity, cost, and sample requirements.

One of the major responsibilities of an analytical chemist is to select the most appropriate analytical procedure for a particular determination. The selection of a suitable method depends on several factors, including:

- Nature and physical state of the sample
- Concentration of the analyte
- Required degree of accuracy and precision
- Sensitivity and selectivity of the method
- Availability of instruments and laboratory facilities
- Time required for analysis
- Cost of the analytical procedure
- Number of samples to be analyzed

On the basis of the use of analytical instruments, the techniques of analysis may be broadly classified into two major categories (Figure 1.4):

1. Non-instrumental methods of analysis
2. Instrumental methods of analysis

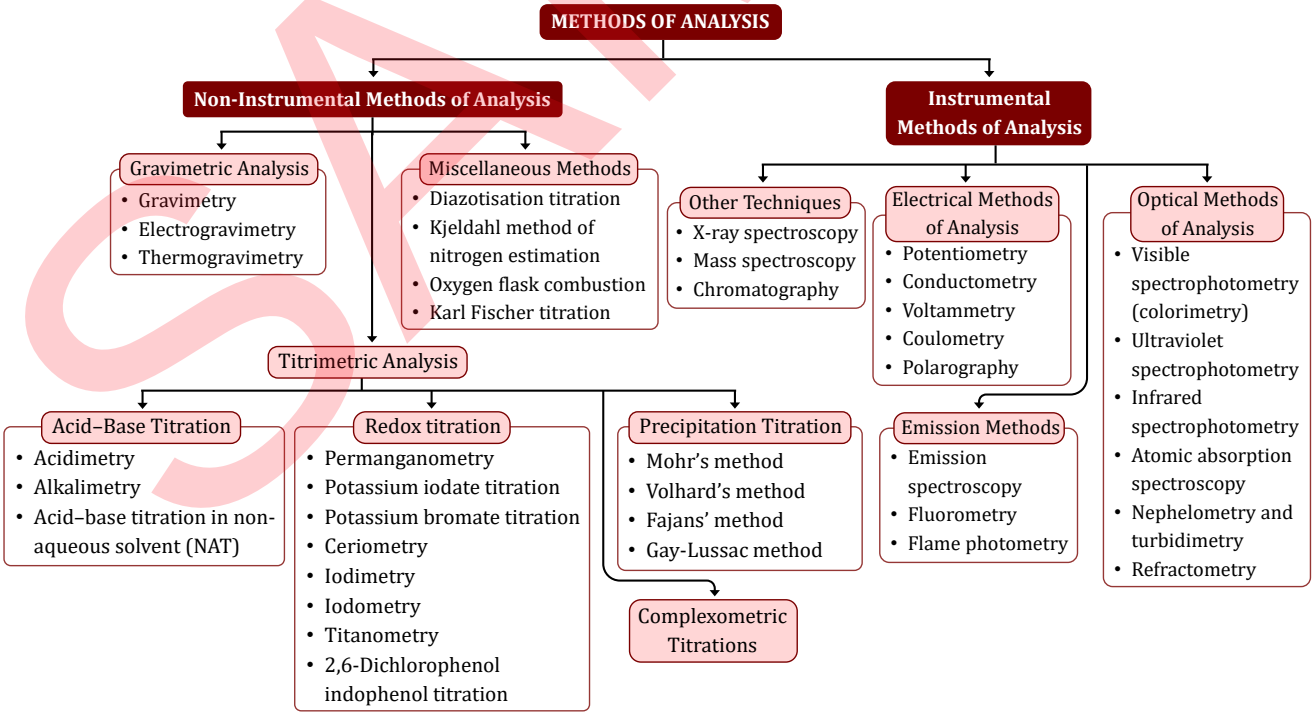


Figure 1.4: Different Analytical Techniques Available for the Qualitative and Quantitative Analysis

1.5.5 Precision

Precision refers to the degree of agreement among a series of measurements made on the same quantity under specified conditions. In other words, it indicates the consistency or closeness of repeated analytical results. Accuracy represents the closeness of a measured value to the true or accepted value, whereas precision represents the closeness of repeated measurements to one another. Although precision commonly accompanies accuracy, a highly precise result is not necessarily accurate. This distinction can be understood from the following example.

A substance was known to contain 49.10 ± 0.02% of constituent A. Two analysts examined the same substance using the same analytical method and obtained the following results.

Results Obtained by Analyst 1 (Figure 1.20)

Percentage of A: 49.01, 49.25, 49.08 and 49.14

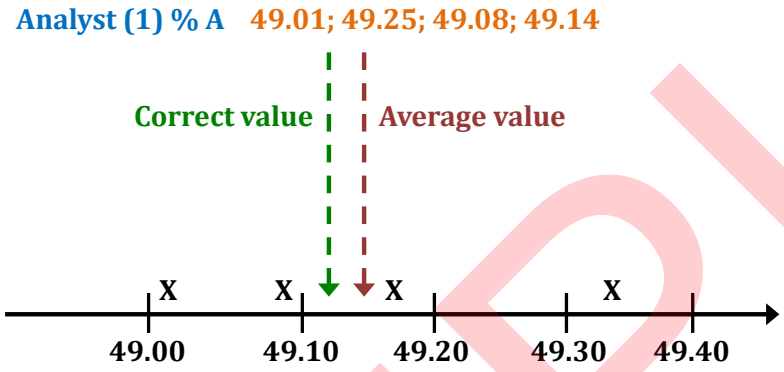


Figure 1.20: Results Obtained by Analyst 1

- Correct value: **49.10%**
- Arithmetic mean: **49.12%**
- Range: **49.01–49.25%**

The average value obtained by Analyst 1 is very close to the correct value. Therefore, the results are considered accurate. However, the individual values show considerable variation, indicating relatively poor precision.

Results Obtained by Analyst 2 (Figure 1.21)

Percentage of A: 49.40, 49.44, 49.42 and 49.42

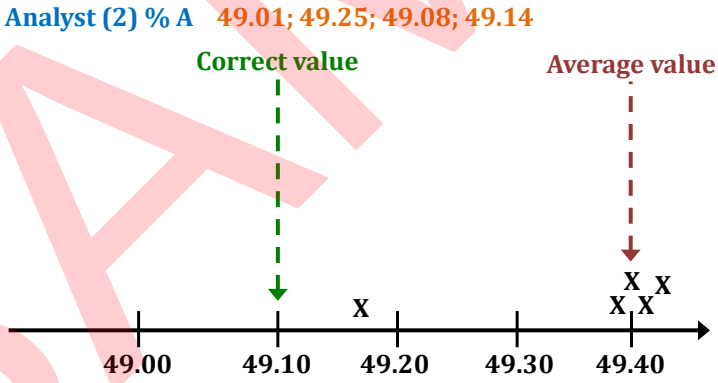


Figure 1.21: Results Obtained by Analyst 2

- Correct value: **49.10%**
- Arithmetic mean: **49.42%**
- Range: **49.40–49.44%**

The results obtained by Analyst 2 are very close to one another and therefore show a high degree of precision. However, their average value differs considerably from the correct value. Hence, the results are precise but inaccurate.

Comparison of the results

The observations may be summarised as follows:

1. Analyst 1: The mean value is close to the correct value, but the individual results are widely scattered. Therefore, the analysis is accurate but less precise.
2. Analyst 2: The individual results are closely grouped, but their mean differs from the correct value. Therefore, the analysis is precise but inaccurate.
3. The results of Analyst 1 lie on both sides of the mean value, suggesting the presence of random errors.
4. The results of Analyst 2 are consistently higher than the correct value, indicating the presence of a constant or systematic error.

Thus, precision may be classified into:

- Within-run precision (Repeatability)

2 PHARMACEUTICAL IMPURITIES

Definition, types, contents and regulatory importance.
Sources and types of impurities in Pharmaceuticals, limit tests for chloride, sulphate, iron, arsenic, lead, heavy metals, and modified limit test for chloride and sulphate.

2.1 DEFINITIONS, TYPES, CONTENTS AND REGULATORY IMPORTANCE

2.1.1 Introduction

Pharmaceutical products are expected to possess suitable identity, strength, quality, purity and stability throughout their shelf life. However, an absolutely pure pharmaceutical substance is difficult to obtain because small quantities of unwanted chemicals or foreign materials may enter or develop during synthesis, purification, formulation, packaging, transportation and storage. These unwanted substances are collectively known as pharmaceutical impurities.

The presence of impurity does not necessarily make a pharmaceutical product unsafe. Its acceptability depends on its identity, concentration, biological activity, toxicity and the patient's level of exposure. Nevertheless, impurities must be scientifically identified, evaluated and controlled because they can affect the safety, efficacy, appearance and stability of medicines. Impurities in pharmaceuticals are undesired chemical substances that are present in a drug substance or finished pharmaceutical product. They may originate from the manufacturing process, remain as residual materials after synthesis, be introduced during formulation, or develop during storage due to chemical degradation or ageing.

An impurity is defined as any component present in a drug substance other than the active pharmaceutical ingredient (API). In a finished pharmaceutical product, an impurity is any substance that is neither the API nor an intentionally added excipient or formulation ingredient. For example, 2-Bromo-1-(3,5-dichlorophenyl)propan-1-one is a process-related impurity that may be present as an intermediate or by-product during the synthesis of certain pharmaceutical compounds.

2.1.2 Types of impurities in pharmaceutical substances

Chemical compounds manufactured on a commercial scale may contain various impurities, although the total quantity of these impurities is generally very small. Such impurities may originate from raw materials, manufacturing processes, dust, atmospheric moisture, equipment, storage conditions, or handling procedures. The impurities commonly found in pharmaceutical substances and preparations may be classified as follows:

1. Toxic Impurities

These impurities may produce harmful or poisonous effects even when present in small quantities. Examples include salts of lead and arsenic.

2. Activity-Depressing Impurities

Certain impurities reduce the therapeutic or functional activity of a pharmaceutical substance. For example, the presence of water in hard soap may decrease its effectiveness and quality.

3. Impurities Causing Incompatibility

Some impurities may make a substance chemically or physically incompatible with other ingredients used in a pharmaceutical formulation. Such incompatibility may result in precipitation, decomposition, colour change, or loss of therapeutic activity.

4. Impurities Causing Technical Difficulties

Certain impurities can interfere with the preparation, handling, testing, stability, or therapeutic use of pharmaceutical substances. These impurities may alter the quality, purity, or performance of a drug and can affect analytical results or product safety. For example, the presence of potassium iodate (KIO_3) as an impurity in potassium iodide (KI) and carbonate impurities in ammonia solutions can adversely influence their chemical properties and pharmaceutical applications.

5. Colouring- and Flavouring-Related Impurities

Some impurities may adversely affect the physical characteristics of pharmaceutical substances by producing undesirable colour, odour, taste, or changes in appearance. They may also alter the stability and handling properties of the product. For example, sodium salicylate may become discoloured due to the presence of phenolic impurities, while sodium chloride may become damp as a result of hygroscopic magnesium salts.

6. Moisture-Related Impurities

Traces of moisture absorbed from the atmosphere may adversely affect pharmaceutical substances. Moisture may cause powders to lose their free-flowing properties, promote chemical decomposition, or increase susceptibility to oxidation.

7. Impurities Affecting Physical and Chemical Properties

Some impurities alter the physical or chemical characteristics of a substance, such as its appearance, solubility, melting point, stability, or reactivity. Such changes may make the substance unsuitable for medicinal use.

soluble chloride ions and silver nitrate in the presence of dilute nitric acid. Silver nitrate reacts with chloride ions to form a fine white precipitate of silver chloride. When chloride is present in a very small quantity, the silver chloride remains dispersed in the solution and produces turbidity or opalescence.

$$Cl^- + AgNO_3 \rightarrow AgCl\downarrow + NO^-$$

For example:

$$NaCl + AgNO_3 \rightarrow AgCl\downarrow + NaNO_3$$

The turbidity produced by the test solution is compared with that produced by a standard chloride solution containing a known amount of chloride. Silver chloride is insoluble in dilute nitric acid. Therefore, the precipitate remains suspended and produces a visible opalescence.

Figure 2.1: Formation of Silver Chloride Opalescence

Role of Dilute Nitric Acid

Dilute nitric acid is added for the following reasons:

1. It provides the acidic medium required for the test.
2. It prevents the precipitation of other silver salts.
3. It reduces interference from ions such as carbonate, phosphate and similar acid radicals.
4. It ensures that the turbidity is mainly due to the formation of silver chloride.

Nitric acid does not itself produce the turbidity; the turbidity is produced by the finely divided silver chloride precipitate.

Reagents Required

- Dilute nitric acid
- Silver nitrate solution
- Standard sodium chloride solution
- Distilled or chloride-free wate

Procedure

Table 2.1: Method According to I.P. 1985

Step	Test Solution	Standard Solution
1	Dissolve the specified quantity, generally 1 g, of the substance in approximately 10 mL of distilled water. Transfer the solution to a Nessler cylinder labelled Test.	Transfer 1 mL of 0.05845% w/v sodium chloride solution to a Nessler cylinder labelled Standard.
2	Add 10 mL of dilute nitric acid.	Add 10 mL of dilute nitric acid.
3	Dilute the solution to 50 mL with distilled water.	Dilute the solution to 50 mL with distilled water.
4	Add 1 mL of 0.1 M silver nitrate solution.	Add 1 mL of 0.1 M silver nitrate solution.
5	Stir immediately with a glass rod and allow the solution to stand for 5 minutes.	Stir immediately with a glass rod and allow the solution to stand for 5 minutes.
6	Compare the turbidity of the test solution with that of the standard solution.	Use the standard solution as the reference for comparison.

The two Nessler cylinders are placed side by side and the turbidity is compared transversely against a dark, preferably black, background. Both solutions should be examined under identical lighting conditions.

Observation and Interpretation

If the turbidity or opalescence of the test solution is not greater than that of the standard solution, the sample passes the limit test for chlorides.

If the turbidity of the test solution is greater than that of the standard solution, the sample contains chloride impurities above the prescribed limit and fails the test.

2.3.3 Modified Limit Test for Chlorides

The modified limit test for chlorides is a pharmacopoeial method used to detect small amounts of chloride impurities in pharmaceutical substances. The test is based on the formation of turbidity when chloride ions react with silver nitrate to form silver chloride. In the modified procedure described in the International Pharmacopoeia (6th Edition, 2016), standardized hydrochloric acid is used instead of sodium chloride to prepare the standard chloride solution. This modification changes only the source of chloride ions, while the principle and method of comparison remain unchanged.

Principle

The modified limit test for chlorides is based on the reaction

2	Add 2 mL of 20% w/v iron-free citric acid solution.	Add 2 mL of 20% w/v iron-free citric acid solution.
3	Add 0.1 mL of thioglycollic acid and mix.	Add 0.1 mL of thioglycollic acid and mix.
4	Add ammonia solution until the solution becomes alkaline.	Add ammonia solution until the solution becomes alkaline.
5	Dilute the solution to 50 mL with distilled water.	Dilute the solution to 50 mL with distilled water.
6	Allow the solution to stand for 5 minutes for complete colour development.	Allow the solution to stand for 5 minutes for complete colour development.
7	View the colour vertically and compare it with the standard solution.	Use the standard solution as the reference for comparison.

The purple colour is compared by viewing vertically downward through the solutions under uniform lighting conditions.
The Nessler cylinders used for the test and standard solutions must be identical.

Observation and Interpretation

- If the purple colour produced by the test solution is not more intense than that of the standard solution, the sample passes the limit test for iron.
- If the purple colour of the test solution is more intense than that of the standard solution, the iron impurity exceeds the prescribed limit and the sample fails the test.

2.3.7 Limit Test for Arsenic

Arsenic is a highly toxic impurity that may be present in pharmaceutical substances because of contaminated raw materials, manufacturing processes, reagents, equipment, water or environmental exposure. Therefore, pharmacopoeias prescribe a limit test to ensure that the quantity of arsenic present in a pharmaceutical substance does not exceed the specified permissible limit.

In the limit test for arsenic, the amount of arsenic is expressed in terms of elemental arsenic, As. The test is commonly performed using the Gutzeit method, in which arsenic is converted into arsine gas and subsequently detected by the formation of a yellow-to-brown stain on mercuric chloride paper.

Principle

The pharmacopoeial limit test for arsenic is based on the reduction of arsenic compounds to arsine gas, AsH_3. When arsine comes into contact with mercuric chloride paper, it produces a yellow-to-brown stain consisting of arsenic–mercury compounds.

The intensity of the stain is directly related to the amount of arsenic present in the sample. The stain produced by the test solution is compared with a standard stain prepared under identical experimental conditions using a known quantity of arsenic.

The substance complies with the test when the stain produced by the test solution is not more intense than the stain produced by the standard arsenic solution.

Chemical Reactions

Arsenic may be present in either the trivalent or pentavalent oxidation state. Trivalent arsenic exists in acidic solution mainly as arsenious acid:

$$As^{3+} \rightarrow As(OH)_3 \text{ or } H_3AsO_3$$

Trivalent — Arsenious acid

Pentavalent arsenic exists mainly as arsenic acid:

$$As^{5+} \rightarrow H_3AsO_4$$

Pentavalent — Arsenic acid

Pentavalent arsenic is first reduced to the trivalent state by reducing agents such as stannous chloride and potassium iodide.

$$H_3AsO_4 \xrightarrow[KI]{SnCl_2} H_3AsO_3$$

The trivalent arsenic is subsequently reduced to arsine gas by nascent hydrogen generated through the reaction of zinc with hydrochloric acid.

$$Zn + 2HCl \longrightarrow ZnCl_2 + 2[H]$$

$$H_3AsO_3 + 6[H] \longrightarrow AsH_3 + 3H_2O$$

Thus, the overall conversion may be represented as:

$$\underset{\text{Arsenic acid}}{H_3AsO_4} \longrightarrow \underset{\text{Arsenious acid}}{H_3AsO_3} \longrightarrow \underset{\text{Arsine acid}}{AsH_3}$$

Formation of the Stain

The arsine gas formed in the generating bottle is carried upward by hydrogen gas. It passes through lead acetate-treated cotton wool and finally comes into contact with mercuric chloride paper.

Initially, arsine produces a yellow arsenic–mercury chloride compound. With increasing quantities of arsenic, the colour becomes darker and may change from yellow to brown. The reaction may be represented in a simplified form as:

$$AsH_3 + HgCl_2 \longrightarrow ZnCl_2 + 2[H]$$

Further reaction with mercuric chloride may produce more highly substituted arsenic–mercury compounds:

$$AsH_2HgCl + 2HgCl_2 \longrightarrow As(HgCl)_3 + 2HCl$$

The depth and intensity of the stain depend on the amount of arsenic present in the substance.

Factors Affecting Stain Formation

The rate at which hydrogen and arsine are generated must be carefully controlled. It is influenced by:

- Quantity of zinc used
- Particle size and surface area of zinc
- Concentration of hydrochloric acid

Short Answer Type Questions

1. Define pharmaceutical impurities and explain their significance.
2. Give regulatory importance of Impurities.
3. Give the classification of Impurities.
4. What are the major sources of impurities in pharmaceutical substances?
5. Define a limit test. State its purpose.
6. Explain the principle of the limit test for chlorides.
7. State the role of dilute nitric acid in the limit test for chlorides.
8. Explain the principle of the limit test for sulphates.
9. Give the role of thioglycollic acid in the limit test for iron.
10. Write about the Gutzeit method for the limit test of arsenic.

Long Answer Type Questions

1. Define pharmaceutical impurities. Discuss their types, classification, contents of an impurity profile, and regulatory importance.
2. Explain in detail the various sources of impurities in pharmaceutical substances with suitable examples.
3. Describe the limit test for chlorides.
4. Explain the limit test for sulphates and modified method.
5. Describe the limit test for iron.
6. Explain the limit test for arsenic.
7. Describe the limit test for lead.
8. Explain the limit test for heavy metals.

Multiple Choice Questions

1. Which ICH guideline deals with residual solvents?
(a) Q3A (b) Q3B (c) Q2 (d) Q3C

2. Heavy metals are detected by forming:
(a) Metallic oxides (b) Metallic sulphides
(c) Metallic chlorides (d) Metallic nitrates

3. The purple colour in the iron limit test is due to:
(a) Ferric chloride
(b) Ferric hydroxide
(c) Iron citrate
(d) Ferrous thioglycollate complex

4. Pharmaceutical impurities are:
(a) Active pharmaceutical ingredients
(b) Excipients
(c) Preservatives
(d) Unwanted chemical substances present in pharmaceuticals

5. The limit test for sulphates uses:
(a) Barium chloride (b) Silver nitrate
(c) Potassium permanganate (d) Sodium hydroxide

6. Arsine gas reacts with:
(a) Litmus paper (b) Starch paper
(c) Mercuric chloride paper (d) Phenolphthalein

7. Dilute nitric acid is added in the chloride limit test to:
(a) Remove chloride ions
(b) Produce colour
(c) Increase pH
(d) Provide an acidic medium and prevent interference

8. Which of the following is a Class 1 residual solvent?
(a) Ethanol (b) Acetone
(c) Isopropyl alcohol (d) Benzene

9. White turbidity in the sulphate limit test is due to:
(a) Silver chloride (b) Barium sulphate
(c) Lead sulphide (d) Calcium sulphate

10. Which of the following is an organic impurity?
(a) Lead (b) Sodium chloride
(c) Starting material (d) Calcium carbonate

11. Dithizone forms a _____ coloured complex with lead.
(a) Violet (b) Blue
(c) Yellow (d) Orange

12. The arsenic limit test is commonly performed by the:
(a) Mohr method (b) Gutzeit method
(c) Volhard method (d) Fajans method

3 ACID–BASE CHEMISTRY & BUFFER SYSTEMS IN PHARMACY

Definition of Acids, Bases, Buffers, pH Scale And its Significance, Buffer Equation, Calculation of pH for Buffer Solution, Isotonicity and its Application in IV Fluids and Ophthalmic Solutions.

3.1 ACIDS AND BASES

Several theories have been proposed to explain the nature and behaviour of acids and bases. In general, an acid has a sour taste, turns blue litmus paper red and possesses a pH value lower than 7. A base has a bitter taste, turns red litmus paper blue and possesses a pH value higher than 7.

Mineral acids such as hydrochloric acid, nitric acid and sulphuric acid are almost completely ionized in dilute aqueous solutions and exhibit apparent dissociation constants greater than one.

3.1.1 Arrhenius Theory

According to the Arrhenius theory (1887), an acid is a substance that dissociates in water to produce hydrogen ions or protons (H^+), whereas a base is a substance that dissociates in water to produce hydroxyl ions (OH^-).

$$HCl \rightleftharpoons H^+ + Cl^-$$

(Acidic)

$$NaOH \rightleftharpoons Na^+ + OH^-$$

(Basic)

Acids and bases react with each other to form water and a salt. This reaction is known as neutralization.

$$HCl + NaOH \rightarrow H_2O + NaCl$$

An acid that produces a high concentration of hydrogen ions in an aqueous solution is called a strong acid. Similarly, a base that produces a high concentration of hydroxyl ions is called a strong base. Acids and bases that undergo only partial ionization in solution are known as weak acids and weak bases, respectively.

Limitations of the Arrhenius Theory

The Arrhenius theory has the following limitations:

- Ionization occurs only in an aqueous solution.
- The theory is not applicable to substances in the solid state.
- It does not adequately explain the basic nature of substances such as ammonia and sodium carbonate, which do not contain hydroxyl groups.
- It does not explain the acidic nature of compounds such as carbon dioxide and sulphur dioxide, which do not contain ionizable hydrogen.
- It is not applicable to acid–base reactions occurring in non-aqueous systems.
- According to this theory, neutralization between an acid and a base cannot occur in the absence of a solvent.

3.1.2 Bronsted–Lowry Theory

The Brønsted–Lowry theory was proposed independently by Johannes Nicolaus Bronsted and Thomas Martin Lowry in 1923. According to this theory, an acid is a substance capable of donating a proton, whereas a base is a substance capable of accepting a proton.

Thus, acid is a proton donor and base is a proton acceptor.

When an acid donates a proton, it is converted into its conjugate base. Similarly, when a base accepts a proton, it is converted into its conjugate acid. Therefore, acids and bases occur as conjugate acid–base pairs.

Formation of a Conjugate Base

The general ionization of an acid may be represented as:

$$\underset{\text{acid}}{HA} \rightleftharpoons \underset{\text{donated proton}}{H^+} + \underset{\text{conjugate base}}{Cl^-}$$

Examples include:

$$HCl \rightleftharpoons H^+ + Cl^-$$
$$H_2SO_4 \rightleftharpoons H^+ + HSO_4^-$$
$$CH_3COOH \rightleftharpoons H^+ + CH_3COO^-$$
$$NH_4^+ \rightleftharpoons H^+ + NH_3$$
$$H_2PO_4^- \rightleftharpoons H^+ + HPO_4^{2-}$$
$$H_3PO_4 \rightleftharpoons H^+ + H_2PO_4^-$$

In each of these reactions, the species formed after the loss of a proton is the conjugate base of the original acid.

Formation of a Conjugate Acid

A Brønsted–Lowry base may be an electrically neutral molecule, such as ammonia (NH3), or a negatively charged ion, such as OH^-, Cl^-, CH_3COO^- or HPO_4^{2-}.

When a base accepts a proton, it forms its conjugate acid:

$$\underset{\text{base}}{B} + \underset{\text{proton}}{H^+} \rightleftharpoons \underset{\text{conjugate acid}}{BH^+}$$

Examples include:

$$OH^- + H^+ \rightleftharpoons H_2O$$
$$H_2O + H^+ \rightleftharpoons H_3O^+$$
$$SO_4^{2-} + H^+ \rightleftharpoons HSO_4^-$$
$$NH_3 + H^+ \rightleftharpoons NH_4^+$$
$$H_2PO_4^- + H^+ \rightleftharpoons H_3PO_4$$

The product formed by the acceptance of a proton is known as the conjugate acid of the base.

10^{-10}	10	10^{-4}	4	Increasing basicity
10^{-13}	13	10^{-1}	1	
10^{-14}	14	10^{0}	0	

Increasing alkalinity

A change of one pH unit corresponds to a tenfold change in hydrogen ion concentration. Consequently, the pH scale is logarithmic rather than linear. Small numerical changes in pH therefore represent large differences in acidity or alkalinity.

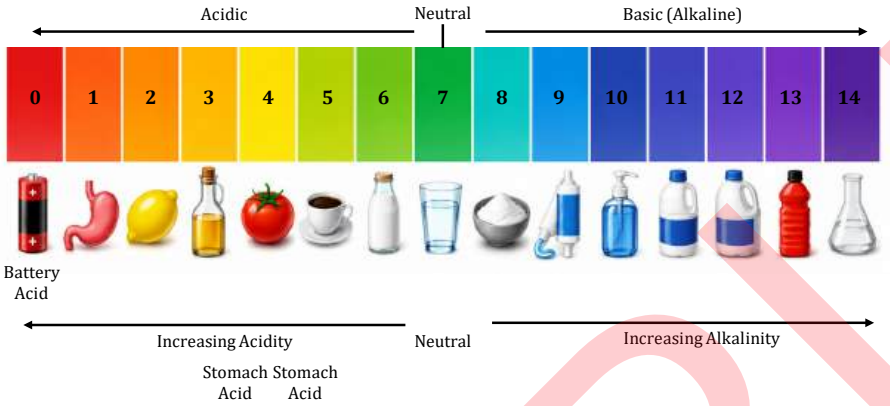


Figure 3.1: pH Scale

Table 3.3: Relationship among pH, pOH, and Hydrogen ion Concentration

pH	pOH	$[H^+]$ (mol/L)	$[H^+]$ (g-equiv/L)
7	7	1×10^{-7}	1×10^{-7}
8	6	1×10^{-8}	1×10^{-8}
9	5	1×10^{-9}	1×10^{-9}
10	4	1×10^{-10}	1×10^{-10}
11	3	1×10^{-11}	1×10^{-11}
12	2	1×10^{-12}	1×10^{-12}
13	1	1×10^{-13}	1×10^{-13}
14	0	1×10^{-14}	1×10^{-14}

3.3.2 Significance of pH Scale

The pH scale is of great physiological importance because it helps maintain the acid-base balance necessary for normal functioning of the human body. One of its most significant roles is in the transport of oxygen by blood. Since oxygen is only slightly soluble in blood plasma, its transport primarily depends on haemoglobin, the oxygen-carrying protein present in red blood cells. Haemoglobin binds oxygen in the lungs and releases it to body tissues for cellular respiration. This process functions efficiently only when the blood pH is maintained at approximately 7.4.

1. Oxygen Uptake in the Lungs

In the lungs, oxygen diffuses from the alveoli into the pulmonary capillaries and enters the red blood cells, where it combines with reduced haemoglobin (HHb) to form oxyhaemoglobin ($HHbO_2$). During this reaction, hydrogen ions are released according to the following equilibrium:

$$O_2 + Hb \rightarrow HHbO_2 \rightarrow H^+ + HbO_2$$

The high oxygen concentration in the lungs shifts the equilibrium towards the formation of oxyhaemoglobin, in accordance with Le Chatelier's principle. The released hydrogen ions are immediately buffered by bicarbonate ions, thereby maintaining the blood pH within the normal physiological range.

2. Bicarbonate Buffer System

The bicarbonate buffer system is the major mechanism responsible for maintaining blood pH and is represented by the following equilibrium:

$$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$$

Bicarbonate ions combine with hydrogen ions to form carbonic acid, preventing excessive changes in blood pH. This buffering action also favours the continued formation of oxyhaemoglobin in the lungs.

3. Oxygen Release in Tissues

In actively metabolizing tissues, cells continuously produce carbon dioxide and hydrogen ions. The increased hydrogen ion concentration shifts the oxyhaemoglobin equilibrium in the reverse direction, causing oxyhaemoglobin to release oxygen. The released oxygen then diffuses into the surrounding cells, where it is utilized for energy production. Thus, oxygen delivery to tissues is a pH-dependent process, with a lower pH promoting the release of oxygen from haemoglobin.

4. Chloride Shift

As hydrogen ions bind to haemoglobin, bicarbonate ions accumulate within red blood cells and diffuse into the plasma. To maintain electrical neutrality, chloride ions move from the plasma into the red blood cells. This exchange, known as the chloride shift (or Hamburger phenomenon), plays an essential role in carbon dioxide transport and in maintaining the acid-base balance of blood.

5. pH Measurement in Nonaqueous Solvents

A pH value measured in a nonaqueous solvent with an electrode standardized in aqueous buffer has limited thermodynamic significance. The major uncertainty arises from the unknown

(b) Number of moles of strong acid or base required to change the pH of one litre of buffer by one unit
(c) Concentration of hydrogen ions in a buffer
(d) Total volume of a buffer solution

10. Which of the following is NOT a desirable property of a pharmaceutical buffer?
(a) Should maintain the required pH
(b) Should not react with formulation ingredients
(c) Should not alter drug solubility
(d) Should support microbial growth

11. Which standard buffer is commonly used in the pH range of approximately 8.0–10.0?
(a) Hydrochloric acid buffer
(b) Acid phthalate buffer
(c) Phosphate buffer
(d) Alkaline borate buffer

12. Which physiological buffer system primarily maintains the pH of blood?
(a) Acetate buffer system
(b) Borate buffer system
(c) Phosphate buffer system
(d) Bicarbonate buffer system

13. Red blood cells placed in a hypertonic solution undergo:
(a) Haemolysis (b) Swelling
(c) Agglutination (d) Crenation

14. Which of the following is commonly used as an isotonicity-adjusting agent in ophthalmic preparations?
(a) Potassium permanganate (b) Boric acid
(c) Calcium carbonate (d) Magnesium sulphate

15. Which of the following is an example of an isotonic intravenous fluid?
(a) Distilled water
(b) 10% Sodium chloride solution
(c) 15% Dextrose solution
(d) Ringer's lactate solution

Answer Keys

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

4 MAJOR EXTRA & INTRACELLULAR ELECTROLYTES

Functions of major physiological ions; electrolytes used in replacement therapy: Sodium chloride, Potassium chloride, Calcium chloride, and Oral Rehydration Salt (ORS); physiological acid–base balance.

4.1 ELECTROLYTES

Acids, bases and salts dissociate into positively and negatively charged ions when dissolved in water. Their aqueous solutions are capable of conducting electricity. When an electric current is passed through such a solution, the dissolved substance may undergo chemical decomposition. This process is known as electrolysis, and the substances that produce ions and conduct electricity in solution are called electrolytes.

Electrolytes play an essential role in maintaining the normal internal environment of the body. The concentrations of inorganic and organic substances in body fluids are carefully regulated to provide stable conditions for the proper functioning of cells and tissues. Various physiological mechanisms regulate ionic balance, osmotic pressure, acid–base balance, fluid volume, and blood pH to maintain normal body homeostasis.

Disturbances in the composition or volume of body fluids may result in fluid and electrolyte imbalance. Such conditions may be corrected by administering suitable preparations containing electrolytes, acids, bases, carbohydrates, amino acids, proteins or blood products.

4.1.1 Distribution of Body Fluids

The human body contains 60-70% water distributed across three main compartments: intracellular fluid (inside cells), interstitial fluid (between cells), and vascular fluid (blood plasma). These compartments are separated by membranes permeable to water and many solutes but nearly impermeable to proteins and selectively permeable to specific ions like Na^+, K^+, and Mg^{2+}. Body water is distributed into intracellular and extracellular fluid compartments.

a. Intracellular Fluid

Intracellular fluid is the fluid present within the cells. It constitutes approximately 45–50% of the total body weight.

b. Extracellular Fluid

Extracellular fluid is the body fluid present outside the cells and includes interstitial fluid, plasma (vascular fluid), cerebrospinal fluid, lymph, pleural fluid, peritoneal fluid, and synovial fluid.

Interstitial fluid constitutes approximately 12–15% of body weight, whereas plasma or vascular fluid constitutes about 4–5% of body weight.

Approximately four litres of interstitial fluid are present within dense connective tissues, such as bones and cartilage. This fluid does not participate rapidly in exchange with the remaining body fluids. The remaining interstitial fluid, approximately 6.5 litres, together with about 3.5 litres of plasma, forms the active extracellular fluid compartment.

4.1.2 Composition of Body-Fluid Compartments

The various fluid compartments are separated by biological membranes. These membranes are generally permeable to water and many small organic and inorganic solutes. However, they are almost impermeable to macromolecules, such as proteins, and selectively permeable to ions such as sodium, potassium and magnesium. Because of selective membrane permeability, each body-fluid compartment possesses a characteristic electrolyte composition.

Table 4.1: Composition of Electrolytes in Body Fluids (expressed as mEq/L)

Extracellular Fluid (Plasma)			
Cations	**mEq/L**	**Anions**	**mEq/L**
Na^+	142	Cl^-	103
K^+	5	HCO_3^-	27
Ca^{2+}	5	HPO_4^{2-}	2
Mg^{2+}	3	SO_4^{2-}	1
		Proteins	16
		Organic acids	6
Intracellular Fluid (Muscle)			
Cations	**mEq/L**	**Anions**	**mEq/L**
K^+	150	HPO_4^{2-}	140
Na^+	10	HCO_3^-	10
Mg^{2+}	40	Cl^-	2
Ca^{2+}	2	SO_4^{2-}	5
		Proteins	40
		Organic acids	5

Despite differences in ionic composition, each fluid compartment remains electrically neutral. Therefore, the total concentration of positively charged ions, or cations, is equal to the total concentration of negatively charged ions, or anions.

faecal electrolyte losses.

Potassium

Significant potassium loss may occur in children suffering from diarrhoeal illness. Most oral rehydration solutions contain approximately 20 to 25 mmol/litre of potassium to replace this loss and prevent hypokalaemia.

Base

A suitable base is included in oral rehydration preparations to prevent or correct metabolic acidosis caused by bicarbonate loss in the stools, reduced renal acid excretion, and poor tissue perfusion during severe dehydration. Citrate, bicarbonate or lactate salts may be used as alkalinising agents in oral rehydration preparations.

Carbohydrate

Glucose is the carbohydrate most commonly used in oral rehydration preparations. It promotes the simultaneous absorption of sodium and water from the intestine.

Sucrose is less expensive and more readily available than glucose. After digestion into glucose and fructose, it can also support the absorption of sodium and water.

The effective concentration of glucose in oral rehydration preparations is generally within the range of 56 to 140 mmol/litre, with a commonly preferred range of approximately 80 to 120 mmol/litre, or about 2.0% to 2.5%.

Excessively high concentrations of glucose should be avoided because they increase the osmolarity of the solution. A hypertonic solution may retain water within the intestinal lumen and cause osmotic diarrhoea due to the presence of unabsorbed carbohydrate. Increasing the glucose concentration beyond the optimum level does not further enhance sodium absorption.

4.3.4.2 Oral Rehydration Salts Formulations

Oral Rehydration Salts (ORS) are specially formulated mixtures of glucose and electrolytes used for the prevention and treatment of dehydration caused mainly by diarrhoea and vomiting. Different ORS formulations have been introduced over time to improve their stability, effectiveness, and safety.

Oral Rehydration Therapy (ORT) was developed in the 1940s as a simple yet life-saving treatment for dehydration. Oral Rehydration Salts (ORS) preparations became widely available in the market from 1970 onwards, revolutionizing the approach to managing dehydration. The formulation of ORS is designed to enhance the uptake of sodium and water by the intestine, effectively rehydrating the body at a cellular level.

1. Older WHO Bicarbonate Formula

The older ORS formula recommended by the World Health Organization contained sodium bicarbonate as the alkalizing agent. The composition required for the preparation of one litre of ORS solution is given in Table 4.2.

Table 4.2: Composition of the Older WHO Bicarbonate ORS Formula

Ingredient	Quantity
Glucose anhydrous	20 g
Sodium chloride	3.5 g
Potassium chloride	1.5 g
Sodium bicarbonate	2.5 g
Purified water	Sufficient to make 1 litre

The total weight of the ingredients in this formulation was 27.5 g. All the ingredients were dissolved in a sufficient quantity of purified water, and the final volume was adjusted to one litre.

2. UNICEF Citrate Formula

In the UNICEF citrate-based ORS formulation, sodium bicarbonate was replaced by trisodium citrate dihydrate. The composition of the formulation is presented in Table 4.3.

Table 4.3: Composition of the UNICEF Citrate ORS Formula

Ingredient	Quantity
Glucose anhydrous	20 g
Sodium chloride	3.5 g
Potassium chloride	1.5 g
Trisodium citrate dihydrate	2.9 g
Purified water	Sufficient to make 1 litre

The total weight of the ingredients in this formulation was 27.9 g. Trisodium citrate dihydrate was introduced in place of sodium bicarbonate because the bicarbonate-containing formulation was comparatively less stable during storage. It could also undergo discoloration, particularly under hot and humid conditions. Therefore, the citrate formulation provided improved stability and a longer storage life.

3. Current WHO–UNICEF Reduced-Osmolarity Formula

The World Health Organization and UNICEF currently recommend a common reduced-osmolarity ORS formulation. It contains lower quantities of glucose and sodium chloride than the older formulation. The composition of the current formula is shown in Table 3.

Table 4.4: Composition of the Current WHO–UNICEF Reduced-Osmolarity ORS Formula

Ingredient	Quantity
Glucose anhydrous	13.5 g
Sodium chloride	2.6 g
Potassium chloride	1.5 g
Trisodium citrate dihydrate	2.9 g

The total osmolarity of the prepared solution is 245 mOsm/L. The contents of one packet are dissolved in a sufficient quantity of clean or purified water to make exactly one litre of solution. Thus, the current official ORS formula recommended jointly by WHO and UNICEF is the reduced-osmolarity formulation. It provides effective replacement of water and electrolytes and reduces the undesirable effects associated with the higher osmolarity of older ORS formulations.

5 ACID–BASE TITRATIONS

- Theories of Acid–Base indicators.
- Classification of Acid–Base Titrations.
- Preparation and Standardization of Titrants, viz. Hydrochloric Acid and Sodium Hydroxide.
- Theory involved in Titrations of Strong, Weak and Very Weak Acids and Bases.
- Neutralization curves.
- Assay of ammonium hydroxide.

5.1 INTRODUCTION

Acid–base titrations are volumetric analytical methods based on the neutralization reaction between an acid and a base. These titrations are commonly used to determine the unknown concentration of acidic or basic substances. Strong acids and strong bases undergo complete ionization in aqueous solution. Their neutralization reaction can be represented as:

$$H_3O^+ + OH^- \rightarrow 2H_2O$$

During the titration of a strong acid with a strong base, the pH of the solution is measured after each addition of the base. The relationship between the pH and the volume of titrant added is represented by a titration curve.

At the beginning of the titration, the solution is highly acidic and has a very low pH, which may be approximately zero. As the strong base is gradually added, the pH initially increases only slightly. Near the equivalence point, a small addition of the base produces a sharp and rapid increase in pH.

At the equivalence point, chemically equivalent amounts of the acid and base have reacted completely. This point corresponds to the steepest portion of the titration curve and possesses the maximum slope. It is therefore known as the inflection point of the curve. Beyond the equivalence point, the pH increases slowly and eventually becomes nearly constant in the alkaline region.

5.1.1 Acid–Base Concepts

Acid–base titrations, also known as neutralization titrations, are based on the chemical reaction occurring between an acid and a base. These titrations are widely used in quantitative analysis to determine the concentration or strength of acidic and basic substances.

Several theories have been proposed to explain the acidic and basic behaviour of substances. The most important among them are the Arrhenius theory, Brønsted–Lowry theory, and Lewis theory. The Arrhenius theory is mainly applicable to aqueous solutions, whereas the Brønsted–Lowry and Lewis theories provide broader explanations and may also be applied to non-aqueous systems.

1. Arrhenius Theory

The Arrhenius theory of acids and bases was proposed by Svante Arrhenius during the development of his theory of electrolytic dissociation. According to this theory, acids and bases produce characteristic ions when dissolved in water.

An Arrhenius acid is a substance that ionizes partially or completely in water to produce hydrogen ions. Since free hydrogen ions do not normally exist independently in aqueous solution, they combine with water molecules to form hydronium ions (H_3O^+). The ionization of a general acid may be represented as:

$$HA + H_2O \rightleftharpoons H_3O^+ + A^-$$

In this reaction, HA represents the acid, while A^- is the ion formed after the loss of a proton.

An Arrhenius base is a substance that produces hydroxide ions (OH^-) when dissolved in water. Weak bases may react partially with water to produce hydroxide ions:

$$B + H_2O \rightleftharpoons BH^+ + OH^-$$

Strong bases, such as sodium hydroxide, undergo almost complete dissociation in water. The dissociation of a metal hydroxide may be expressed as:

$$M(OH)n \rightarrow Mn^+ + nOH^-$$

For example:

$$NaOH \rightarrow Na^+ + OH^-$$

The major limitation of the Arrhenius theory is that it explains acid–base behaviour only in aqueous solutions. It cannot adequately describe acid–base reactions occurring in non-aqueous solvents or reactions involving substances that do not directly produce hydrogen or hydroxide ions.

2. Brønsted–Lowry Theory

The Brønsted–Lowry theory was independently proposed by Johannes Brønsted and Thomas Lowry in 1923. This theory explains acid–base reactions in terms of the transfer of protons. According to the Brønsted–Lowry concept, an acid is a proton donor, whereas a base is a proton acceptor. A general acid dissociation reaction may be represented as:

$$Acid \rightleftharpoons H^+ + Base$$

both equilibria, the dissociation of HInd is suppressed by the common-ion effect. As a result, the equilibrium of the indicator shifts towards the left. The indicator therefore remains predominantly in its undissociated form, HInd, and the solution exhibits the colour of the undissociated indicator.

Behaviour in an Alkaline Medium

When the acidic indicator is added to an alkaline solution containing a base, BOH, the following equilibria are involved:

$$HInd \rightleftharpoons H^+ + Ind^-$$
$$BOH \rightleftharpoons B^+ + OH^-$$

The hydroxide ions supplied by the base combine with hydrogen ions released by the indicator to form water:

$$H^+ + OH^- \rightarrow H_2O$$

The removal of hydrogen ions shifts the indicator equilibrium towards the right. Consequently, the dissociation of HInd increases, and the concentration of Ind^- becomes greater than that of HInd. The solution therefore exhibits the colour of the ionized form of the indicator.

Indicator as a Weak Base

A basic indicator may be represented as IndOH. It ionizes according to the following equilibrium:

$$IndOH \rightleftharpoons Ind^+ + OH^-$$

In an alkaline medium, the presence of excess hydroxide ions suppresses the ionization of the indicator. Therefore, the indicator remains mainly in its unionized form.

In an acidic medium, hydrogen ions combine with hydroxide ions to form water. The removal of hydroxide ions increases the ionization of the indicator, and the colour of the ionized form becomes visible.

Examples

Phenolphthalein is a weak acidic indicator that is colourless in acidic solution (unionized form) and pink in alkaline solution (ionized form).

Methyl orange behaves as a weak basic indicator. Its ionized and unionized forms possess different colours. It appears red in an acidic medium and yellow in an alkaline medium. An intermediate orange colour may be observed within its transition range.

5.2.2 Quinonoid Theory

According to the quinonoid theory, the colour change of an acid–base indicator is due to a reversible structural change between its benzenoid and quinonoid forms. These two forms possess different colours. The relative proportion of the benzenoid and quinonoid forms depends on the pH of the solution. Thus, an indicator may exist predominantly in one structural form in an acidic medium and in another structural form in an alkaline medium. The conversion of one form into another produces the characteristic colour change of the indicator.

Example

Phenolphthalein exists predominantly in the benzenoid or lactone form in an acidic medium. This form is colourless. When phenolphthalein is added to an alkaline solution, the lactone ring opens and the molecule is converted into a resonating quinonoid ion. This quinonoid form is pink in colour. The structural transformation may be represented as:

Benzenoid form (Colourless) ⇌ Quinonoid form (Pink)

In an acidic medium, phenolphthalein exists in the benzenoid (lactone) form and is colourless, whereas in an alkaline medium, it changes to the quinonoid form and becomes pink. When phenolphthalein is treated with a large excess of concentrated alkali, it may again become colourless due to the formation of another colourless ionic structure. The complete transformation can be represented as:

A (Colourless) ⇌ B (Pink) ⇌ C (Colourless)

Where:

- Structure A: Colourless benzenoid or lactone form
- Structure B: Pink quinonoid form
- Structure C: Colourless form produced in strongly alkaline conditions

Therefore, according to the quinonoid theory, the colour change of phenolphthalein is due to the reversible conversion between its benzenoid and quinonoid structural forms.

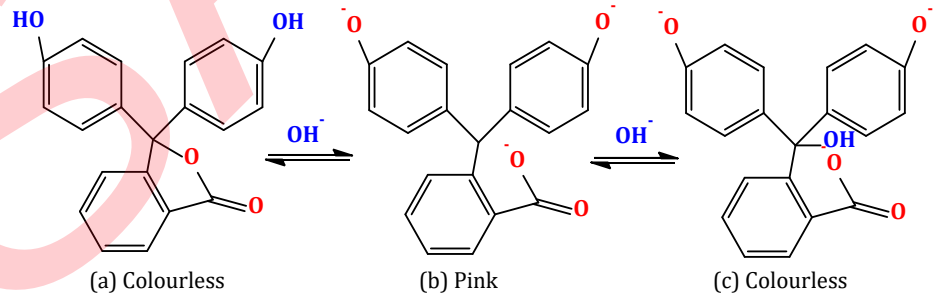


Figure 5.1: (a) Benzenoid or Lactone Form; (b) Quinonoid Form; (c) Carbinol (pseudobase) form

5.3 CLASSIFICATION OF ACID–BASE TITRATIONS

Acid–base titrations are a type of neutralization titration in which an acid reacts with a base to form salt and water. During

tion of the solution changes continuously. This change is reflected in the shape of the neutralization curve. Near the equivalence point, a comparatively sharp change in pH is usually observed. The nature and extent of this pH change depend upon the strengths of the acid and base involved in the titration.

Importance of Neutralization Curves

Neutralization curves are useful in acid–base titrations for the following reasons:

1. The curve helps in understanding the progress of the neutralization reaction by showing the change in hydrogen-ion concentration and pH during the titration.
2. It provides a clear graphical representation of the various stages of an acid–base titration, from the initial addition of titrant to the completion of the reaction.
3. The sharp change in pH near the equivalence point helps in locating the endpoint of the titration.
4. The steepness of the curve near the equivalence point indicates the sensitivity of the titration. A sharp pH change produces a more clearly detectable endpoint and reduces the possibility of titration error.
5. The appropriate indicator is selected by comparing its pH transition range with the steep portion of the neutralization curve. An indicator should change colour within or very close to the pH range of the equivalence point.

The pH value at the end point of an acid–base titration depends on the relative strengths of the acid and base involved. Based on the nature and strength of the reacting substances, acid–base titrations are classified into the following types:

1. Neutralization of a strong acid with a strong base.
2. Neutralization of a weak acid with a strong base.
3. Neutralization of a weak base with a strong acid.
4. Neutralization of a weak acid with a weak base

1. Neutralization of a Strong Acid with a Strong Base

In this type of acid–base titration, a strong acid such as hydrochloric acid is titrated against a strong base such as sodium hydroxide. Since both hydrochloric acid and sodium hydroxide are strong electrolytes, they dissociate completely into ions in aqueous solution. The neutralization reaction is represented as:

$$HCl + NaOH \rightarrow NaCl + H_2O$$

During the titration of 25 mL of 0.1 M hydrochloric acid with 0.1 M sodium hydroxide, the pH initially increases slowly because the solution contains an excess of hydrogen ions. As sodium hydroxide is gradually added, these hydrogen ions are neutralized.

Near the equivalence point, the amount of sodium hydroxide added becomes nearly equal to the amount of hydrochloric acid present. At this stage, the pH changes very rapidly, even with the addition of a very small quantity of sodium hydroxide.

Equivalence Point

The equivalence point is the stage in a titration at which chemically equivalent or stoichiometric amounts of acid and base have reacted.

In the titration of hydrochloric acid with sodium hydroxide, the equivalence point occurs at pH 7.0. This is because the product formed, sodium chloride, is a salt of a strong acid and a strong base and therefore does not undergo hydrolysis.

At the equivalence point:

$$H^+ + OH^- \rightarrow H_2O$$

The pH changes sharply from approximately 3.0 to 11.0 near the equivalence point.

Selection of Indicator

An appropriate indicator is used to detect the end point of the titration. The indicator should change colour within the sharp pH-change range of the titration curve. Phenolphthalein may be used as an indicator because it changes from colourless to pink within the pH range of 8.2–10.0.

Although the colour change of phenolphthalein occurs on the alkaline side, only a fraction of a drop of sodium hydroxide is required to produce a large change in pH near the equivalence point.

Bromocresol green, which changes colour within the pH range of 3.8–5.4, may also be used. Since the pH change near the equivalence point is very large, several other acid–base indicators are also suitable for this titration.

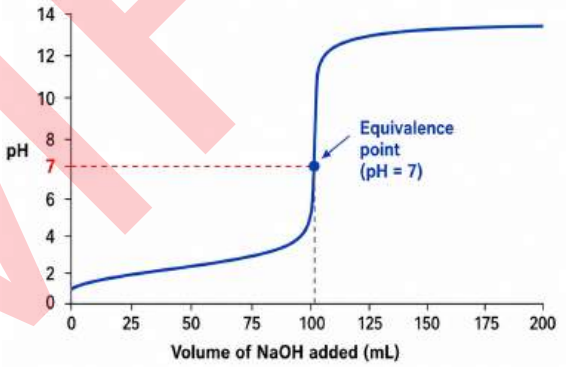


Figure 5.6: Neutralization Curve of 25 Ml Of 0.1 M Hydrochloric Acid With 0.1 M Sodium Hydroxide Shows An S-Shaped Pattern.

Initially, the curve rises gradually. Near the equivalence point, it becomes almost vertical because of the sudden increase in pH. After the equivalence point, the pH again increases slowly due to the presence of excess sodium hydroxide.

Table 5.6: Variation of pH During Titration

Volume of NaOH Added (mL)	pH
0	1.00
5	1.18
10	1.37
15	1.60
20	1.95
21	2.06
22	2.20
23	2.38
24	2.69

Calculations

Percentage of Ammonium Hydroxide

$$\% NH_4OH = \frac{V \times M \times 35.05 \times 100}{W \times 1000}$$

When 1 M hydrochloric acid is used, the expression becomes:

$$\% NH_4OH = \frac{V \times 3.505}{W}$$

Percentage of Ammonia

$$\% NH_3 = \frac{V \times M \times 17.03 \times 100}{W \times 1000}$$

When 1 M hydrochloric acid is used, the expression becomes:

$$\% NH_3 = \frac{V \times 1.703}{W}$$

Example

Suppose 2.0 g of ammonium hydroxide solution requires 12.0 mL of 1 M hydrochloric acid for complete neutralization. When the result is expressed as ammonia, the calculation is as follows:

$$\% NH_3 = \frac{12 \times 1.703}{2} = 10.218\%$$

Therefore, the solution contains approximately 10.22% w/w of NH_3.

Short Answer Questions

1. Define acid–base titration and state its principle.
2. Explain the Arrhenius theory of acids and bases with one example.
3. What is the Brønsted–Lowry concept of acids and bases? Define conjugate acid–base pair.
4. Define Lewis acids and Lewis bases with suitable examples.
5. What is the common-ion effect? Explain with an example.
6. Define pH and pOH. Write the relationship between pH and pOH.
7. State Ostwald's theory of acid–base indicators.
8. Differentiate between the benzenoid and quinonoid forms of phenolphthalein.
9. Why is phenolphthalein suitable for the titration of a weak acid with a strong base?
10. Write the principle of the assay of ammonium hydroxide.

Long Answer Questions

1. Describe the Arrhenius, Brønsted–Lowry, and Lewis theories of acids and bases. Compare their advantages and limitations.
2. Explain the role of solvents in acid–base titrations. Discuss self-dissociation, dielectric constant, and acid–base character of solvents.
3. Explain Ostwald's theory of acid–base indicators. Discuss the behaviour of acidic and basic indicators in acidic and alkaline media with suitable examples.
4. Describe the quinonoid theory of acid–base indicators. Explain the colour change of phenolphthalein according to this theory with suitable diagrams.
5. Classify acid–base titrations based on the strength of acids and bases. Discuss the characteristics and suitable indicators for each type.
6. Describe the preparation and standardization of hydrochloric acid.
7. Explain the preparation and standardization of sodium hydroxide.
8. Explain the theory involved in the neutralization of a strong acid with a strong base. Draw and explain the neutralization curve and justify the choice of indicator.
9. Discuss the neutralization curves.
10. Describe the assay of ammonium hydroxide.

Multiple Choice Questions

1. Acid–base titrations are primarily based on which type of reaction?

(a) Oxidation–reduction (b) Neutralization
(c) Precipitation (d) Complex formation

2. According to the Arrhenius theory, an acid is a substance that:

(a) Accepts an electron pair
(b) Produces hydroxide ions in water

6 NON – AQUEOUS TITRATION

- Types Of Solvents Used.
- Acidimetric and Alkalimetric Titration using Nonaqueous Solvents.
- Preparation and Standardization of Acidic and Basic Titrants.
- Estimation of Weakly Acidic and Basic Substances using Nonaqueous Titrants.
- Estimation of Sodium Benzoate.

6.1 Introduction

Over the past several decades, a large number of complex organic medicinal compounds have been introduced into therapeutic practice. The quantitative analysis and quality control of these compounds, both as pure substances and in pharmaceutical dosage forms, often present considerable difficulties. These difficulties mainly arise because many medicinal compounds possess the following characteristics:

1. Poor solubility in water
2. Weak acidic or basic reactivity in aqueous medium

Because of these limitations, conventional aqueous titration methods are not always suitable for their accurate estimation. Earlier, several indirect and comparatively complicated procedures were employed to analyse such substances.

Earlier Methods of Analysis

1. Analysis of Amine Salts

Amine salts were first converted into their corresponding free bases. The liberated free base was then extracted using a suitable organic solvent. An excess quantity of a standard acid was added to the extract, after which the organic solvent was evaporated. The amount of unreacted acid remaining in the solution was finally determined by back-titration with a standard alkali. Although this method could be used for the estimation of amine salts, it involved several steps and was therefore time-consuming.

2. Analysis of Sodium Salts of Organic Acids

Sodium salts of organic acids were initially acidified to liberate the corresponding water-insoluble organic acid. The free organic acid was then extracted with a suitable organic solvent. After removal of the solvent, the residue was dried and weighed.

This gravimetric procedure was lengthy and could introduce errors during extraction, solvent evaporation and drying.

3. Analysis of Nitrogen-Containing Compounds

Nitrogen-containing medicinal compounds were commonly estimated by the micro-Kjeldahl method. In this method, the nitrogen present in the compound was converted into an ammonium salt and subsequently determined quantitatively.

However, the method was indirect, required several operational steps and was not equally suitable for all nitrogen-containing pharmaceutical substances.

6.1.1 Need for Non-Aqueous Titrations

The earlier analytical procedures were often complicated, lengthy and susceptible to errors. They involved operations such as extraction, evaporation, drying, weighing and back-titration. These procedures could adversely affect the accuracy and precision of the analysis.

To overcome these limitations, non-aqueous titration methods were introduced. In non-aqueous titration, a solvent other than water is used as the reaction medium. The selection of a suitable non-aqueous solvent increases the solubility and enhances the acidic or basic behaviour of substances that react weakly in water.

Thus, non-aqueous titration provides a simple and reliable method for the quantitative determination of weak organic acids, weak organic bases and many pharmaceutical compounds that cannot be satisfactorily analysed in aqueous media.

6.1.2 Advantages of Non-Aqueous Titrations

Non-aqueous titrations offer the following important advantages:

1. Improvement in Solubility

Many organic medicinal compounds are poorly soluble or practically insoluble in water. Such compounds may dissolve readily in suitable non-aqueous solvents. The use of an appropriate solvent therefore eliminates the problem of poor aqueous solubility and provides a homogeneous medium for titration.

2. Enhancement of Weak Reactivity

Weak acids and weak bases may not ionise sufficiently in water and therefore may not react quantitatively with ordinary aqueous titrants. A properly selected non-aqueous solvent enhances their acidic or basic character and allows the neutralisation reaction to proceed more completely.

3. Selective Titration

Non-aqueous titration permits the selective determination of acidic or basic components of physiologically active salts. Selectivity can be achieved by choosing an appropriate solvent and titrant that react specifically with the component to be estimated.

4. Simple and Rapid Procedure

Non-aqueous titrations maintain the speed, simplicity, precision and accuracy associated with classical volumetric methods. They eliminate several complicated steps such as extraction, evaporation, drying and weighing that were required in older analytical procedures.

5. Estimation of Very Weak Bases

Weak bases having dissociation constant values, (K_b), below ap-

1:1 molar ratio.

Titrant, Solvent and Indicators

Common titrant: 0.1 M perchloric acid in glacial acetic acid

Common solvents: Glacial acetic acid, acetic anhydride, dioxane, chloroform, or a glacial acetic acid-acetic anhydride mixture

Suitable indicators: Crystal violet, malachite green, quinaldine red and naphtholbenzein

Acetic anhydride is frequently added to remove traces of water from the titration medium. Water decreases the effective strength of perchloric acid in the non-aqueous solvent and may produce a less distinct end point. Potentiometric end-point detection may be used when the solution is coloured or when the visual colour change is not sufficiently sharp.

General Procedure

An accurately weighed quantity of the weakly basic substance is dissolved in glacial acetic acid. Acetic anhydride may be added when necessary to remove traces of moisture. A suitable indicator is then added, and the solution is titrated with standard perchloric acid until the prescribed colour change is observed. A blank titration is carried out under identical conditions, and the blank correction is applied during calculation.

Examples of Weakly Basic Substances

Example 1: Estimation of Ephedrine

Ephedrine is a weak organic base containing an amino group. In glacial acetic acid, the amino group readily accepts a proton from perchloric acid and forms ephedrine perchlorate.

$$C_{10}H_{15}NO + HClO_4 \rightarrow C_{10}H_{16}NO^+ClO_4^-$$

Titrant: 0.1 M perchloric acid

Solvent: Glacial acetic acid

Indicator: Crystal violet or naphtholbenzein

The amount of perchloric acid consumed is chemically equivalent to the amount of ephedrine present in the sample.

Example 2: Estimation of Atropine

Atropine is a weakly basic alkaloid containing a tertiary nitrogen atom. The tertiary nitrogen accepts a proton in the acidic non-aqueous medium and forms atropine perchlorate.

$$C_{17}H_{23}NO_3 + HClO_4 \rightarrow C_{17}H_{24}NO_3^+ClO_4^-$$

Titrant: 0.1 M perchloric acid

Solvent: Glacial acetic acid

Indicator: Crystal violet

Atropine behaves as a monobasic substance and generally reacts with perchloric acid in a 1:1 molar ratio.

Example 3: Estimation of Lidocaine

Lidocaine is a weakly basic local anaesthetic containing a tertiary amino group. It is dissolved in glacial acetic acid and titrated with perchloric acid to form lidocaine perchlorate.

$$C_{14}H_{22}N_2O + HClO_4 \rightarrow C_{14}H_{23}N_2O^+ClO_4^-$$

Titrant: 0.1 M perchloric acid

Solvent: Glacial acetic acid

Indicator: Crystal violet or potentiometric end-point detection

The tertiary amino group of lidocaine is protonated during the titration.

6.5.2 Estimation of Weakly Acidic Substances

Weakly acidic pharmaceutical substances do not release protons completely in water and therefore may not react quantitatively with aqueous alkalis. Their acidic character is increased by dissolving them in a basic or proton-accepting solvent.

Dimethylformamide, pyridine and dimethyl sulfoxide are commonly employed for this purpose. These solvents accept protons from weak acids and promote their ionization. The ionized acidic substance can then be titrated quantitatively with a strong non-aqueous base.

Principle

A weakly acidic substance is dissolved in a suitable basic solvent and titrated with a standard solution of a strong base such as sodium methoxide, lithium methoxide, potassium methoxide or tetrabutylammonium hydroxide.

$$HA + B^- \rightarrow A^- + HB$$

When sodium methoxide is used as the titrant, the reaction may be represented as follows:

$$HA + CH_3ONa \rightarrow NaA + CH_3OH$$

In this reaction, HA represents the weakly acidic drug, CH_3ONa represents sodium methoxide, and NaA represents the sodium salt formed after removal of the acidic proton.

Titrants, Solvents and Indicators

Common titrants: Sodium methoxide, lithium methoxide, potas-

7 PRECIPITATION TITRATIONS & GRAVIMETRY

Principle and steps involved in gravimetric analysis, Mohr's method, Volhard's method, modified Volhard's method, Fajans method, and estimation of barium sulphate by gravimetry

7.1 INTRODUCTION

Gravimetric Analysis

Gravimetric analysis is a quantitative analytical method based on the accurate measurement of the mass of a pure compound that is chemically related to the analyte. In this method, the substance to be determined is separated from the sample, usually in the form of an insoluble precipitate.

The precipitate is filtered, washed, dried or ignited, and accurately weighed. The quantity of the analyte present in the sample is then calculated from the mass and chemical composition of the precipitate.

Methods of gravimetric analysis

1. **Precipitation gravimetry:** The analyte is separated from a solution of the sample as a precipitate and is converted to a compound of known composition that can be weighed.
2. **Volatilization gravimetry:** The analyte is separated from other constituents of a sample by converting it to a gas of known chemical composition that can be weighed. Sulfides and sulfites can also be determined by volatilization. Hydrogen sulfide or sulfur dioxide evolved from the sample after treatment with acid is collected in a suitable absorbent. the classical method for the determination of carbon and hydrogen in organic compounds is a gravimetric volatilization procedure in which the combustion products (H_2O and CO_2) are collected selectively on weighed absorbents.
3. **Electrogravimetry:** The analyte is separated by deposition on an electrode by an electrical current.

Precipitation Titrations

A precipitation reaction is a chemical reaction in which aqueous solutions of two ionic compounds react to form an insoluble solid called a precipitate. The cation is supplied by one solution and the anion by another. Precipitation titrations are based upon reactions that yield ionic compounds of limited solubility (insoluble). The most important precipitating reagent is silver nitrate. Titrimetric methods based upon silver nitrate are sometimes termed Argentometric methods. In a precipitation titration, the stoichiometric reaction produces, in solution, a slightly soluble salt that precipitates.

To determine the concentration of chloride ion in a particular solution, one could titrate this solution with a solution of a silver salt, say silver nitrate, whose concentration is known.

$$KCl + AgNO_3 \rightarrow AgCl\downarrow + KNO_3$$

$$Ag^+ + Cl^- \rightarrow AgCl\downarrow$$

Removal of ions from the solution as an insoluble precipitate drives the reaction towards completion.

$$AgCl \leftrightarrows Ag^+ + Cl$$

Solubility product:

$$Ksp = [Ag^+].[Cl\ ] / [AgCl]$$

A precipitate is formed in solution of spairingly soluble salts when the concentration of its ions in solution increases to an extent that the product of multiplication of their conc. exceeds the solubility product.

$$[A^+].[B^-] > Ksp$$

Argentometric methods can be divided into mainly in two types :

- Direct determinations in which a standard solution of silver nitrate is added to the sample solution until the endpoint is reached.
- Indirect determinations , in which an excess of silvernitrate is added to the sample solution and the excess silver nitrate is back titrated with another standard solution, usually ammonium or potassium thiocyanate

Direct titrations are preferred, but the method cannot be applied in all cases. If the solubility of the precipitate formed during the titration is too great, the endpoint cannot be detected. In this case, it is better to add excess reagent, thereby reducing the solubility of the precipitate, and determine the excess by another method (Indirect Method).

Requirements for Titrimetric Analysis

- The precipitate should be practically insoluble.
- The reaction should be rapid, complete and quantitative.
- Adsorption and co-precipitation should not affect the result.
- The equivalence point should be clearly detectable.

7.2 PRINCIPLE AND STEPS INVOLVED IN GRAVIMETRIC ANALYSIS

Gravimetric analysis is a quantitative analytical technique in which the analyte is converted into a pure, stable, and insoluble compound of known chemical composition. The resulting precipitate is separated from the solution, washed, dried or ignited, and accurately weighed. The amount of analyte present in the original sample is then calculated from the mass and chemical

Principle

During the titration, silver ions react quantitatively with thiocyanate ions to form a white precipitate of silver thiocyanate. After complete precipitation of silver ions, the first excess drop of thiocyanate reacts with ferric ions. The appearance of a permanent reddish colour marks the end point.

Titrants and Standardization

The principal solutions used in the Volhard method are silver nitrate, ammonium thiocyanate and potassium thiocyanate. Their standardization is carried out as follows:

Table 7.2: Standardization of Reagents Used in Argentometric Titrations

Solution	Standardization
Silver nitrate ($AgNO_3$)	Standardized using sodium chloride as a primary standard.
Ammonium thiocyanate (NH_4SCN)	Standardized against a previously standardized silver nitrate solution.
Potassium thiocyanate (KSCN)	Standardized against a previously standardized silver nitrate solution.

Chemical Reactions

Precipitation reactions:

$$AgNO_3 + NH_4SCN \rightarrow AgSCN\downarrow + NH_4NO_3$$
$$AgNO_3 + KSCN \rightarrow AgSCN\downarrow + KNO_3$$

End-point reaction:

$$Fe^{3+} + SCN^- \rightleftharpoons [Fe(SCN)]^{2+}$$

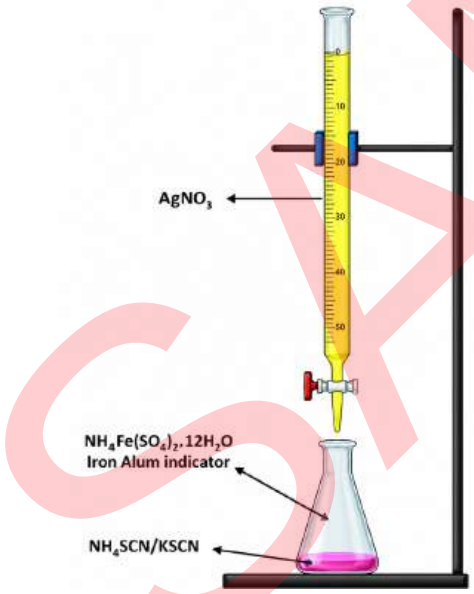


Figure 7.3: Experimental Setup for Volhard's Argentometric Titration

Indicator

A ferric salt is used as the indicator. The commonly employed indicator is ferric ammonium sulphate, also known as ammonium iron(III) sulphate or iron alum. Its formula is $NH_4Fe(SO_4)_2 \cdot 12H_2O$. At the end point, ferric ions combine with the excess thiocyanate ions to form the reddish-coloured complex $[Fe(SCN)]^{2+}$.

Titration Medium

The titration is carried out in the presence of nitric acid. The acidic medium prevents the precipitation of ferric ions as ferric hydroxide, $Fe(OH)_3$, and thereby ensures the proper functioning of the indicator.

End Point: Appearance of a permanent reddish colour due to formation of the ferric thiocyanate complex.

Applications

The Volhard method is used for the determination of silver ions and substances such as halides, thiocyanates, cyanides, sulphides, carbonates, chromates, oxalates and arsenates. It may also be employed as a back-titration method for the estimation of halides.

7.3.3 Modified Volhard's Method

Modified Volhard's method is an improved form of the classical Volhard argentometric titration used for the quantitative determination of chloride ions, particularly in pharmaceutical substances such as sodium chloride. It is an indirect (back) titration in which a known excess of standard silver nitrate solution is added to the chloride-containing sample. The chloride ions react completely with silver ions to form an insoluble precipitate of silver chloride (AgCl).

Principle

The method is based on the precipitation of chloride ions with an excess of standard silver nitrate, followed by the back titration of the unreacted silver ions using a standard solution of ammonium thiocyanate (NH_4SCN) or potassium thiocyanate (KSCN). The amount of chloride present is calculated from the difference between the total silver nitrate added and the excess silver nitrate remaining after the back titration.

Role of Nitrobenzene

In the modified Volhard method, nitrobenzene is added after the precipitation of silver chloride. Nitrobenzene coats the surface of the AgCl precipitate, preventing it from reacting with thiocyanate ions during the back titration. This modification eliminates the need for filtration of the precipitate and significantly improves the accuracy and convenience of the method.

$$NaCl + AgNO_3 \rightarrow AgCl\downarrow + NaNO_3$$
$$AgCl + SCN^- \rightarrow AgSCN\downarrow + Cl^-$$
$$AgCl\downarrow + \text{Nitrobenzene} \longrightarrow AgCl \text{ (coated with nitrobenzene)}$$
$$AgNO_3 + NH_4SCN \rightarrow AgSCN\downarrow + NH_4NO_3$$

Reaction Medium

The titration is performed in an acidic medium, generally maintained by the addition of nitric acid. The acidic environment prevents the formation of ferric hydroxide and other interfering silver salts, ensuring accurate endpoint detection.

Indicator

Ferric ammonium sulphate (Iron alum) is used as the indicator. Ferric ions do not participate in the titration until all the excess silver ions have reacted with thiocyanate ions. After complete consumption of silver ions, the first excess of thiocyanate reacts with ferric ions to produce a reddish-brown ferric thiocyanate complex, indicating the end point.

8 COMPLEXOMETRIC TITRATIONS

Classification, metal ion indicators, masking and demasking reagents, preparation and standardization of disodium EDTA. Estimation of Magnesium sulphate and Calcium gluconate*.

8.1 Introduction

Complexometric titrations are volumetric analytical methods in which a suitable complexing agent is used for the quantitative estimation of polyvalent metal ions, such as divalent, trivalent and tetravalent ions. The method is based on the formation of a stable and soluble complex between the metal ion and the complexing agent.

A complexing agent is an electron-donating ion or molecule capable of forming one or more coordinate covalent bonds with a metal ion. The electron-donating species is known as a ligand. The complex formed usually possesses physical and chemical properties that are different from those of the free metal ion.

When a ligand forms only one coordinate bond with a metal ion, it is called a unidentate or monodentate ligand. When it forms two or more coordinate bonds with the same metal ion, it is known as a polydentate ligand. Polydentate ligands form ring-like structures with metal ions, and such compounds are called chelates. Therefore, a polydentate ligand capable of forming a chelate is known as a chelating agent.

When the complex formed between a metal ion and a complexing agent is soluble in water and prevents the metal ion from participating in other reactions, the complexing agent is referred to as a sequestering agent.

8.1.1 Werner's Coordination Number

Werner's coordination number is defined as the number of atoms or groups that can be directly attached to the central metal atom or ion in a coordination complex. It is not necessarily related to the valency of the metal ion. Instead, it depends mainly on the size of the metal ion, the size of the ligand and the spatial arrangement of the coordinating groups.

In general, elements of the second period may accommodate approximately four coordinating groups, while elements of the third and fourth periods may accommodate six and eight groups, respectively. Knowledge of the coordination number helps in predicting the maximum number of ligand groups that can be arranged around a central metal ion.

8.1.2 Complexing Agents

Complexing agents may be classified according to the functional groups or electron-donating atoms present in their molecules.

1. Neutral Electron-Donating Molecules

Certain neutral molecules possess lone pairs of electrons on atoms such as nitrogen, oxygen, sulphur or halogens. These lone pairs may be donated to a metal ion to form coordinate bonds. Ammonia, for example, forms a coordination complex with copper ions, as represented below:

$$[Cu(NH_3)_4]^{2+}$$

2. Compounds Containing Replaceable Protons

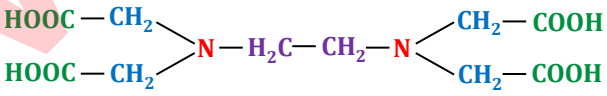
Compounds containing functional groups such as carboxylic acid (–COOH), phenolic hydroxyl (–OH), and enolic hydroxyl (–OH) can lose a proton (H^+) and coordinate with metal ions, forming stable metal–ligand complexes through the donation of electron pairs from the oxygen atoms.

3. Sequestering Agents

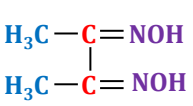
Sequestering agents generally contain several coordinating groups, such as –COOH, $–SO_3H$, $–NH_2$ and –OH. These groups allow the molecule to form several coordinate bonds with a metal ion, resulting in a stable, water-soluble complex.

Dimethylglyoxime and salicylaldoxime are common examples of chelating agents, whereas ethylenediaminetetraacetic acid, commonly known as EDTA, is an important sequestering agent.

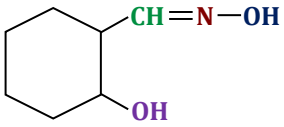
Structure of Complexing Agents



Ethylenediamine tetra acetic acid



Dimethylglyoxime



Salicylaldoxime

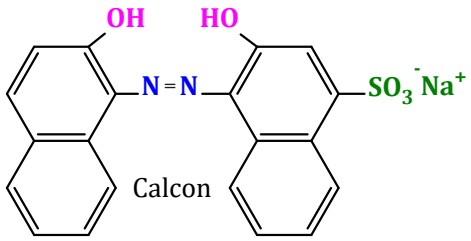
Ethylenediaminetetraacetic acid is one of the most widely used complexing agents in complexometric titrations. Its molecule contains two nitrogen atoms and four carboxylic acid groups. These atoms provide six possible coordination sites. Therefore, EDTA acts as a hexadentate ligand.

EDTA can combine with divalent, trivalent and tetravalent metal ions. Irrespective of the valency of the metal ion, EDTA generally forms a complex in a 1:1 molar ratio. The general complex-formation reactions may be represented as follows:

$$M^{2+} \text{ (divalent ion)} + H_2X^{2-} \rightarrow MX^{2-} + 2H^+$$
$$M^{3+} \text{ (trivalent ion)} + H_2X^{2-} \rightarrow MX^{-} + 2H^+$$
$$M^{4+} \text{ (tetravalent ion)} + H_2X^{2-} \rightarrow MX + 2H^+$$

Calcon Mixture

Calcon is chemically known as sodium 2-hydroxy-1-(2-hydroxy-1-naphthylazo)-naphthalene-4-sulphonate. It is also known as Solochrome Dark Blue. Calcon is commonly used as an indicator in the complexometric assay of calcium carbonate and calcium chloride, where it forms a coloured complex with calcium ions and undergoes a distinct colour change when all calcium ions are completely complexed by EDTA.



Other Indicators

Several other metallochromic indicators used for specific complexometric titrations include Catechol Violet, Methyl Thymol Blue, Alizarin Fluorine Blue, Sodium Alizarin Sulphonate, Diphenyl Carbazone, Tiron, and Pyridyl Azo Naphthol (PAN). The choice of indicator depends on the nature of the metal ion, the stability of the metal–indicator complex, the pH of the solution and the stability of the metal–EDTA complex.

8.2 Classification of Complexometric Titrations

Complexometric titrations are analytical methods in which metal ions are estimated through the formation of stable, soluble complexes with a suitable complexing agent, commonly disodium edetate. These titrations are classified into four main types:

1. Direct titration
2. Back titration
3. Replacement or displacement titration
4. Alkalimetric titration of metals

1. Direct Titration

In direct complexometric titration, an accurately weighed quantity of the substance is dissolved in a suitable medium. A measured volume of buffer solution and a few drops of an appropriate metal-ion indicator are then added. The resulting solution is titrated directly with a standard disodium edetate solution until the required colour change indicates the end point.

A blank titration is also carried out using all the reagents except the substance being estimated. The volume of disodium edetate consumed in the blank titration is subtracted from the volume used in the original titration to obtain the corrected titre value.

Examples of substances estimated by direct complexometric titration include bismuth nitrate, carbonate, oxynitrate, and subnitrate; calcium chloride, gluconate, and lactate; magnesium carbonate, oxide, stearate, sulphate, and trisilicate; and zinc sulphate, oxide, and undecenoate.

2. Back Titration

Back titration is employed when direct titration is unsuitable or when a sharp end point cannot be obtained. It is particularly useful in the following situations:

- when the metal ion precipitates as a hydroxide at the pH required for titration;
- when the substance is insoluble, such as lead sulphate or calcium oxalate;
- when the substance reacts slowly with disodium edetate; and
- when the metal forms a more stable chelate with edetate than with the indicator.

Method: A known excess of standard disodium edetate solution is added to the substance along with a suitable buffer solution and a few drops of indicator. The mixture may be heated to promote complete complex formation and is then cooled. The unreacted excess of disodium edetate is back-titrated with a standard solution of magnesium sulphate or zinc sulphate.

Examples include, Alum [$KAl(SO_4)_2 \cdot 12H_2O$], aluminium hydroxide gel, dried aluminium hydroxide gel and calcium phosphate.

3. Replacement or Displacement Titration

Replacement titration is used when a sharp end point cannot be obtained by either direct or back titration. In this method, the metal ion to be determined displaces an equivalent amount of magnesium or zinc from its comparatively less stable edetate complex. The liberated magnesium or zinc ions are then titrated with standard disodium edetate solution.

$$M^{2+} + ZnX^{2-} \rightarrow MX^{2-} + Zn^{2+}$$

Here, M^{2+} represents the metal ion being determined and X represents edetate. This method is commonly used for the estimation of cadmium, lead and mercury.

4. Alkalimetric Titration of Metals

In alkalimetric titration, a polyvalent metal ion reacts with the acidic form of edetate and liberates hydrogen ions. The reaction may be represented as follows:

$$M^{n+} + H_2X^{2-} \rightarrow MX^{(n-4)} + 2H^+$$

The hydrogen ions released during complex formation produce acidity, which is quantitatively titrated with a standard alkali in an unbuffered solution. An acid-base indicator is generally sufficient and may be used instead of a metal-ion indicator. Alternatively, the end point may be determined by a potentiometric method.

8.3 Metal Ion Indicators

The accuracy of an EDTA complexometric titration largely depends on the precise detection of the end point. In most complexometric titrations, the end point is detected visually with the help of metal ion indicators, also known as metallochromic indicators. These indicators form coloured complexes with metal ions and produce a distinct colour change when the metal ions are completely complexed by EDTA.

Metal ion indicators are generally organic dyes containing several donor atoms capable of coordinating with metal ions. Since these indicators can also accept or release hydrogen ions, their colour is influenced by both the metal-ion concentration and the pH of the solution. Therefore, they may function simultaneously as pM indicators and acid–base indicators.

9 REDOX TITRATIONS

Concepts of oxidation and reduction, Types of redox titrations viz. Permanganometry, Cerimetry, Iodimetry, Iodometry and titrations with potassium iodate.

9.1 INTRODUCTION

Redox titrations are volumetric analytical methods based on oxidation-reduction reactions. Unlike acid-base titrations, which involve the transfer of protons, redox titrations involve the transfer of electrons between two reacting substances. A redox reaction may be represented by the following general equation:

$$Ox_1 + Red_2 \rightarrow Red_1 + Ox_2$$

In this equation, the subscript 1 refers to the substance being titrated, whereas the subscript 2 refers to the titrant. During a redox reaction, one substance loses electrons and is oxidized, while another substance gains electrons and is reduced. Therefore, oxidation and reduction always occur simultaneously.

Reduction Potential

The tendency of a substance to accept electrons is expressed in terms of its reduction potential. A substance with a high positive reduction potential is readily reduced, acts as a powerful oxidizing agent and can remove electrons from substances having lower reduction potentials. The standard reduction potentials of some commonly encountered redox systems are presented in Table 9.1.

Table 9.1: Reduction Potentials of Typical Redox Pairs

Oxidized form	Reduced form	E_0 (V)
$Ce^{4+} + e^-$	Ce^{3+}	1.61
$MnO_4^- + 8H^+ + 5e^-$	$Mn^{2+} + 4H_2O$	1.51
$Br_2 + 2e^-$	$2Br^-$	1.05
$Fe^{3+} + e^-$	Fe^{2+}	0.55
$I_2 + 2e^-$	$2I^-$	0.54
$2H^+ + 2e^-$	H_2	0.00
$Fe^{2+} + 2e^-$	Fe	−0.44
$Ca^{2+} + 2e^-$	Ca	−2.89

A substance with a higher reduction potential can oxidize another substance having a lower reduction potential. For a redox titration to proceed quantitatively, the equilibrium constant of the reaction must be sufficiently high so that the reaction proceeds almost completely towards product formation. The difference between the reduction potential of the titrant and that of the analyte is known as the reaction potential. It is expressed as:

$$\Delta E = E_0^T - E_0^A$$

where,

E_0^T is the reduction potential of the titrant.

E_0^A is the reduction potential of the analyte.

ΔE is the reaction potential.

In practical redox titrations, the value of ΔE should generally not be less than approximately 0.1–0.2 V. A larger difference in reduction potentials produces a more complete reaction and a sharper change in potential at the equivalence point.

Redox Titration Curve

During a redox titration, the potential of the solution changes gradually as the titrant is added. Near the equivalence point, the potential increases or decreases sharply. This sudden change in potential is used to determine the endpoint of the titration. For example, iron(II) ions can be titrated with cerium(IV) ions according to the following reaction:

$$Fe^{2+} + Ce^{4+} \rightarrow Fe^{3+} + Ce^{3+}$$

In this titration, the cell potential changes sharply at the equivalence point because there is a considerable difference between the reduction potentials of the Fe^{3+}/Fe^{2+} and Ce^{4+}/Ce^{3+} redox systems. When the difference between the reduction potentials is small, the change in potential at the equivalence point becomes less pronounced. Thus, a larger reaction potential produces a sharper titration curve and allows more accurate endpoint detection.

Detection of the Endpoint

The endpoint of a redox titration may be detected by either:

1. Redox indicators
2. Potentiometric methods
3. Self-indicators
4. External indicators
5. Specific Indicators

1.Redox Indicators

Redox indicators are substances that undergo oxidation or reduction depending upon the potential of the solution. Their oxidized and reduced forms possess different colours.

A suitable redox indicator should undergo a colour change within the potential range corresponding to the equivalence point. The indicator must be used in a very small quantity so that it does not consume a significant amount of the electrons involved in the titration reaction.

3. It cannot be conducted in neutral or basic (alkaline) solutions. If the pH rises, the active Ce^{4+} ions undergo rapid hydrolysis, forming insoluble precipitates like $Ce(OH)_4$ which ruin the titration accuracy.
4. Cerium(IV) salts, such as ceric ammonium sulfate, are significantly more expensive than other common redox titrants like potassium permanganate ($KMnO_4$) or potassium dichromate ($K_2Cr_2O_7$)

9.3.3 Iodimetry

Iodimetry is a direct redox titration method in which a standard iodine solution is used as the titrant. The method is mainly employed for the quantitative determination of reducing substances.

Iodine acts as a mild oxidizing agent. It accepts electrons from the reducing substance and is reduced to iodide ions according to the following half-reaction:

$$I_2 + 2e^- \rightarrow 2I^-$$

Substances Determined by Iodimetry

Reducing substances that react rapidly and quantitatively with iodine can be determined by this method. Important examples include stannous chloride and sodium thiosulphate.

Reaction with Stannous Ions: In this reaction, stannous ions are oxidized to stannic ions, whereas iodine is reduced to iodide ions.

$$Sn^{2+} + I_2 \rightarrow Sn^{4+} + 2I^-$$

Reaction with Thiosulphate Ions: In this reaction, thiosulphate ions are oxidized to tetrathionate ions, while iodine is converted into iodide ions.

$$2S_2O_3^{2-} + I_2 \rightarrow S_4O_6^{2-} + 2I^-$$

Procedure of Iodimetric Titration

A measured quantity of the reducing substance is transferred into a glass-stoppered conical flask, commonly called an iodine flask. Standard iodine solution is added gradually from the burette while the contents of the flask are mixed continuously.

Starch solution or sodium starch glycolate may be used as an indicator. Sodium starch glycolate is often preferred because it gives a stable and distinct colour change. As long as the reducing substance is present, the iodine added from the burette is immediately reduced to iodide ions. After the reducing substance has been completely oxidized, the first slight excess of iodine combines with starch and produces a permanent blue colour.

Standardization of Sodium Thiosulphate with Iodine

A standard iodine solution may also be placed in an iodine flask and titrated against sodium thiosulphate solution taken in the burette. The thiosulphate solution is added until the iodine colour becomes pale yellow. Starch indicator is then added, producing a deep blue colour, and the titration is continued until the blue colour disappears completely.

The normality of the sodium thiosulphate solution is calculated by using the known concentration of the standard iodine solution.

Conditions for Iodimetry determinations

1. 1. Potential of the I2/2I- system is not high.
2. Since iodine is volatile in nature, titration is conducted in the cold condition. Also, sensitivity
3. of starch reduces with rise in temperature.
4. Iodometry titration cannot be performed in strongly alkaline solution as it forms hypoiodide.

$$2\ NaOH + I_2 \rightarrow NaOI + NaI + H_2O$$

5. Since the solubility of iodine in water is low, a greater amount of KI must be used.

9.3.4 Iodometry

Iodometry is an indirect redox titration method used for the quantitative determination of oxidizing agents. In this method, the oxidizing agent reacts with an excess of potassium iodide and liberates an equivalent quantity of iodine. The liberated iodine is subsequently titrated with a standard sodium thiosulphate solution.

Oxidizing Agents Determined by Iodometry

- Copper sulphate ($CuSO_4$)
- Potassium dichromate ($K_2Cr_2O_7$)
- Potassium permanganate ($KMnO_4$)

Principle

When excess potassium iodide is added to a solution containing an oxidizing agent, usually in an acidic medium, iodide ions are oxidized to iodine. The iodide ions lose electrons according to the following half-reaction:

$$2I^- \rightarrow I_2 + 2e^-$$

The oxidizing agent accepts the electrons released by iodide ions and is itself reduced. Therefore, the amount of iodine liberated is chemically equivalent to the amount of oxidizing agent present in the sample.

Iodometric Determination of Copper Sulphate

Copper sulphate behaves as an oxidizing agent in this determination. When an excess of potassium iodide is added to a solution of copper sulphate, cupric ions accept electrons and are reduced to cuprous ions. At the same time, iodide ions are oxidized to iodine. Iodide ions lose electrons and are oxidized to molecular iodine.

$$2I^- \rightarrow I_2 + 2e^-$$

Cupric ions accept electrons and are reduced to cuprous ions.

$$2Cu^{2+} + 2e^- \rightarrow 2Cu^+$$

$$2Cu^{2+} + 2I^- \rightarrow 2Cu^+ + I_2$$

Because iodide ions are present in excess, the cuprous ions formed react immediately with iodide ions and produce an insoluble precipitate of cuprous iodide.

$$2Cu^+ + 2I^- \rightarrow 2CuI\downarrow$$

The overall reaction is therefore represented as:

$$2Cu^{2+} + 4I^- \rightarrow 2CuI\downarrow + I_2$$

Stoichiometric Relationship

The amount of iodine liberated is equivalent to the amount of cupric ions or copper sulphate present in the sample. Two moles of copper sulphate liberate one mole of iodine.

$$2CuSO_4 \equiv I_2$$

Titration of Liberated Iodine

The iodine liberated in the above reaction is titrated with a stan-

10 GASTROINTESTINAL AGENTS

- **Acidifiers:** Sodium acid phosphate and Dilute Hydrochloric acid.
- **Antacids:** Ideal properties of antacids, combinations of antacids, Sodium bicarbonate*, Aluminium hydroxide gel*.
- **Agents promote Bowel Movements:** Magnesium hydroxide, Sodium orthophosphate, Sodium Potassium tartrate and magnesium trisilicate.
- **Antimicrobials:** Mechanism, classification, Potassium permanganate, Boric acid, Hydrogen peroxide*, Chlorinated lime*, Iodine and its preparations

10.1 INTRODUCTION

The digestive system, also known as the gastrointestinal tract (GIT), consists of a group of organs responsible for digestion, absorption, and elimination. It extends from the oesophagus to the anus, with the buccal cavity acting as the entry point of food. The major parts of the gastrointestinal tract include the stomach, small intestine, large intestine, rectum, and anus. The small intestine consists of the duodenum, jejunum, and ileum, while the large intestine includes the caecum, ascending colon, transverse colon, descending colon, and rectum.

The stomach plays an important role in the digestion of proteins. Protein digestion occurs in an acidic medium with the help of the enzyme pepsin. Both hydrochloric acid (HCl) and pepsin are secreted by specialised cells present in the stomach.

The small intestine is the main site for digestion and absorption. The following important functions take place in the small intestine:

1. Digestion of proteins occurs in an alkaline medium in the presence of enzymes.
2. Digestion of carbohydrates and lipids occurs with the help of enzymes and bile salts.
3. Absorption of digested food, vitamins, and minerals takes place.

When the normal functions of the gastrointestinal tract are disturbed, various diseases or undesirable conditions may occur. Some important conditions are described below:

1. Inadequate secretion of gastric acid may lead to achlorhydria or hypochlorhydria.
2. Excess secretion of gastric acid may disturb the acid-enzyme balance and may cause hyperacidity and ulcers. In such cases, the gastric wall and sometimes the duodenal wall become sensitive, resulting in acute pain.
3. Accumulation of toxic substances or gases may occur in the gastrointestinal tract.
4. Inadequate absorption of fluids and minerals from the large intestine may result in diarrhoea.
5. Reduced peristaltic movement of the large intestine may lead to constipation.
6. Inadequate secretion of saliva may cause difficulty in swallowing food.
7. Accidental or intentional ingestion of poisonous substances may produce toxic effects.

These conditions can be corrected by the administration of suitable drugs. Several inorganic compounds are useful in the management of gastrointestinal disorders. These include acidifiers, antacids, protectives, adsorbents, saline cathartics, and other related agents used in gastrointestinal conditions.

10.2 ACIDIFIERS

Acidifying agents are the acid or substances used to increase the acid content or decrease the pH of the organ (stomach, urinary tract or blood). Inadequate secretions of acid result in achlorhydria or hypochlorhydria that require treatment with acidifying agents. Some acidifiers are used to increase gastric hydrochloric acid, while others are used to correct systemic alkalosis or to acidify urine.

Acidifiers are mainly classified into the following four types:

1. Gastric Acidifiers

Gastric acidifiers are drugs used to temporarily restore the acidity of the stomach in patients suffering from achlorhydria or hypochlorhydria.

Some patients suffering from achlorhydria respond to stimulation by histamine. In such cases, histamine phosphate may be used, particularly in patients suffering from chronic alcoholism, tuberculosis, hyperthyroidism, and in elderly persons above 50 years of age.

However, in certain conditions such as carcinoma of the stomach, chronic gastritis, or after gastrectomy, complete achlorhydria may occur. In such patients, hydrochloric acid or a suitable acidifying agent may be administered.

In pernicious anaemia, the lack of intrinsic factor is also associated with the absence of hydrochloric acid. Therefore, dilute hydrochloric acid may be used to counteract the effects of achlorhydria.

2. Urinary Acidifiers

Urinary acidifiers are drugs used to make the urine acidic. They

5. Non-absorbable or minimally toxic if absorbed
6. Non-sensitizing
7. Compatible with soaps and detergents

Spectrum of Activity

Most antiseptics and disinfectants have a broad spectrum because they act non-selectively on microbial cells. However, some agents are selective. For example, chlorhexidine, hexachlorophene, quaternary ammonium compounds, gentian violet, and acriflavine are more active against gram-positive bacteria. Silver nitrate is highly active against gonococci, while benzoyl peroxide is useful against Propionibacterium acnes.

Mechanism of Action

Germicides act by the following mechanisms:

1. Oxidation of microbial protoplasm
2. Denaturation of bacterial proteins and enzymes
3. Alteration of cell membrane permeability
4. Detergent-like action on microbial membranes

Factors Affecting Germicidal Activity

The activity of antiseptics and disinfectants is affected by:

1. Concentration of the agent
2. Duration of contact
3. Temperature
4. pH
5. Presence of organic matter
6. Type and number of microorganisms
7. Nature of the surface or tissue

Table 10.2: Classification of Antiseptics and Disinfectants

S. No.	Class	Example	Mechanism	Uses	Description
1	Phenolic Compounds	Hexachlorophene	Denatures proteins and damages microbial cell membrane.	Used in antiseptic soaps and surgical scrubs.	Mainly active against gram-positive bacteria. Action is slow but persistent. Forms a thin film on skin. Earlier used for baby baths. More than 2% preparations are restricted due to neurotoxicity, especially in premature infants.
2	Oxidizing Agents	Potassium Permanganate	Releases oxygen and oxidizes bacterial protoplasm.	Used for gargling, douching, wound irrigation, cavity irrigation, and water disinfection.	Occurs as purple crystals. Highly soluble in water. Dilute solutions are used. Action is slow. Higher concentration may cause burns and blistering.
		Hydrogen Peroxide	Releases nascent oxygen. Foaming occurs due to decomposition by catalase in tissues.	Used to remove slough, debris, and ear wax.	Has weak and temporary antiseptic action. Foaming helps mechanical cleaning. Loses potency on storage.
		Benzoyl Peroxide	Acts against *Propionibacterium acnes*.	Used in treatment of acne vulgaris.	Specifically useful in acne due to activity against P. acnes.
3	Halogens	Iodine	Acts by iodination and oxidation of microbial protoplasm.	Used on cuts and for skin preparation before surgery.	Rapidly acting broad-spectrum microbicidal agent. Effective against bacteria, fungi, and viruses. Strong solutions may irritate or burn skin.
		Iodophores	Slowly release free iodine from organic carrier complexes.	Used for surgical scrubbing, wound dressing, burns, ulcers, fungal infections, vaginitis, and instrument disinfection.	Povidone-iodine is the most common iodophore. Non-irritating, non-staining, and provides prolonged germicidal action.
		Chlorine	Powerful oxidizing germicide.	Used for disinfection of water supplies.	Rapidly acting potent germicide. Organic matter reduces activity. Excess chlorine is added to maintain free chlorine; this is called chlorine demand of water.
		Chlorophores	Slowly release hypochlorous acid.	Used as disinfecting agents.	Provide slow release of active chlorine.
		Chlorinated Lime	Releases chlorine.	Used for disinfecting drinking water, swimming pools, privies, and contaminated areas.	Also called bleaching powder. Effective disinfectant for public health sanitation.

$$2Sb + 3I_2 \rightarrow 2SbI_3$$
$$P_4 + 6I_2 \rightarrow 4PI_3$$
$$Hg + I_2 \rightarrow HgI_2$$

2. Oxidizing Action

In aqueous medium, iodine behaves as an oxidizing agent. It oxidizes hydrogen sulphide to sulphur, sulphur dioxide to sulphuric acid, nitrites to nitrates, sulphites to sulphates, arsenites to arsenates, and sodium thiosulphate to sodium tetrathionate.

$$I_2 + H_2O \rightarrow HI + HIO$$
$$H_2S + I_2 \rightarrow S + 2HI$$
$$SO_2 + 2H_2O + I_2 \rightarrow H_2SO_4 + 2HI$$
$$KNO_2 + I_2 + H_2O \rightarrow KNO_3 + 2HI$$
$$Na_2SO_3 + I_2 + H_2O \rightarrow Na_2SO_4 + 2HI$$
$$Na_3AsO_3 + I_2 + H_2O \rightarrow Na_3AsO_4 + 2HI$$
$$2Na_2S_2O_3 + I_2 \rightarrow Na_2S_4O_6 + 2NaI$$

3. Reaction with Sodium Hydroxide

Iodine reacts with cold sodium hydroxide solution to form sodium iodide and sodium hypoiodite. Sodium hypoiodite hydrolyses to form hypoiodous acid.

$$I_2 + 2NaOH \rightarrow NaI + NaIO + H_2O$$
$$NaIO + H_2O \rightarrow HIO + NaOH$$

With hot sodium hydroxide solution, or even with cold alkali on prolonged contact, iodine forms iodate.

$$6NaOH + 3I_2 \rightarrow 5NaI + NaIO_3 + 3H_2O$$
$$6NH_4OH + 3I_2 \rightarrow 5NH_4I + NH_4IO_3 + 3H_2O$$

4. Reaction with Liquor Ammonia

Iodine reacts with liquor ammonia to form nitrogen triiodide, which is a black explosive compound.

$$2NH_3 + 3I_2 \rightarrow NI_3 + 3HI$$

5. Dissociation

At about 700°C, iodine dissociates into atomic iodine.

$$I_2 \rightleftharpoons 2I$$

6. Reaction with Potassium Chlorate

Iodine reacts with concentrated potassium chlorate solution in the presence of a small amount of nitric acid on heating to form potassium iodate.

$$2KClO_3 + I_2 \rightarrow 2KIO_3 + Cl_2$$

7. Reaction with Organic Compounds

Iodine reacts slowly with organic compounds to form alkyl iodides.

$$CH_4 + I_2 \rightarrow CH_3I + HI$$
$$CH_2{=}CH_2 + I_2 \rightarrow CH_2I{-}CH_2I$$

8. Reducing Action

Iodine can also act as a reducing agent. In the presence of strong oxidizing agents, it is oxidized to iodic acid (HIO_3) and iodates.

$$I_2 + 5Cl_2 + 6H_2O \rightarrow 2HIO_3 + 10HCl$$
$$3I_2 + 5KClO_3 + 3H_2O \rightarrow 6HIO_3 + 5KCl$$

9. Reaction with Starch

Iodine reacts with starch mucilage to produce a deep blue colour. This colour disappears on heating and reappears on cooling. This reaction is commonly used as an identification test for iodine.

Tests for Purity

Iodine is tested for the presence of impurities such as chlorides, bromides, cyanogen, and non-volatile matter.

Test for Chlorides and Bromides

An aqueous extract of iodine is first decolourized with zinc dust. The solution is then treated with silver nitrate in the presence of nitric acid.

Silver iodide is almost insoluble in dilute ammonia, whereas silver chloride is freely soluble and silver bromide is less soluble. The soluble silver halides are reprecipitated on the addition of excess dilute nitric acid.

Test for Cyanogen

Cyanogen impurity, present as ICN, is detected by the Prussian blue test.

Incompatibilities

Iodine is incompatible with iodine oxides, hypophosphites, sulphites, and many reducing agents.

It also reacts with volatile oils, fixed oils, turpentine, ammonia water, ammoniated mercury, alkali hydroxides, and carbonates. Iodine precipitates many alkaloids and gives a characteristic colour reaction with starch.

Identification Tests

1. When iodine is gently heated, it gives violet-coloured vapours. These vapours condense to form a bluish-black crystalline sublimate.
2. When iodine is treated with potassium iodide solution and starch, a deep blue colour is produced. This colour disappears on boiling and reappears on cooling.

Assay

The assay of iodine is based on iodometric titration. In this method, iodine is titrated with standard sodium thiosulphate solution using starch as an indicator.

An aqueous solution containing iodine, potassium iodide, and dilute acetic acid is titrated with 0.1 N sodium thiosulphate. The end point is indicated by the disappearance of the blue colour.

Each ml of 0.1 N sodium thiosulphate is equivalent to 0.01269 g of iodine.

$$2Na_2S_2O_3 + I_2 \rightarrow Na_2S_4O_6 + 2NaI$$

Here, sodium thiosulphate is oxidized to sodium tetrathionate.

Preparations of Iodine

1. Povidone-Iodine

Povidone-iodine is an iodophor, consisting of iodine complexed with povidone (polyvinylpyrrolidone or PVP). This complex acts as a reservoir that gradually releases free iodine, thereby providing sustained antimicrobial activity while reducing the irritant effects associated with elemental iodine. The official preparation contains 9–12% available iodine, calculated on the dried substance.

Properties

Povidone-iodine occurs as a yellowish-brown amorphous powder with a faint characteristic odour. It loses not more than 8% of its weight on drying. The compound is freely soluble in water

11 RADIOPHARMACEUTICALS

Basics of radioactivity, applications of radioisotopes of Sodium Iodide I-131, Technetium-99m, Cobalt-60, Phosphorus-32 including safe handling, storage, and disposal of radiopharmaceuticals, adhering to regulatory guidelines for safety.

11.1 Introduction

Radiopharmaceuticals are medicinal preparations that contain one or more radionuclides and are intended for use in diagnosis, functional investigation or treatment. Unlike ordinary medicines, their usefulness depends not only on chemical and biological properties but also on the type, energy and half-life of the radiation emitted by the radionuclide.

In diagnostic nuclear medicine, a small quantity of a radiolabelled compound is administered to the patient. The compound follows a physiological or biochemical pathway, and the emitted radiation is detected outside the body to obtain information about organ structure, perfusion, metabolism or function. In therapy, the radiopharmaceutical is selected so that radiation is delivered preferentially to diseased tissue, thereby producing a local cytotoxic effect.

Radiopharmaceuticals are generally classified as unsealed radioactive sources because they are supplied as liquids, gases, colloids, capsules or injectable solutions that are removed from their primary container and administered to the patient. By contrast, a sealed source is enclosed or encapsulated so that radioactive material cannot escape during normal use. Sealed sources are commonly used in external-beam therapy, brachytherapy, calibration instruments and industrial radiography.

A radiopharmaceutical is a pharmaceutical dosage form containing a radionuclide, either alone or attached to a biologically active molecule, intended for diagnostic or therapeutic use.

11.2 Basics of Radioactivity

11.2.1 Radioactivity

Nuclides

A nuclide is a particular species of atom identified by the composition of its nucleus. It is characterized by the number of protons and neutrons present in the nucleus, as well as by its nuclear energy state. Each nuclide possesses a definite atomic number and mass number.

The atomic number, represented by (Z), indicates the number of protons present in the nucleus of an atom. It determines the identity of the element. The mass number, represented by (A), is the total number of protons and neutrons present in the nucleus.

Isotopes

Atoms of the same element may contain the same number of protons but different numbers of neutrons. Such atoms are known as isotopes. Therefore, isotopes are nuclides having the same atomic number but different mass numbers.

Although isotopes of an element have nearly identical chemical properties, they may differ in certain physical properties, such as atomic mass, density, diffusion rate and radioactive behaviour. Some isotopes are stable, and the differences between them arise mainly because of variations in their nuclear mass.

However, several isotopes possess unstable nuclei. These unstable isotopes undergo spontaneous nuclear transformation and emit radiation in order to attain a more stable state. Such isotopes are known as radioactive isotopes or radioisotopes. Uranium-235 is a common example of a naturally occurring radioactive isotope. Apart from naturally occurring radioactive isotopes, radioactive nuclides can also be produced artificially. These are prepared by bombarding stable atoms with suitable subatomic particles, such as neutrons, protons or alpha particles. This process converts a stable nuclide into an unstable radioactive form.

Radionuclides

A radionuclide is, therefore, a nuclide that possesses an unstable nucleus and undergoes spontaneous radioactive decay. During this process, it emits radiation and is transformed into another nuclide. The newly formed nuclide may either be stable or may undergo further radioactive decay until a stable nuclear configuration is achieved.

11.2.2 Representation of Nuclides

A nuclide is represented by the chemical symbol of the element together with its mass number and atomic number. The general form of nuclide notation is:

$$A_ZX$$

where:

- (X) represents the chemical symbol of the element,
- (A) represents the mass number, and
- (Z) represents the atomic number.

The mass number is written as a superscript on the upper left side of the chemical symbol, while the atomic number is written as a subscript on the lower left side. For example, hydrogen occurs naturally in three isotopic forms: ${}^{1}_{1}H\ {}^{2}_{1}H\ {}^{3}_{1}H$

All three isotopes have the same atomic number because each contains one proton. They differ in mass number because protium contains no neutron, deuterium contains one neutron and tritium contains two neutrons. Protium and deuterium are stable, whereas tritium is radioactive.

Similarly, the three naturally occurring isotopes of uranium are represented as: 23892U 23592U 23492U. Each uranium isotope contains 92 protons but differs in the number of neutrons present in its nucleus. All naturally occurring uranium isotopes are radio-

Table 11.2: Radioactive Decay: Fraction and Percentage Activity Remaining After Successive Half-Lives

Number of half-lives	Fraction remaining	Percentage activity remaining
0	1	100%
1	1/2	50%
2	1/4	25%
3	1/8	12.5%
4	1/16	6.25%
5	1/32	3.125%
10	1/1024	approximately 0.098%

Physical, Biological and Effective Half-Life

- **Physical half-life:** Time required for one-half of the radioactive atoms to decay by a nuclear process.
- **Biological half-life:** Time required for the body or an organ to eliminate one-half of the administered substance by biological processes.
- **Effective half-life:** Time required for the activity in the body or organ to fall to one-half as a result of both physical decay and biological elimination.

$$1/T_e = 1/T_p + 1/T_\beta$$

$$T_e = (T_p \times T_\beta)/(T_p + T_\beta)$$

The effective half-life is always shorter than either the physical or the biological half-life. It is especially important in internal dosimetry because it determines how long radioactive material remains capable of irradiating tissue.

Specific Activity

Specific activity is the activity per unit mass of a radioactive substance. It may be expressed as Bq/g, MBq/mg, Ci/g or another suitable unit. Carrier-free radionuclides have very high specific activity because essentially all atoms of the element are radioactive. High specific activity is valuable when only a very small chemical mass can be administered without disturbing the biological system under study.

11.2.4 Units Used in Radiation Science

Several quantities must be distinguished in radiation science. Activity describes the number of nuclear transformations, exposure describes ionization produced in air, absorbed dose describes energy deposited per unit mass, and equivalent or effective dose incorporates the biological effectiveness of radiation.

Table 11.3: Units and Conversions Used in Radiation Measurement

Quantity	SI unit	Older unit	Important Relationship
Radioactivity (activity)	Becquerel (Bq)	Curie (Ci)	1 Bq = 1 disintegration per second; 1 Ci = 3.7×10^{10} Bq; 1 Bq ≈ 2.703×10^{-11} Ci.
Energy	Joule (J); electron volt (eV)	—	1 eV = 1.602×10^{-19} J; 1 keV = 10^3 eV; 1 MeV = 10^6 eV.
Exposure in air	Coulomb per kilogram (C/kg)	Roentgen (R)	1 R = 2.58×10^{-4} C/kg.
Absorbed dose	Gray (Gy)	rad	1 Gy = 1 J/kg = 100 rad; 1 rad = 0.01 Gy.
Equivalent/effective dose	Sievert (Sv)	rem	1 Sv = 100 rem; 1 rem = 0.01 Sv.
Count rate	counts/s or counts/min	cps or cpm	Instrument response; it is not identical to true activity unless efficiency and geometry are known.

- Millicurie (mCi): 10^{-3} Ci.
- Microcurie (μCi): 10^{-6} Ci.
- Kilobecquerel (kBq): 10^3 Bq.
- Megabecquerel (MBq): 10^6 Bq.
- Gigabecquerel (GBq): 10^9 Bq.

11.2.5 Types of Nuclear Radiation

The principal emissions encountered in radiopharmacy are alpha particles, beta-minus particles, beta-plus particles and gamma rays. Electron capture, internal conversion and Auger-electron emission are also important in selected radionuclides.

Alpha Radiation

An alpha particle is the nucleus of a helium atom and contains two protons and two neutrons. It has a mass number of 4, a charge of +2 and comparatively high kinetic energy. Alpha particles travel in nearly straight paths and produce dense ionization along a short range.

- Very high linear energy transfer and strong ionizing ability.
- Very low penetrating power; stopped by paper, the outer dead layer of skin or a few centimetres of air.
- Potentially very hazardous when an alpha-emitting radionu-

12 MISCELLANEOUS COMPOUNDS

- **Expectorants:** Potassium iodide, Ammonium chloride*.
- **Emetics:** Copper sulphate*, Sodium potassium tartrate.
- **Haematinics:** Ferrous sulphate*, Ferrous gluconate.
- **Poison and Antidote:** Definition, classification of antidotes, Sodium thiosulphate.

12.1 INTRODUCTION

Miscellaneous drugs are medicines that do not belong to any specific or well-established drug class because they have unique mechanisms of action or special therapeutic uses. These drugs are used for various purposes, such as treating rare or complicated conditions, supporting combination therapy, or reversing the harmful effects of toxins and other drugs. Examples of miscellaneous drugs include antidotes, enzyme inhibitors, and medicines used to manage side effects caused by other treatments. They are usually grouped together in textbooks, reference materials, and formularies because they do not clearly fit into major drug categories such as antibiotics, analgesics, or other standard therapeutic groups.

12.2 EXPECTORANTS

Cough is a protective physiological reflex that helps to clear the airway. It may occur due to infections, chemical irritants, retained bronchial secretions, or the presence of foreign bodies in the respiratory tract. These factors stimulate the nerve endings in the respiratory tract and produce coughing.

An irritative cough is a dry cough. It may be caused by cold, inhalation of irritating dust, or gases. It does not produce sputum or any other discharge.

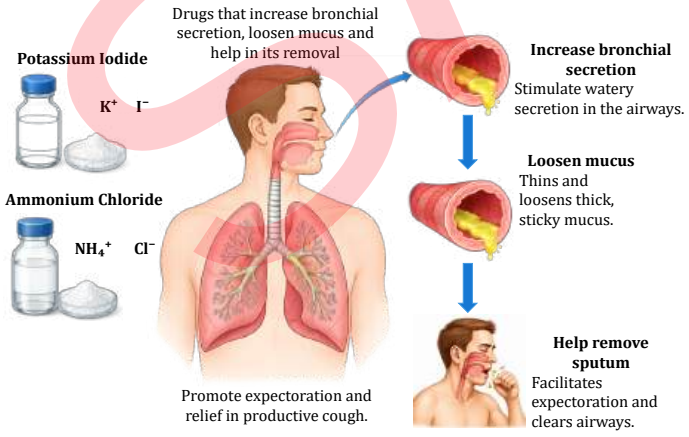


Figure 12.1: Expectorants: Mechanism of Action

A productive cough produces sputum or exudate and is commonly associated with conditions such as asthma and bronchitis. Any cough that persists for more than one week should be examined by a physician to find out the cause.

Expectorants are drugs that help to remove sputum/mucus from the respiratory tract by increasing bronchial secretions and reducing the thickness/viscosity of mucus.

They make thick sputum thin and watery, so it can be easily expelled by coughing.

Table 12.1: Classification of Expectorants

Drug Class	Examples
Bronchial secretion enhancers	Sodium or Potassium citrate, Potassium iodide, Guaiphenesin (Glyceryl guaiacolate), balsum of Tolu, Vasaka, Ammonium chloride
Mucolytics	Bromhexine, Ambroxol, Acetyl cysteine, Carbocisteine

Action and Uses of Expectorants

Expectorants increase the volume of secretions in the respiratory tract and help in their removal by ciliary action and coughing. These drugs are useful in the treatment of cough caused by irritation of the respiratory tract, especially when the secretion is thick and viscid and requires liquefaction.

Expectorants stimulate the output of respiratory tract fluid. Some agents act directly on bronchial secretory cells, while others act reflexly by irritating the gastric mucosa and stimulating respiratory tract secretions.

Examples of Expectorants

Terpin hydrate acts directly on bronchial secretory cells. Other expectorants include ammonium chloride, glyceryl guaiacolate, potassium guaiacolsulphonate, syrup of ipecac, iodinated glycerin, potassium iodide, and hydriodic acid syrup.

12.2.1 Potassium Iodide

Formula: KI

Molecular Weight: 166.0

Potassium iodide contains not less than 99.0% of KI.

Preparation

Potassium iodide is prepared by treating iron filings with iodine

Molecular Weight: 249.7 g/mol
Synonyms: Blue vitriol, Bluestone, Roman vitriol, Cupric sulphate
Standard: Copper sulphate contains not less than 98% and not more than 101% of copper sulphate.

Preparation:

1. Laboratory Method:

Copper sulphate is prepared by heating copper with concentrated sulphuric acid in the presence of air.

$$2Cu + 2H_2SO_4 + O_2 \rightarrow 2CuSO_4 + 2H_2O$$

2. Large Scale Method:

On a large scale, copper sulphate is prepared by heating scrap copper with dilute sulphuric acid while continuously passing air through the liquid.

$$2Cu + 2H_2SO_4 + O_2 \rightarrow 2CuSO_4 + 2H_2O$$

Properties

The substance is deep blue in colour, odourless, and has a metallic taste. It occurs in the form of prisms or crystalline powder. It is very soluble in boiling water, slowly soluble in glycerine, and insoluble in alcohol. Its aqueous solution is acidic in nature. Chemically, when it is heated at a high temperature, it decomposes to form black cupric oxide, sulphur dioxide, and oxygen. The reaction is: $2CuSO_4 \rightarrow 2CuO + 2SO_2 + O_2$.

Identification Test

The aqueous solution of copper sulphate gives characteristic reactions for copper ions and sulphate ions.

Table 12.3: Tests for Purity

Test	Limit as per IP
Arsenic impurity	Not more than 8 ppm
Iron impurity	Not more than 0.1%
Acidity	Acidic to litmus
Clarity and colour	Clear blue solution

Assay

The assay of copper sulphate is carried out by the iodometric method of titration, which is also called a redox titration.

This assay is based on the oxidizing property of copper sulphate. When copper sulphate is treated with potassium iodide in the presence of acetic acid or sulphuric acid, iodine is liberated. The liberated iodine is then titrated against standard sodium thiosulphate solution, using starch as an indicator.

During the reaction, cupric iodide is first formed, but it is unstable and decomposes to form cuprous iodide and iodine. Potassium thiocyanate is added near the end of the titration to complete the reaction. The endpoint is indicated by the disappearance of the blue colour.

In this titration, iodine is reduced to iodide, while sodium thiosulphate is oxidized to sodium tetrathionate. Since oxidation and reduction occur simultaneously, it is known as a redox titration.

$$2CuSO_4 + 4KI \rightarrow 2CuI + I_2 + 2K_2SO_4$$

$$I_2 + 2Na_2S_2O_3 \rightarrow Na_2S_4O_6 + 2NaI$$

Weigh 0.200 g of copper sulphate sample and dissolve it in 50 mL of water. Add 4 mL of acetic acid or 2 mL of sulphuric acid, followed by 3 g of potassium iodide. Titrate the liberated iodine with 0.1 N sodium thiosulphate, using 1 mL starch solution as an indicator. Add 2 g potassium thiocyanate near the end of titration.

Equivalent Factor

Each mL of 0.1 N sodium thiosulphate is equivalent to 0.02497 g of $CuSO_4 \cdot 5H_2O$.

Storage

Copper sulphate should be stored in a dry, tightly closed container and protected from air, heat, and moisture.

Dose

Copper sulphate may be used as an emetic in a dose of 300 mg in 30 mL of water.

Uses

Copper sulphate is used as an emetic in small doses and as a chemical antidote in phosphorus poisoning. It is also used in Fehling's and Benedict's reagents for laboratory tests. Externally, it acts as an astringent and fungicide. In agriculture, it is used to prepare Bordeaux mixture for controlling fungal diseases. It is also used as an algicide to control algae growth in water. Anhydrous copper sulphate is used to detect the presence of water/moisture.

12.3.2 Sodium Potassium Tartrate

Molecular Formula: $KNaC_4H_4O_6 \cdot 4H_2O$
Molecular Weight: 282.2 g/mol
Synonyms: Rochelle salt, Seignette's salt
Standard: Sodium potassium tartrate contains not less than 98% and not more than 101% of sodium potassium tartrate.

Preparation

Sodium potassium tartrate is prepared by neutralizing a solution of sodium carbonate with potassium bitartrate also known as cream of tartar.

$$2KHC_4H_4O_6 + Na_2CO_3 \rightarrow 2KNaC_4H_4O_6 + H_2O + CO_2$$

Properties

Sodium potassium tartrate is a white or colourless crystalline powder. It is odourless and has a saline taste. It is freely soluble in water but insoluble in alcohol. On heating, it decomposes and forms sodium carbonate and potassium carbonate along with carbon dioxide and water.

$$2KNaC_4H_4O_6 + 5O_2 \rightarrow K_2CO_3 + Na_2CO_3 + 4H_2O + 6CO_2$$

Identification Test

The aqueous solution of sodium potassium tartrate gives characteristic reactions of its respective ions.

Table 12.4: Test for Purity

Test	Limit as per IP
Lead impurity	Not more than 0.002%
Loss on drying	Not more than 2.7% at 105°C

Author Profile

DR. DEBARSHI KAR MAHAPATRA

Dr. Debarshi Kar Mahapatra is an accomplished pharmaceutical scientist, academician and researcher specialising in pharmaceutical and medicinal chemistry. He holds B.Pharm., M.Pharm. and Ph.D. degrees in Pharmaceutical Sciences and was awarded a University Gold Medal during his postgraduate studies. He currently serves as an Associate Professor in the Department of Pharmaceutical Chemistry at Chitkara College of Pharmacy, Chitkara University. His research interests include drug design, computational chemistry, novel drug-delivery systems, natural products and anticancer agents. He has extensive experience in teaching, research, academic administration, mentoring and scientific publishing. Dr. Mahapatra has authored numerous research articles, book chapters, textbooks and laboratory manuals and also holds granted patents. He has been recognised among the world's top scientists in Pharmacy and Pharmacology for several consecutive years. He is committed to advancing pharmaceutical research, innovation and professional education.

DR. NIVEDITA BHARDWAJ

Dr. Nivedita Bhardwaj is a pharmaceutical researcher and academician specialising in pharmaceutical and medicinal chemistry. She earned her Ph.D. in Pharmaceutical Chemistry from the Indian Institute of Technology (Banaras Hindu University), Varanasi. She is associated with the DPGU School of Pharmacy and Research, Pune, where she contributes to pharmaceutical education and research. Her research interests include medicinal chemistry, organic synthesis, natural products, drug discovery and spectroscopic techniques. She has contributed to scientific publications involving biologically active compounds and advanced drug-delivery approaches. Dr. Bhardwaj has also received several academic awards and recognitions for her research, debates and public-health initiatives. She is committed to promoting innovation, scientific learning and healthcare-oriented pharmaceutical research.

DR. KALYAN GHOSH

Dr. Kalyan Ghosh, B.Pharm., M.Pharm., PhD (IIT Guwahati), is a researcher in the fields of pharmaceutical sciences, biochemistry, and structural biology. He completed his PhD from the Department of Biosciences and Bioengineering, Indian Institute of Technology (IIT) Guwahati under the prestigious Prime Minister's Research Fellowship (PMRF) awarded by the Ministry of Education, Government of India. His research focuses on understanding the molecular mechanisms of antimicrobial resistance, membrane protein biology, protein-ligand interactions, and structure-based drug discovery using multidisciplinary approaches. He has authored 15 peer-reviewed research articles in reputed national and international journals. His research contributions have garnered recognition through numerous awards at both national and international scientific conferences. He has also served as a Guest Faculty at North Guwahati College, Assam, India. Dr. Ghosh is a recipient of the prestigious CIRTA 2026 award from the Canadian Institutes of Health Research (CIHR), Government of Canada, and will be joining University of British Columbia (UBC), Vancouver, Canada, as a Postdoctoral Fellow, where he will continue his research on understanding the structure, function, and molecular mechanisms of transporter proteins in cardiac cells.

PHARMACY INDIA
Street No.-4, Dayalpuram, Khatauli, Muzaffarnagar, 251201
8171313561, 8006781759
pharmacyindia24@gmail.com
Pharmacyindia.co.in

NOW WE ARE AVAILABLE ON
Flipkart amazon

ISBN : 978-81-689235-1-5

PRICE:- ₹360.00/-