PHARMACEUTICAL INORGANIC AND ANALYTICAL CHEMISTRY

(THEORY)

Editors

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Neha Sharma
Nicky Kumar Jaiswal
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Finally, this book is dedicated to students, teachers, researchers, and professionals of pharmaceutical sciences. We sincerely hope that it will support their academic learning, strengthen their understanding of pharmaceutical analysis, and encourage further interest in the scientific principles that contribute to the quality, safety, purity, and effectiveness of medicines

- **Editors**

Meenu Beniwal, Neha Sharma, Nicky Kumar Jaiswal, Anshkumar Bhuva, Rimpy Hooda, Savneet Kailley

Preface

Pharmaceutical analysis and pharmaceutical inorganic chemistry form the backbone of pharmaceutical education and practice. A sound understanding of analytical principles, chemical behaviour, quality control, and therapeutic relevance is essential for pharmacy students. This book has been designed to present these concepts in a clear, systematic, and student-friendly manner.The content is organized into five units, beginning with pharmaceutical analysis, covering its scope, techniques, solution strength, standardization, errors, accuracy, precision, impurities, and limit tests. The second unit focuses on acid–base chemistry, pH, buffer systems, isotonicity, and physiological electrolytes, which are vital in formulation science. The third unit deals with volumetric analysis, including various titrimetric methods and their pharmaceutical applications. The fourth unit discusses gastrointestinal agents, antimicrobials, and radiopharmaceuticals, highlighting their properties, mechanisms, assays, and safety aspects. The fifth unit includes miscellaneous compounds such as haematinics, expectorants, poisons, and antidotes, linking chemistry with therapeutic use. A student-centered approach has been adopted with learning objectives, summaries, examples, and review questions. The language is kept simple yet scientifically accurate, ensuring conceptual clarity and practical relevance. This book is intended for students, teachers, and professionals in pharmaceutical sciences. We hope it will strengthen understanding, encourage scientific thinking, and support academic and professional growth in pharmacy.

- **Editors**

Meenu Beniwal, Neha Sharma, Nicky Kumar Jaiswal, Anshkumar Bhuva, Rimpy Hooda, Savneet Kailley

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UNIT I

INTRODUCTION TO PHARMACEUTICAL ANALYSIS

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Chapter 1

Learning Objectives

After studying this chapter, the student will be able to:

1. Define pharmaceutical analysis and explain its importance.
2. Describe the role of pharmaceutical analysis in drug development and quality assurance.
3. Classify various analytical techniques used in pharmaceutical sciences.
4. Explain different methods of expressing the strength of solutions.
5. Differentiate between primary and secondary standards.
6. Understand the preparation and standardisation of solutions.
7. Apply analytical concepts in pharmaceutical industries and research laboratories.

1.1 Introduction to Pharmaceutical Analysis

Pharmaceutical analysis is the study that focuses on the identification of drugs, their separation, determination and measurement, which is part of pharmaceutical sciences. It uses chemical, physicochemical, physical and instrumental approaches for quality assurance of pharmaceutical products based on their quality, purity, safety and effectiveness. The development, production and quality control of medicines are areas in which pharmaceutical analysis plays an important role. This can be used to detect impurities, to assess the quality of a formulation and to compare a formulation with the Indian Pharmacopoeia (IP). All the raw materials, intermediate products and dosage forms are analysed to ensure the quality of the product. Lastly, pharmaceutical analysis plays a crucial role

in the quality control and compliance process, ensuring the safety and efficacy of pharmaceutical products and ultimately, patient health.

1.2 Scope and Importance of Pharmaceutical Analysis

Pharmaceutical Analysis has tremendous applications in the pharmaceutical industry, Research Laboratories, Hospitals, regulatory agencies and Academic Institutions. Can be used for identification and quantification of active pharmaceutical ingredients (APIs), excipients, impurities and degradation products in pharmaceutical preparations. Analytical methods are essential in the drug discovery process, formulation development, quality control, stability and regulatory approval. Pharmaceutical analysis also plays a very significant role in the quality control of the raw material and the final product, to ensure compliance with the Pharmacopoeia.

Pharmaceutical Analysis is crucial because of the safety, efficacy, purity and quality of pharmaceuticals. It is important to detect contaminants, to keep away from adulteration and to ensure consistency with pharmaceutical products. Accurate analytical testing helps meet regulatory requirements and safeguard public health by ensuring that only safe and good-quality medicines are available to patients by delivering the information that is required. Hence, the study of pharmaceutical analysis is an indispensable part of present-day pharmaceutical science and healthcare.

1.3 Different Techniques of Analysis

Pharmaceutical analysis is a branch of science that is used to identify, characterise, separate and quantify pharmaceutical substances by various methods. Quality, purity, safety and effectiveness of medicines and pharmaceutical products are ensured with these techniques. The method of analysis will depend on the type of sample, accuracy required, sensitivity and purpose of analysis. The pharmaceutical product life cycle includes analytical techniques in drug discovery, Drug formulation, QC, Stability testing and Regulatory compliance. The wide variety of pharmaceutical analysis uses throughout the stages of drug development and quality assurance is depicted in Figure 1.1. Based on the application and principles, analytical methods are classified into chemical, physical, physicochemical and instrumental methods.

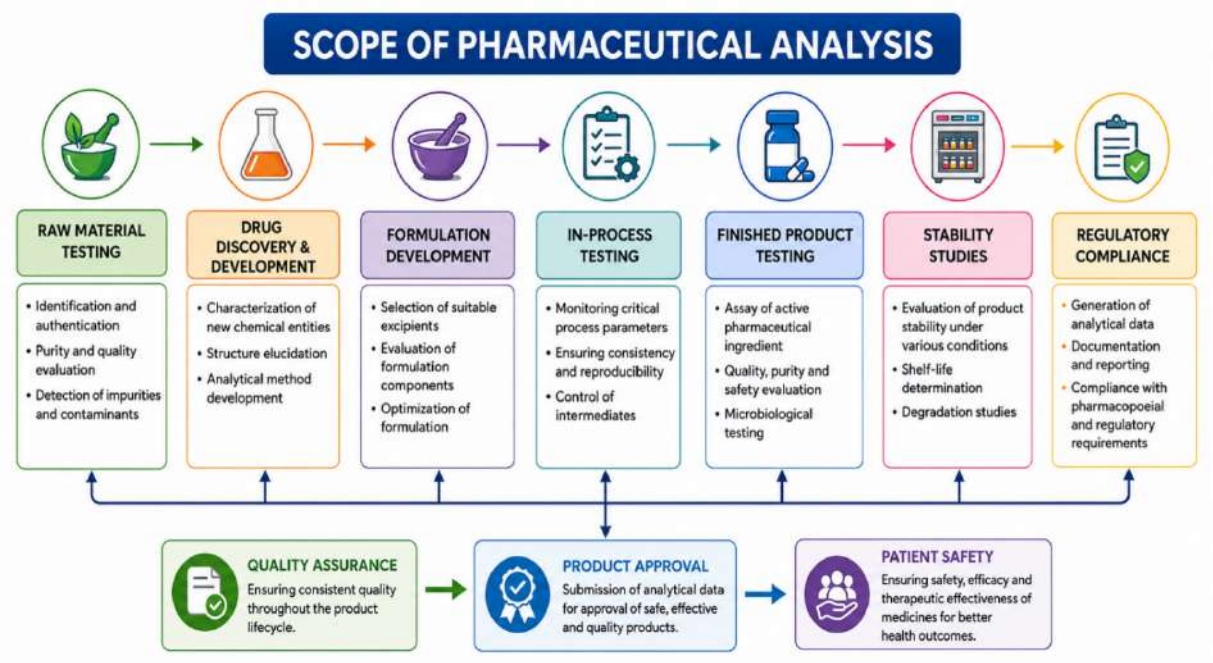


Figure 1.1 Scope of Pharmaceutical Analysis

1.3.1 Chemical Analysis

Chemical Analysis is based on a chemical reaction that takes place between the reagent added and the chemically constituent of the sample (analyte). It is one of the oldest and widely used qualitative and quantitative analysis methods in a pharmaceutical laboratory. Methods are based on a set of relationships between the amounts of the chemicals present in the reactions and being changed. These are typically acid-base, redox, precipitation and complexometric titrations. Chemical methods have the advantages of being simple, reliable and economical, and they can be used for routine quality control testing. They are widely employed in the pharmacopoeial assays and purity testing. Table 1.1 summarises the various types of analytical techniques, their major features, principles, examples and uses.

Table 1.1 Classification of Analytical Techniques

Analytical Technique	Principle	Common Methods/Examples	Major Applications in Pharmacy
Chemical Analysis	Based on chemical reactions between analyte and reagent	Acid–base titration, Redox titration, Precipitation titration, Complexometric titration	Assay of pharmaceutical substances, purity testing, and quality control

Physical Analysis	Based on the measurement of physical properties without chemical change	Melting point determination, Boiling point determination, Density measurement, Refractive index measurement	Identification and characterisation of drugs and excipients
Physicochemical Analysis	Combines physical measurements with chemical principles	pH measurement, Potentiometry, Conductometry, Polarography	Study of solution properties, stability testing, formulation development
Instrumental Analysis	Utilises sophisticated instruments for qualitative and quantitative analysis	UV-Visible Spectroscopy, IR Spectroscopy, HPLC, GC, Atomic Absorption Spectroscopy (AAS)	Quality assurance, impurity profiling, drug analysis, research,0 and development

1.3.2 Physical Analysis

Physical analysis involves the measurement of physical properties of a substance without causing any change in its chemical composition. These are helpful for information regarding the identity, purity and quality of pharmaceutical products. The physical properties that are usually measured are the melting point and boiling point, density, viscosity, refractive index and optical rotation. Physical methods are generally quick, easy and harmless and are suitable for routine testing and preliminary investigations. These are very simple to prepare, and can provide results fairly quickly. In the field of quality control, physical analytical techniques are widely employed in drug product laboratories for the analysis of raw materials, intermediates and pharmaceutical products. The classification of the various analytical methods is shown in Figure 1.2, in relation to their location.

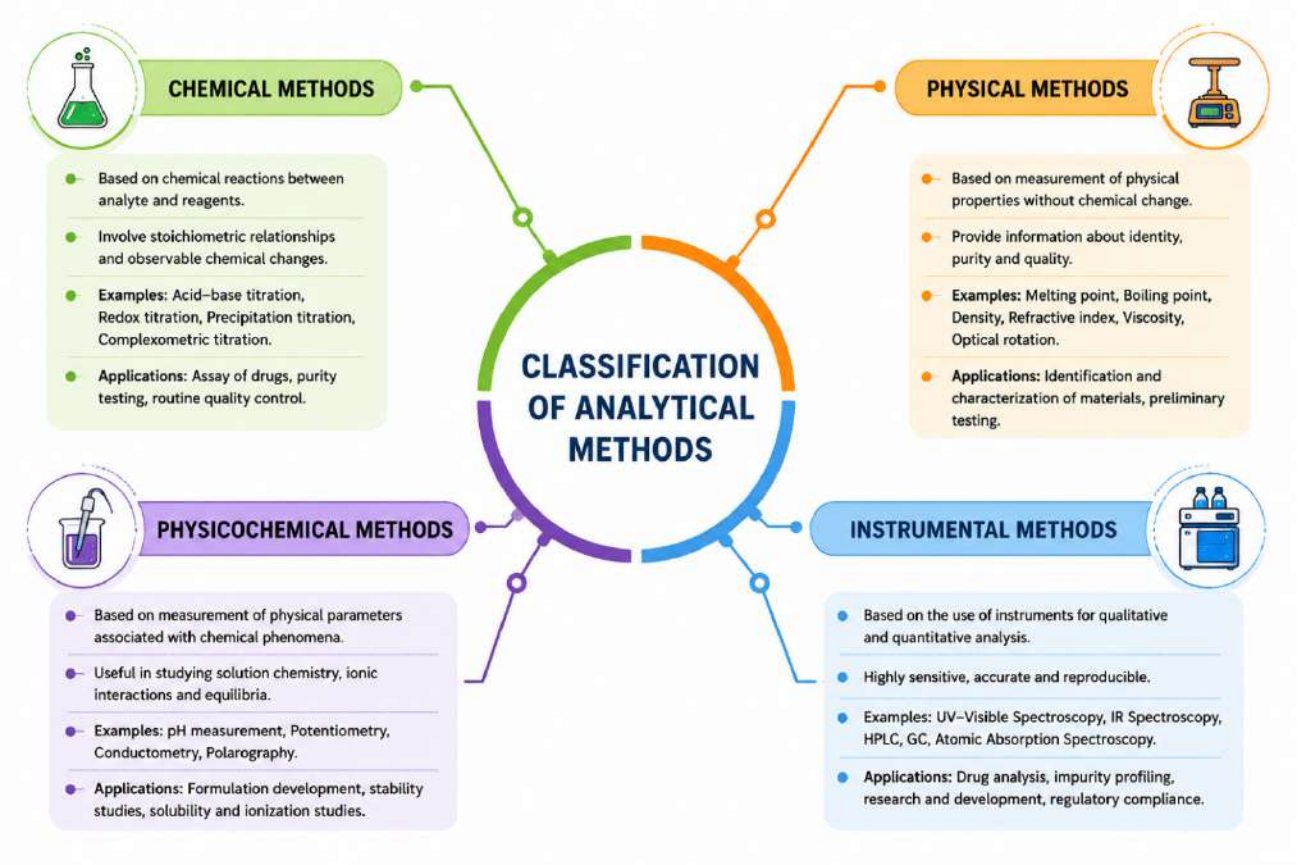


Figure 1.2 Classification of Analytical Methods Used in Pharmaceutical Analysis

1.3.3 Physicochemical Analysis

Physicochemical analysis is the study that uses both physical and chemical science to study the properties and reactions of therapeutic agents, and chemical analysis is the study of the properties and reactions of therapeutic agents using chemical science. They are techniques that are typical of what seem to be physical changes in the context of chemical phenomena, but are more applicable for studying solution chemistry and ionic interactions. Physicochemical methods have reproducible and accurate results and are also widely utilised in the formulation development and evaluation of pharmaceuticals. These are: pH measurement, potentiometry, conductometry and polarography. The methods can be used for the study of the stability, solubility and chemical properties of a drug under different conditions. Chemical Physochemical Techniques are important due to their versatility and reliability, and they play an important bridge between the conventional chemical techniques and advanced instrumental analytical techniques.

1.3.4 Instrumental Analysis

The use of complex analytical instruments is called instrumental analysis, that would yield highly sensitive, accurate and reproducible results. They are very useful for the detection and determination of minute amounts of substances and are important in today's pharmaceutical industries. The benefits

of instrumental techniques are: high-precision, Quick Analysis, automation, and low human error. They are widely employed for research, quality control, stability testing and regulatory affairs. They are frequently performed using instrumental techniques like ultraviolet-visible spectroscopy, infrared spectroscopy, high-performance liquid chromatography, gas chromatography and atomic absorption spectroscopy. These methods are applied systematically in pharmaceutical testing and quality assurance; this can be shown in the application of Figure 1.3. The techniques of instrumental analysis have improved the efficiency and reliability of pharmaceutical analytical procedures to a great extent.

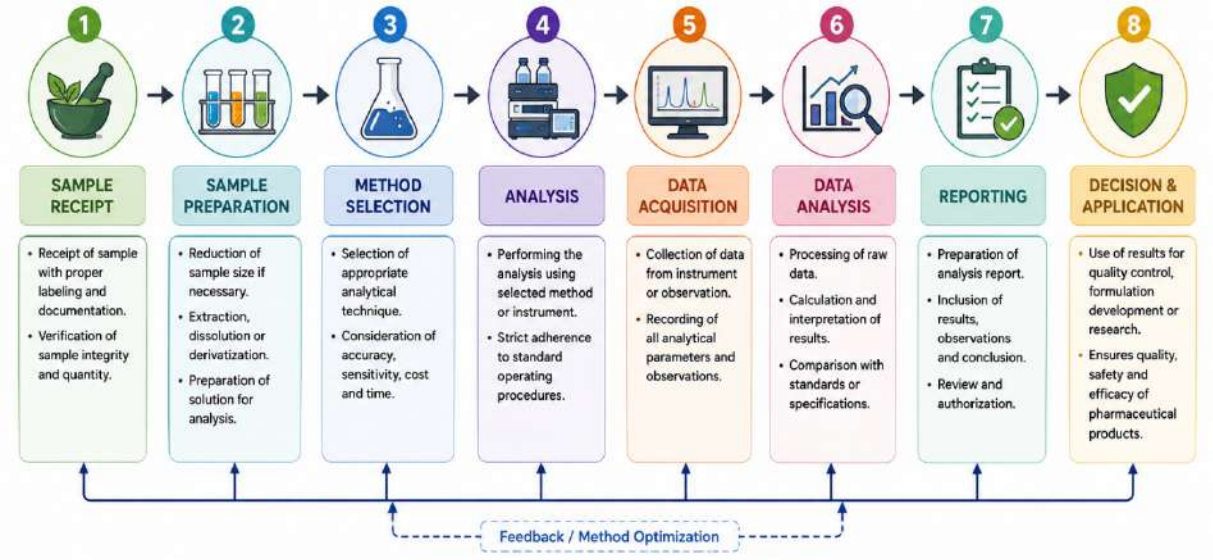


Figure 1.3 Workflow of Pharmaceutical Analysis

1.4 Methods of Expressing Strength of Solutions

The strength of a solution is the amount of solute in a certain amount of solvent or solution. In pharmaceutical analysis, the concentration of a solution is necessary to ensure the preparation of pharmaceutical formulations, in analytical testing and in determining dosages. Various techniques are used depending on the contents of the solute, solvent and the analysis desired. The different units of measurement of solutions are: percentage strength, ratio strength, parts per million (ppm), molarity, molality and normality. All the methods have different representations of concentration and are extensively used in pharmaceutical calculations, quality control and research. The strength of a solution is described accurately, consistently and precisely for use in the pharmaceutical industry.

1.4.1 Percentage Strength

The concentration of a solute in 100 parts of solution is called the percentage strength of the solute. A very popular way of indicating the concentration of pharmaceutical preparations. Percentage strength can be indicated as weight per volume (w/v), volume per volume (v/v) or weight per weight (w/w). For example, 5% w/v glucose means that there are 5g of glucose in every 100ml solution. It is a procedure that is simple, convenient and easy to understand and can be used in common

pharmaceutical applications. Syrups, lotions, injections and topical products are many types of formulations that use percentage strength. It is a good immediate indicator of the concentration and can accurately be used to serialise the preparation and dispensing of pharmaceutical products.

1.4.2 Ratio Strength

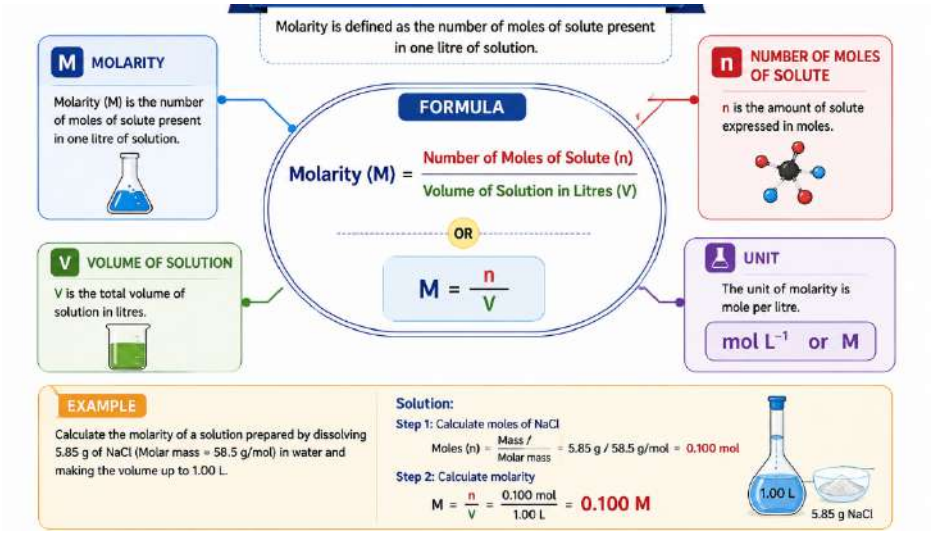
The strength of a solution is indicated by the ratio of one part of solute to a given number of parts of solution and is called the ratio strength. Represented by 1 in n or 1. For instance, 1:1000 is a strength solution ratio of 1g/1000mL. The ratio strength is convenient, but the percentage strength may be inconvenient with very dilute solutions. It is a technique that is commonly used in pharmaceutical formulations that contain strong medicines, preservatives, disinfectants and antiseptics. A ratio of strength is used to easily represent low concentrations, and to easily compare dilute solutions with one another. Still an important concentration expression technique in pharmaceutical calculations and compounding skills.

1.4.3 Parts per Million (ppm)

Parts per million (ppm) is used as a unit to measure small amounts of a substance in a solution. It is equal to 1 number of solute molecules per 1 million number of molecules of solution. 1 ppm is roughly 1mg of the solute in 1 litre of solution in an aqueous solution. Where ppm is very useful in measuring trace levels of impurities, contaminants and residual substances is in pharmaceutical products, water samples, and environmental analyses. ppm is a useful and convenient unit of measurement often used to report the levels of substances in pharmaceutical quality requirements, which often require detection of very low levels of substances. It's very common in impurity profiling, water quality monitoring and regulatory compliance studies.

1.4.4 Molarity

Molarity is one of the common ways of stating the concentration of a solution in pharmaceutical and chemical analysis. The concentration of the solution in terms of the number of moles of solute in 1 litre of the solution is called molarity [M] and is applied only to quantitative analysis and calculations involving the mole ratio. Molality is very commonly used in volumetric analysis, assay procedures, quality control in pharmaceutical industries, to prepare standard solutions, etc. The molarity is determined by the volume of the solution, and so will change if solvents are present and the volume of the solution changes with temperature. The relationship between molarity and the relationship is indicated below:



1.4.5 Molality

The molality of the solute is the number of moles of solute in 1kg of solvent. It is denoted by the symbol m and is related to molarity only in that it is based on the mass of the solvent, not the volume of the solution. The molality remains constant when there is a change in temperature because mass is not affected. This property can be used in the study of colligative properties such as freezing point depression and boiling point elevation. This is because concentration measurements at various temperatures are often required in physical pharmacy and solution chemistry, and molality is used frequently in such applications. It is not so often used in routine pharmaceutical analysis as the molarity method, but it does provide a very accurate means of concentration measurement – particularly in research and other specialist applications.

1.4.6 Normality

The number of moles of the solute per litre of solution is called the normality. The chemical symbol N, it is used in volumetric analysis, such as acid-base analysis, oxidation-reduction analysis, precipitation analysis, etc. Normality is a reaction-specific term as it refers to the equivalent weight of a substance, which is different depending on the type of reaction. For instance, 1 litre of 1 N hydrochloric acid solution contains 1 gram equivalent of hydrochloric acid. Normality is directly proportional to the reacting capacity of the substances, and makes the calculations of chemical reactions easier. Normality is still used in pharmaceutical analysis and pharmacopoeial assay methods, but molarity is becoming more common in modern analytical chemistry.

1.5 Standard Solutions

A solution with a precisely determined concentration which is not influenced by particular conditions. Standard solutions are also very useful in pharmaceutical analysis, particularly in volumetric analysis, because they are used in determining the concentration of an unknown solution. The accuracy of the

analytical results is greatly influenced by the proper preparation and standardisation of standard solutions. Solutions are made from materials of known purity and concentration and are often utilised in assay procedures, quality control tests and in pharmaceutical research. Based on the purity and stability of the substance used to prepare the standard solution, standard solutions can be roughly divided into primary and secondary.

1.5.1 Primary Standards

Definition

A Primary standard is a substance that is pure, is not hygroscopic, has a high degree of stability and can be directly weighed, which can be used to prepare a solution of accurately known concentration. The secondary standard solutions are prepared and standardised using primary standard solutions. They are highly pure and stable, hence give very accurate analytical results, and they are also employed as the reference substances in volumetric analysis.

Characteristics

There are some desirable properties of a primary standard. It must be chemically stable, non-hygroscopic and available in high purity. It should have a comparatively high molecular weight, so as to decrease the error of measurement of the weight, and should be easily soluble in the solvent chosen. Also, it should be completely and stoichiometrically reacted with the analyte during the analysis. These properties allow for the preparation of solutions at a known concentration and help to make analytical results more reliable.

Examples

Sodium carbonate (Na_2CO_3), Potassium hydrogen phthalate (KHP), Oxalic acid, Potassium dichromate ($K_2Cr_2O_7$) and Arsenic trioxide (As_2O_3) are all primary standards. They are standardised in the pharmaceutical industry to standardise acids, bases, oxidising and reducing agents.

1.5.2 Secondary Standards

Definition

A substance whose concentration in a solution must be determined by using a primary standard. Secondary standards are less pure or less stable than primary standards and need to be periodically restandardized to ensure their accuracy.

Characteristics

Secondary standards have the ability to absorb water or react with atmospheric gases, or to chemically change during storage. These are generally less pure than primary standards, and are not as pure. So a primary standard should be used to determine a precise concentration, which is not possible using direct measurement. The disadvantages listed above are not important, and the secondary standard is used for routine analytical work due to its convenience and availability.

Examples

Common secondary standards are hydrochloric acid (HCl), sodium hydroxide (NaOH), potassium permanganate ($KMnO_4$), silver nitrate ($AgNO_3$) and solution of iodine (I_2). These solutions are then standardised in primary standardisation, for use as titrants in pharmaceutical and chemical analysis.

1.6 Preparation of Standard Solutions

Pharmaceutical analysis is an important process of which the standard solutions are an important part and are used as reference standards in quantitative analytical methods. The common method is to accurately weigh a known amount of pure substance, then dissolve it in a suitable solvent (usually distilled or deionised water) to obtain a definite volume of standard solution. The first step in the preparation is to choose an appropriate primary or secondary standard. The needed quantity of the substance is precisely weighed on an analytical balance and placed into a volumetric flask. It is then completely dissolved in a small amount of solvent, and the volume of the solvent is adjusted to the calibration mark of the flask. The mixing will lead to the uniformity of concentration of the solution. Secondary standards can be used only to prepare a standard solution of a primary standard to determine the exact concentration. In pharmaceutical analysis, standard solutions should be stable and reliable, and precautions should be taken for their storage, handling and accurate measurement.

1.7 Pharmaceutical Applications

Standard solutions are commonly used in a variety of applications such as research, pharmaceutical analysis, quality control and manufacturing processes. They are mainly employed for the determination of the concentration, purity and potency of pharmaceutical substances in volumetric analysis. Standard solutions are the solutions used to get quantitative results in acid-base, redox, precipitation and complexometric titrations. The pharmaceutical industries use these for regular quality control testing of raw materials, intermediates and finished products. The standard solutions are also used in the following methods of assay given in the Pharmacopoeia, such as the Indian Pharmacopoeia (IP), British Pharmacopoeia (BP) and United States Pharmacopoeia (USP). They are used in research laboratories for method development, validation and calibration of the analytical instrument. In addition, the standard solutions are critical for stability testing, impurity testing and regulatory compliance testing. Ensuring that pharmaceutical products are safe, effective, of good quality and consistent is one of the essential components of good preparation and use.

Chapter Summary

Pharmaceutical analysis is one of the disciplines of pharmaceutical science, which deals with the identification, separation, characterisation and quantitation of pharmaceutical substances. Very important process in drug/Pharmaceutical products quality, safety, efficacy and purity. For pharmaceutical testing and quality control, various analytical methods are used such as chemical, physical, physicochemical and instrumental. Solutions can be expressed in terms of strengths in many different ways, including percentage strength, ratio strength, parts per million (ppm), molarity, molality and normality. A standard solution is very important in quantitative analysis, and based on the purity and stability of the solution, it can be classified as a primary standard solution or a secondary standard solution. The level of accuracy of the analytical result is related to the correct preparation and standardisation of solutions. Pharmaceutical analysis is a fundamental component of pharmaceutical practice and is applied during the development of a drug, in stability studies, for routine quality control, regulatory affairs and in quality control.

Key Points

- Pharmaceutical analysis deals with the identification, separation, and quantification of pharmaceutical substances.
- It ensures the quality, safety, purity, and efficacy of medicines.
- Analytical techniques are classified into chemical, physical, physicochemical, and instrumental methods.
- Percentage strength, ratio strength, ppm, molarity, molality, and normality are common methods of expressing solution concentration.
- Primary standards are highly pure substances used to prepare standard solutions directly.
- Secondary standards require standardisation against primary standards.
- Standard solutions are essential for volumetric and quantitative analyses.
- Proper preparation and storage of standard solutions are necessary for accurate results.
- Pharmaceutical analysis is widely used in quality control, research, and regulatory testing.
- Accurate analytical methods contribute to patient safety and product quality.

Review Questions

Short Answer Questions

1. Define pharmaceutical analysis.

2. Discuss the importance of pharmaceutical analysis in quality control.
3. Classify analytical techniques used in pharmaceutical analysis.
4. Define percentage strength with an example.
5. What is ratio strength?
6. Explain the term parts per million (ppm).
7. Define molarity and state its unit.
8. Differentiate between molarity and molality.
9. Define normality.
10. What is a standard solution?
11. Define primary standard.
12. Define secondary standard.
13. Mention four characteristics of an ideal primary standard.
14. Give two examples each of primary and secondary standards.
15. Explain the significance of standard solutions in pharmaceutical analysis.

Long Answer Questions

1. Discuss the scope and importance of pharmaceutical analysis.
2. Describe different analytical techniques used in pharmaceutical analysis.
3. Explain various methods of expressing the strength of solutions.
4. Differentiate between primary and secondary standards with suitable examples.
5. Describe the preparation of standard solutions.
6. Discuss the pharmaceutical applications of standard solutions.

Multiple Choice Questions (MCQs)

1. Pharmaceutical analysis is primarily concerned with:

A. Drug marketing

B. Drug packaging

C. Identification and quantification of drugs

D. Drug pricing

Answer: C

2. Which of the following is an example of chemical analysis?

A. HPLC

B. Acid-base titration

C. UV spectroscopy

D. Refractometry

Answer: B

3. The concentration expressed as grams of solute in 100 mL of solution is known as:

A. Ratio strength

B. Molarity

C. Percentage strength

D. Normality

Answer: C

4. A ratio strength of 1:1000 means:

A. 1 g in 100 mL

B. 1 g in 1000 mL

C. 1000 g in 1 mL

D. 10 g in 1000 mL

Answer: B

5. One ppm is approximately equal to:

A. 1 g/L

B. 1 mg/L

C. 100 mg/L

D. 10 mg/L

Answer: B

6. Molarity is defined as:

A. Gram equivalents per litre of solution

B. Moles per kilogram of solvent

C. Moles per litre of solution

D. Grams per litre of solvent

Answer: C

7. Molality is expressed as:

A. Moles per litre of solution

B. Moles per kilogram of solvent

C. Equivalents per litre

D. Grams per litre

Answer: B

8. Which of the following is a primary standard?

A. Sodium hydroxide

B. Hydrochloric acid

C. Potassium hydrogen phthalate

D. Potassium permanganate

Answer: C

9. Which of the following is a secondary standard?

A. Sodium carbonate

B. Oxalic acid

C. Potassium dichromate

D. Sodium hydroxide

Answer: D

10. Standard solutions are mainly used in:

A. Volumetric analysis

B. Drug packaging

C. Tablet coating

D. Sterilization

Answer: A

Chapter 2: Errors in Pharmaceutical Analysis

Learning Objectives

After studying this chapter, the student will be able to:

- Define errors in pharmaceutical analysis.
- Explain the various sources of analytical errors.
- Classify errors into determinate, indeterminate, and gross errors.
- Differentiate between accuracy and precision.
- Discuss methods used to minimize analytical errors.
- Apply error control measures in pharmaceutical analysis and quality control.

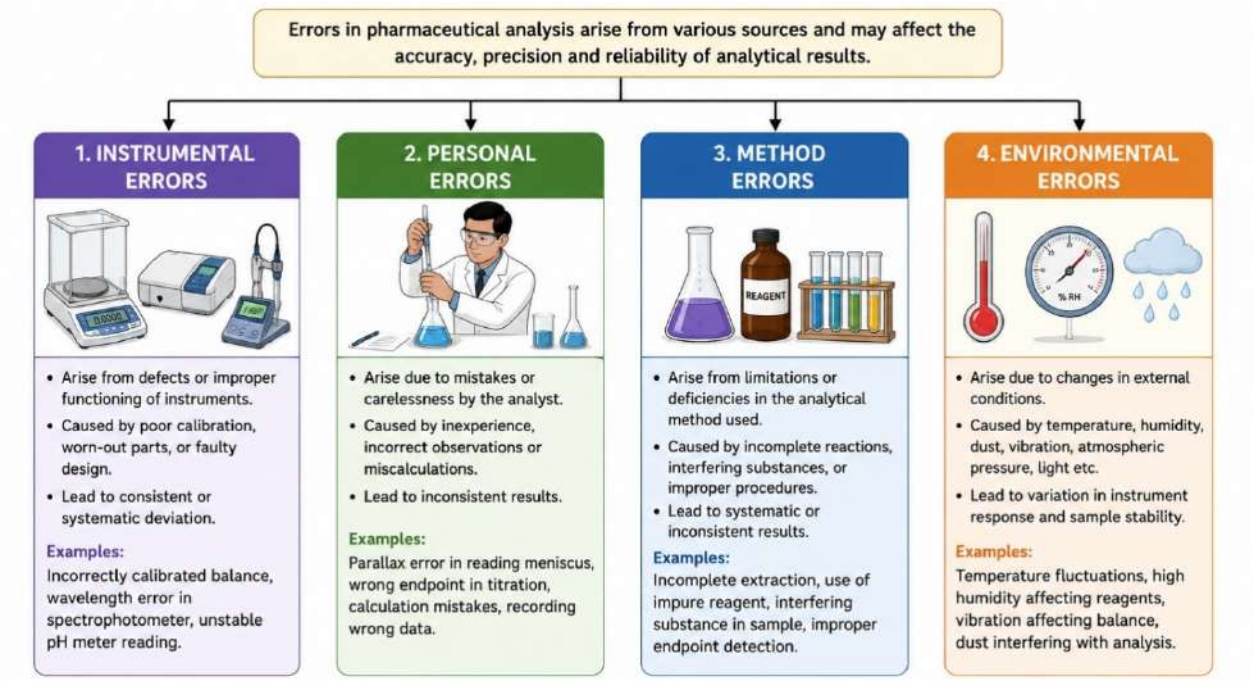
2.1 Introduction

Errors are normal variations that occur when making an analytical measurement and lead to a result that varies from the accepted or true value. Errors can affect both the accuracy and precision of analytical results in pharmaceutical analysis and the reliability and reproducibility of these results. Pharmaceutical products must adhere to several quality specifications and therefore, knowledge and control of error are of paramount importance for the quality and validity of the analytical data. There can be errors related to the instruments, analysts, analytical methods, or the environment. If found in pharmaceutical products, they can lead to misidentification, mispurity or, misstrength or to misquality of the substance. Thus, the analyst should identify the possible sources of errors and take appropriate steps to correct the errors. As illustrated in Figure 2.1, there are many sources of analytical errors that can occur. Understanding and characterisation of errors can help to improve the reliability of pharmaceutical testing and its compliance with pharmacopoeial and regulatory requirements.

2.2 Sources of Errors

Analytical error can occur in the process of measurement in a number of ways. If not properly controlled, these sources can lead to errors and inaccuracies in the results obtained from the analysis. The errors can be caused by an instrumental error, a human error, an error due to the limitations or change of the analytical method or of the environmental conditions. When you can determine the source of an error, you can take action to avoid that error in the future and improve your analysis. They are detected and reduced in the pharmaceutical industry by quality assurance in the quality control laboratory. In pharmaceutical analysis, there are the main errors in analysis as shown in Figure 2.1. The calibration of the instruments, as per the standard operating procedure, training of analysts

and environmental control are important to minimise analytical errors and to make the pharmaceutical testing accurate and precise.



2.2.1 Instrumental Errors

Instrumental error is because of an imperfection, failure or miscalibration of the analytical equipment. The errors might be due to wear and tear, a malfunctioning component, setting errors or lack of maintenance of the instrument, which may also cause inaccuracy in measurement. Typical errors involve errors in balancing the pH meter, drift of the pH meter and/or volumetric glassware error with the wavelength. Inaccuracies in the use of instruments can cause bias in the analytical measurement results, and can have a great impact on the validity of the pharmaceutical testing process. To minimise such errors, instruments should be regularly calibrated, maintained and qualified for their use. Pharmaceutical product manufacturers have regular schedules of calibration and validation that are conducted in their laboratory to ensure that the instruments are accurate. Routine quality control and the use of certified reference standards also lower instrumental error prior to its influencing analytical results.

2.2.2 Personal Errors

Errors that the analyst makes when performing an analytical procedure are called personal errors. The mistakes may be made because of carelessness, inexperience, misobservations, handling of the equipment or data entry. Analytical variability is one of the most common in a pharmaceutical laboratory and may be due to personal errors such as reading the volume on the burette incorrectly, misreading the colour change at the end point of a titration or making calculation errors, transposition, etc. Proper training, establishing a standard working procedure, observation and regular monitoring can help to avoid errors. When analysing, the analyst should concentrate on his/her work and verify all calculations prior to reporting. Such personal errors can be reduced by good laboratory practice and by the process of continual professional development so that the quality of the analytical data is enhanced.

2.2.3 Method Errors

A method error is due to limitations and flaws of the analytical method employed. The errors can be attributed to the method used, which may not be accurate under the specified conditions. Method errors can be due to incomplete chemical reactions, presence of interfering substances, reagent impurities, incomplete extraction, and lack of detection of the endpoint. These errors are likely to produce a systematic error from the true value, and may impact the analytical result. Before the application of the method, it is necessary to validate it to guarantee the accuracy, precision, specificity, robustness and repeatability of the method. An appropriate method development and validation can lead to a validated analytical procedure that is suitable for its intended use. Validation of the methods is required to satisfy the requirements of pharmacopoeia and regulatory requirements, and to demonstrate the need for the accuracy and reliability of the analytical method for performing a pharmaceutical analysis.

2.2.4 Environmental Errors

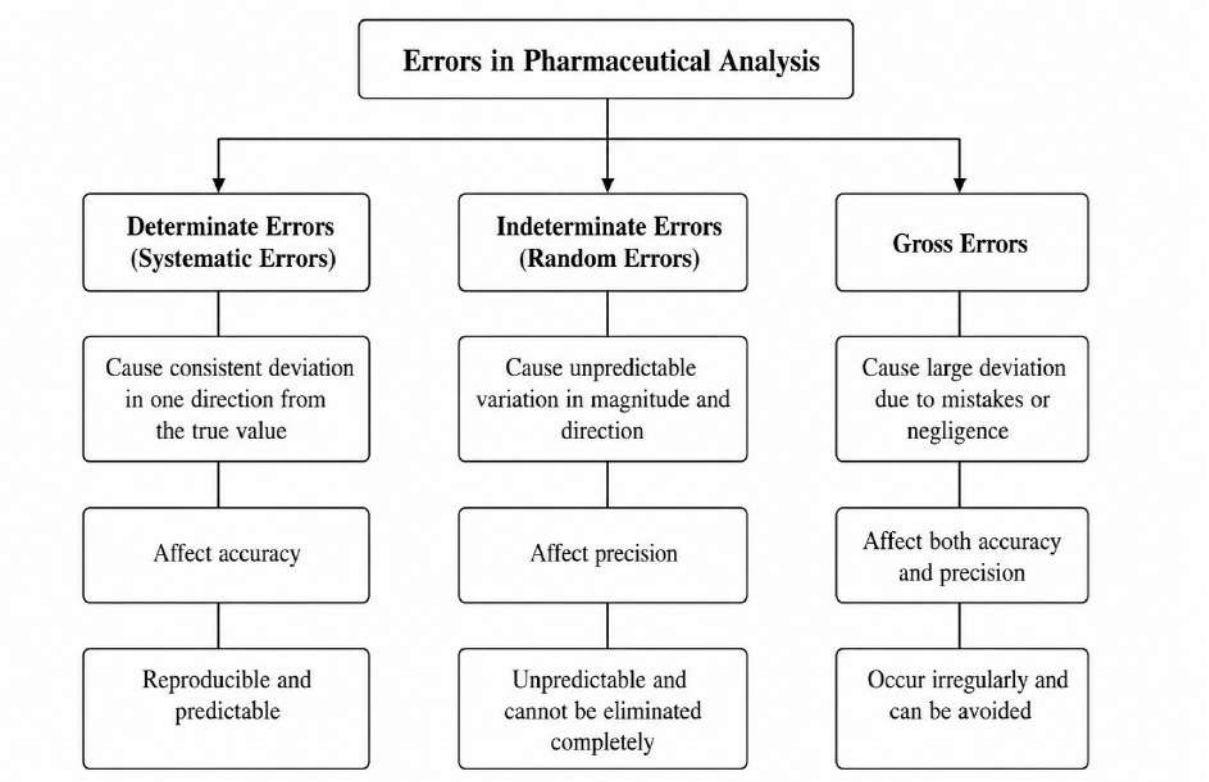
Errors that are due to external factors that affect the analysis's measurement are called environmental errors. The accuracy of analytical instruments or the stability of samples or reagents can be affected by weather conditions (such as temperature, humidity, air pressure, dust, vibrations, electromagnetic interference, lighting). Changes in temperature can bring about changes in the volume of the solution, for example, and too much humidity can bring about a change in hygroscopic substances, for example. Analytical measurements can be affected by environmental factors that can introduce variability and affect the accuracy of the results. Pharmaceutical laboratories are working to reduce the number of such mistakes by controlling problems that might cause the mistake, such as air-conditioning systems, humidity systems, vibration-free workstations and cleanroom facilities. The analytical procedures are carried out under standard conditions, with periodic checks of the laboratory conditions. The significance of the laboratory environment in relation to the acquisition of accurate, precise and reproducible analytical results cannot be overemphasised.

2.3 Types of Errors

Analytical errors may have different types depending on their source, the type and impact on the analytical result. The types of errors classified will help to pinpoint the source of the errors and the corrective actions to take. There are 3 types of pharmaceutical analysis errors: determinate, indeterminate and gross errors. In Fig. 2.2, this classification is denoted. Different types of errors have differing impacts and need to be approached in different ways to detect and control. It is important to understand these types of errors so that the reliability, accuracy and precision of pharmaceutical testing can be improved. Table 2.1 provides an example of some of the types and sources of Analysis Errors:

Table 2.1 Classification of Errors in Pharmaceutical Analysis

Type of Error	Definition	Source/Cause	Effect on Results	Examples
Determinate Errors (Systematic Errors)	Errors that occur predictably and consistently, causing results to deviate in one direction from the true value.	Faulty instrument calibration, contaminated reagents, procedural mistakes, environmental influences.	Affect the **accuracy** of results.	Incorrect calibration of a balance, impure reagent, improperly standardized solution.
Indeterminate Errors (Random Errors)	Errors that occur unpredictably and vary in both magnitude and direction during repeated measurements.	Small uncontrollable variations in experimental conditions, instrument response, or analyst observation.	Affect the **precision** of results.	Slight variation in burette readings, fluctuations in instrument signals, endpoint estimation differences.
Gross Errors	Large errors caused by human negligence, carelessness, or mistakes during analysis.	Improper weighing, incorrect calculations, transcription errors, misuse of instruments.	Significantly affects both the **accuracy and precision** of results.	Recording wrong data, using incorrect reagent, misplacing decimal points in calculations.



2.3.2 Indeterminate Errors

Indeterminate errors (random errors) have random sizes, signs and vary from one measurement to the next. These errors occur due to factors that are beyond the control of the experimenter, instrument performance or human observation. Random errors differ from systematic errors because they will not be removed, but can be minimised by making repeated measurements and applying statistics. Indeterminate errors, if they were to be the major cause, would be caused by errors in the analytical results, rather than errors of precision. Random errors tend to be normally distributed around the true value and are small. Random errors are evaluated and managed in pharmaceutical analysis using statistical techniques like mean, standard deviation and confidence intervals. Proper laboratory practices and repeated analyses lead to greater measurement accuracy and minimisation of the effects of indeterminate errors.

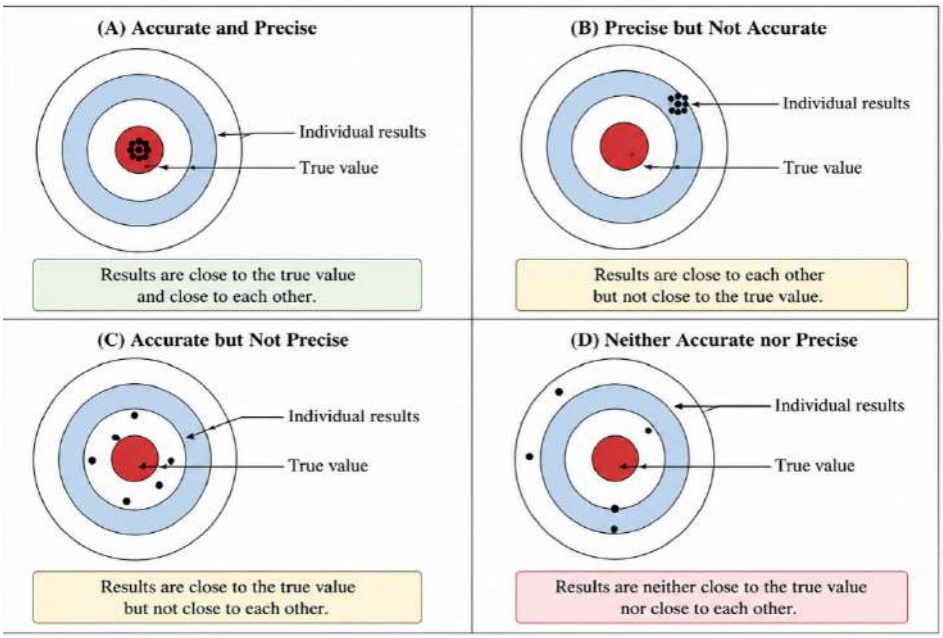
2.3.3 Gross Errors

There are gross errors that are large errors and are usually caused by carelessness or negligence by humans in the analysis procedure. These errors may arise due to weighing errors, sample preparation errors, calculation errors, transcription errors or incorrect use of analytical instruments. Numbers which grossly deviate from the expected value will be much further from the other numbers and will be easily recognised as being "outliers. Gross errors are not normal, and may significantly affect the validity of the analytical data. These are alleviated with lab procedures, documentation, double

checking and adherence to SOP's. Such errors can be minimised by training and supervision of laboratory staff and by the quality and integrity of the analytical results of pharmaceuticals.

2.4 Methods of Minimising Errors

Reducing any analytical error and obtaining accurate, precise and reliable results is very important in the pharmaceutical analysis field. Multiple steps would be performed that would minimise the risk of errors in the analytical procedures and minimise error if they were to occur. The instruments need to be kept in good condition and should be calibrated, validated and tested regularly to ensure that they operate accurately. Analysts should follow standard operating procedures, ensure proper documentation and be properly trained to minimise personal errors. Method-related errors are minimised by the use of analytical methods and high-purity reagents. Proper care of environmental factors, such as temperature, humidity and cleanliness, is important as they can affect the measurement.Analytical reliability is further ensured by replication of analyses, statistical evaluation of the results and quality control checks. Accuracy and precision in analytical measurements have a relation as shown in fig 2.3. These will contribute to the reduction of analytical errors at the pharmaceutical laboratories and enable them to meet regulatory and pharmacopoeial requirements.



2.5 Accuracy

The degree of correctness of a measured value is the degree of conformity of a measured value with a value known or accepted. It is a comparison of the analytical result with the true value of the analyte measured. Another crucial parameter in the pharmaceutical analysis is precision, which guarantees trustworthiness and validity of the analytical data for quality control, research, and regulatory requirements. A True Analytical Method produces results that are in reasonable agreement with the

true concentration, purity or potency of a pharmaceutical substance. Systematic errors could occur because of the incorrect calibration of the instruments, contaminated reagents, incorrect analytical procedures, or environmental influence. In order to ensure high accuracy, pharmaceutical laboratories use certified reference standards, standard operating procedures, instrument calibration and method validation. The per cent recovery or per cent error is typically used to express the accuracy of an analytical method. Measurement is an essential requirement for pharmaceutical products to guarantee their quality, safety and effectiveness, and reliable analytical results rely on accurate measurement.

2.6 Precision

Precision is a measure of how close each of the measurements is to the average of the repeated measurements, obtained under identical conditions of analysis. It does not indicate the nearness of analytical results to the true value but indicates the reproducibility of the results and consistency in results. With a precise method, extremely similar results will be obtained if the same sample is analysed more than once. Random, or indeterminate errors refer to errors that primarily impact precision and are due to small variations in the experimental conditions, instrument performance, reagent characteristics and/or observations made by the analyst. The accuracy of pharmaceutical analysis is judged with statistical parameters like standard deviation, variance and relative standard deviation (%RSD). Repeatability, intermediate precision or reproducibility are all possible ways to measure the precision of a measurement depending on the context of the measurement. High precision is high consistency and high reliability of an analysis method. Precision is not always the same as accuracy, but it is required in order to be accurate, and accuracy is required to have reliable analytical results. Hence, precision is one of the important parameters for the evaluation of the quality and performance of analytical procedures in pharmaceutical laboratories.

2.7 Significant Figures

Significant figures give information about the precision and accuracy of a measured quantity. All of them contain each of the specified digits, as well as the first digit that was drawn when measuring, which was not specified. In pharmaceutical analysis, the number of significant figures might be of value since the precision of the method employed for the experiment should be indicated by the precision of the analysis result, and the precision of the instrument used to measure the quantity should also be indicated by the precision of the result of the analysis. It can be tempting to report more digits than indicated by the measurement or fewer digits, not to mention valuable information, than indicated by the measurement. In a calculation involving weight, volume, concentration, assay or other analytical measurement, significant figures are used. Data are reported to a significant level to make them consistent, reliable and scientifically meaningful. The number of significant places to report in the answer is the lowest number of places in the numbers used in the calculation. By

correctly applying and understanding the significant figure rule, analysts can effectively communicate analytical information and also prevent errors in pharmaceutical calculations and quality control.

Rules of Significant Figures

The following rules are used to determine the number of significant figures in a measured value:

1. **All non-zero digits are significant.**
   Example: 248.7 contains **4 significant figures**.
2. **Zeros between non-zero digits are significant.**
   Example: 1008 contains **4 significant figures**.
3. **Leading zeros are not significant.**
   Example: 0.0045 contains **2 significant figures**.
4. **Trailing zeros to the right of a decimal point are significant.**
   Example: 15.600 contains **5 significant figures**.
5. **Trailing zeros in whole numbers without a decimal point may or may not be significant.**
   Example: 2500 may contain **2, 3, or 4 significant figures**, depending on the notation used.
6. **Exact numbers and defined quantities have an unlimited number of significant figures.**
   Example: 60 minutes = 1 hour.

Rounding-Off Rules

Rounding off is the process of reducing the number of digits while retaining the desired level of accuracy and precision.

1. **If the digit to be removed is less than 5, the preceding digit remains unchanged.**
   Example: 4.372 → 4.37
2. **If the digit to be removed is greater than 5, the preceding digit is increased by one.**
   Example: 7.486 → 7.49
3. **If the digit to be removed is 5 followed by non-zero digits, the preceding digit is increased by one.**
   Example: 8.2556 → 8.26
4. **If the digit to be removed is exactly 5 with no following digits, round to the nearest even number.**
   Example: 6.25 → 6.2
   Example: 6.35 → 6.4

5. **Rounding should be carried out only after completing all calculations to minimize cumulative errors.**

Proper application of significant figures and rounding-off rules improves the accuracy, consistency, and reliability of pharmaceutical analytical results.

2.8 Applications in Pharmaceutical Analysis

Errors, accuracy, precision and significant figures are simple concepts in pharmaceutical analysis and are a factor in the reliability of analysis. These are used in the pharmaceutical laboratories to analyze raw materials, intermediates and finished pharmaceutical products. A parameter of analytical method validation is accuracy and precision, which are important parameters to determine the suitability of the analytical method used. Error analysis can help the researcher identify the reasons for the differences and what they must do to improve the quality of the data. Significant figures and rounding-off rules give precision and do not assert more precision in the results of the analysis than is warranted. The concepts can also be utilized in assay, impurity testing, QC testing and stability testing, as well as dissolution testing. Pharmaceutical products cannot be marketed unless the analytical results are accurate, precise and scientifically valid. Therefore, it is important to understand and use these principles to ensure the quality of the product, compliance with regulations, and patient safety.

Numerical Problems

Problem 1

A pharmaceutical analyst obtained the following assay results for a drug sample: 99.8%, 100.2%, and 100.0%. Calculate the mean value.

Solution:

Mean = (99.8 + 100.2 + 100.0) / 3

Mean = 300.0 / 3

Mean = **100.0%**

Problem 2

The true value of a sample is 50.0 mg, while the experimentally measured value is 49.5 mg. Calculate the absolute error.

Solution:

Absolute Error = True Value − Measured Value

Absolute Error = 50.0 − 49.5

Absolute Error = **0.5 mg**

Problem 3

Round off the value 18.756 to two decimal places.

Solution:

Since the third decimal digit is 6 (>5), increase the second decimal digit by one.

Rounded Value = **18.76**

Problem 4

Determine the number of significant figures in the value 0.003450.

Solution:

Leading zeros are not significant.

Digits 3, 4, 5, and the trailing zero after the decimal are significant.

Number of significant figures = **4**

Problem 5

A balance gives the following readings for the same sample: 5.01 g, 5.00 g, 5.02 g, and 5.01 g. Does the data indicate good precision?

Solution:

The values are very close to each other with minimal variation.

Therefore, the measurements demonstrate **good precision**.

Chapter Summary

Errors – any deviation from the analytical measurement which is not avoidable and could affect the reliability of the analytical results. These errors may be in the instrument, the analyst, the analytical procedure or the environment. The errors of analysis can be of three types: determinate error, indeterminate error and gross error. If they are aware of the types of errors and their causes, they are able to minimise the errors and improve data quality. Accuracy is the degree of agreement between the result obtained and the actual value, while precision is the degree of agreement of repeated measurements. The results of an analysis can be presented in an appropriate way based on the number of significant figures and rounding as appropriate depending on the degree of precision to which the measurement was made. It is necessary for Pharmaceutical Research, Regulatory Requirements,

Method Validation and Quality Control. In pharmaceutical laboratories, error control assists in providing accuracy and precision, thereby ensuring reliability of analytical data and ensuring quality, safety and efficacy of pharmaceutical products.

Key Points

- Errors are deviations of measured values from true values.
- Sources of errors include instrumental, personal, method, and environmental factors.
- Determinate errors are systematic and predictable.
- Indeterminate errors are random and unavoidable.
- Gross errors result from human mistakes or negligence.
- Accuracy represents closeness to the true value.
- Precision indicates the reproducibility of analytical results.
- Significant figures reflect the precision of measurements.
- Proper rounding-off prevents false representation of accuracy.
- Error minimization is essential for obtaining reliable pharmaceutical analytical data.

Review Questions

Short Answer Questions

1. Define analytical error.
2. What are the major sources of errors in pharmaceutical analysis?
3. Explain instrumental errors with examples.
4. Differentiate between personal and method errors.
5. Define determinate errors.
6. What are indeterminate errors?
7. Explain gross errors.
8. Define accuracy.
9. Define precision.
10. What are significant figures?

11. State any four rules of significant figures.
12. Explain rounding-off rules.
13. Why is accuracy important in pharmaceutical analysis?
14. How can analytical errors be minimized?
15. Discuss the importance of precision in quality control.

Long Answer Questions

1. Discuss the various sources of errors in pharmaceutical analysis.
2. Explain the classification of analytical errors with suitable examples.
3. Differentiate between accuracy and precision.
4. Describe the rules of significant figures and rounding off.
5. Discuss the methods used to minimize analytical errors.
6. Explain the applications of error analysis in pharmaceutical quality control.

Multiple Choice Questions (MCQs)

1. An analytical error is:

A. A correct result

B. A deviation from the true value

C. A standard value

D. A calibration factor

Answer: B

2. Which of the following is a source of analytical error?

A. Instrumental factors

B. Personal factors

C. Environmental factors

D. All of the above

Answer: D

3. Systematic errors are also known as:

A. Random errors

B. Gross errors

C. Determinate errors

D. Statistical errors

Answer: C

4. Random errors are also called:

A. Gross errors

B. Indeterminate errors

C. Systematic errors

D. Calibration errors

Answer: B

5. Accuracy refers to:

A. Reproducibility of results

B. Closeness to the true value

C. Number of measurements

D. Speed of analysis

Answer: B

6. Precision refers to:

A. Closeness of repeated measurements

B. Closeness to true value only

C. Calibration accuracy

D. Instrument sensitivity

Answer: A

7. Which error is mainly caused by human negligence?

A. Determinate error

B. Indeterminate error

C. Gross error

D. Random error

Answer: C

8. In the number 0.0045, the number of significant figures is:

A. 2

B. 3

C. 4

D. 5

Answer: A

9. Which statistical parameter is commonly used to evaluate precision?

A. Melting point

B. Standard deviation

C. Density

D. pH

Answer: B

10. Proper rounding-off and significant figures help improve:

A. Drug packaging

B. Marketing strategy

C. Reliability of analytical results

D. Manufacturing speed

Answer: C

Chapter 3: Impurities in Pharmaceuticals

Learning Objectives

After studying this chapter, the student will be able to:

- Define pharmaceutical impurities and explain their significance.
- Discuss the regulatory importance of impurity control.
- Identify various sources of impurities in pharmaceutical products.
- Classify pharmaceutical impurities into different categories.
- Explain the impact of impurities on drug quality, safety, and efficacy.
- Understand regulatory requirements for impurity profiling and control.

3.1 Introduction

Drug products have to conform to high standards of quality, safety and effectiveness before they are available to the patient. In the production, storage and distribution of pharmaceutical products, as well as the desired active pharmaceutical ingredient (API), however, unwanted substances can be present. Any of the substances that are not intended are called impurities. Medicinal products can be affected by impurities in a detrimental way, which can lead to instability, reduced activity or compromised product safety. Hence, identification, control and monitoring of impurities is an essential part of pharmaceutical quality assurance. New analytical methods have been developed, which have allowed the detection of impurities at even lower levels, and thus an even higher quality and safety of the products. The regulatory bodies such as the International Council for Harmonisation of Medicine (ICH), United States Pharmacopoeia (USP) and Indian Pharmacopoeia (IP) have established guidelines for testing and reporting impurities. An understanding of the nature, sources and classification of the impurities is essential to guarantee pharmaceutical quality and regulatory compliance.

3.2 Definition of Impurities

Impurities: Unwanted chemical entities that have not been separated from an active pharmaceutical ingredient or a pharmaceutical product in the manufacturing process, storage or transport. They can be found in the raw materials, intermediates, reagents, solvents, catalysts, degradation reactions, or environmental contamination. The amount of impurities in the product is generally very low and can have a significant impact on the quality, safety, efficacy and stability of the product. As per regulatory definition, impurity is anything other than the regulated drug substance's chemical structure. Too many impurities may change the action of the product; they may make the product unstable, or they

may have a negative effect on the person receiving the product. Therefore, it is imperative for pharmaceutical companies to detect, quantify and monitor the impurities within the specified limits. The most modern analytical techniques like chromatography and spectroscopy are followed for Impurity Profiling and QC. The control of impurities is an essential requirement to allow drug product approval and regulatory compliance.

3.3 Regulatory Importance of Impurities

The control of impurities is one of the most important regulatory requirements for a highly regulated process of pharmaceutical manufacturing. Pharmaceutical products can be affected in terms of safety, effectiveness and quality by impurities. Manufacturers should note that the regulatory agencies have laid down standards for identification, quantification and control of impurities within prescribed limit like International Council for Harmonisation (ICH), the United States Food and Drug Administration (USFDA), the European Medicines Agency (EMA) and the Central Drugs Standard Control Organisation (CDSCO). The recommendations in ICH guidances (Q3A, Q3B) address the reporting, identification and control of impurities in drug substances and drug products. Extensive impurity profiles are needed in drug registration and approval. If the impurities are outside of the range, the product may be rejected, recalled from the market or may be subject to regulatory measures. Patient protection, product standardisation, and therapeutic efficacy are parts of the process that are essential for impurity control. Therefore, pharmaceutical industries have to build up a well-developed quality control system and have developed validated analytical methods to fulfil regulatory expectations and pharmacopoeia requirements.

3.4 Sources of Impurities

There are several sources of pharmaceutical product contamination, either during manufacture or during storage. It is very important to determine the source of the contaminants when quality control is to be effective and/or regulatory standards are to be met. These comprise raw materials, manufacturing, containers, storage and closures. Each of them has a different function in the production of impurities, and if they are not checked, they can adversely influence the quality of the product. As indicated in Figure 3.1, pharmaceutical contaminants are known to come from a number of sources. Pfizer Pharmaceuticals should try to pinpoint what the sources of impurity are and implement safety measures to help decrease the impurity. Appropriate selection of raw materials, validated manufacturing processes, suitable packaging and controlled storage conditions can minimise the risk of impurities to ensure pharmaceutical products are safe and effective.

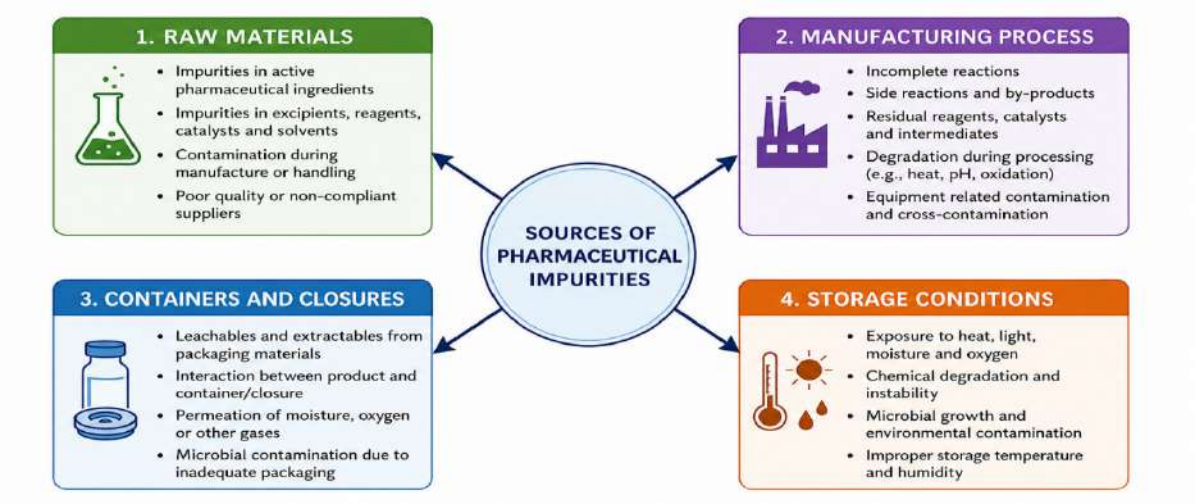


Figure 3.1: Sources of Pharmaceutical Impurities

Raw Materials

The raw materials are one of the main sources of impurities that can be found in pharmaceuticals. Manufacturing contaminants include impurities in products made with API, excipients, reagents, catalysts, solvents or processing aids. The impurities can be caused by the process of synthesis, inadequate purification, handling or inferior raw materials. The risks of contaminants affecting the quality and safety of a final product are present even for small amounts of contaminants. As such, drug companies test and assess raw materials meticulously before they can be used in the manufacturing process. Following Pharmacopoeial standards and a supplier qualification programme adds to the quality of received materials. Very important to have raw material control to minimise the amount of impurities and maintain consistent product quality.

Manufacturing Process

Impurities can also be the product of chemical reaction, side reaction, incomplete reaction, degradation or contamination during the manufacturing process. If purification is inadequate, it may result in the presence of residual reagents, catalysts, intermediates and by-products from the synthesis in the final product. Other sources of impurities are cross-contamination from previous batches or contamination from equipment. Formation of impurities may be greatly dependent upon temperature, pressure, pH and reaction time. So, pharmaceutical companies employ validated processes, in-process controls and good manufacturing practices (GMP) to reduce the process-related impurities. Process optimisation and continuous monitoring are carried out to make sure impurities are not above the regulatory limit.

Containers and Closures

The interactions between the packaging and the pharmaceutical product can lead to an introduction of impurities into the packaging system and containers. The chemicals in the product may leach into it during storage by the glass, plastic, rubber or metal parts. These leachables and extractables may impact the quality, stability and safety of a product. The poor quality of packaging material can also be the cause of moisture loss, oxygen and microbial contamination, which can result in product spoilage. Packaging systems should thus be suitable for the pharmaceutical formulation and should be able to offer sufficient protection during the product's shelf life. One of the regulatory requirements is to test packaging materials in order to guarantee that the product's quality will not be degraded. Proper selection and testing of containers and closures are needed to ensure pharmaceutical quality assurance.

Storage Conditions

The formation of impurities due to degradation and chemical instability is greatly affected by storage conditions. Chemical reactions can occur faster if stimulated by heat, light, moisture, oxygen or environmental contaminants, resulting in the formation of degradation products. Sub-optimal storage can result in product potency loss, product physical changes and patient risks. Certain drugs require particular storage requirements and may be very sensitive to their surroundings. Product stability is performed to understand the impact of storage conditions on product quality, and to recommend the appropriate storage. Appropriate packaging, temperature control and humidity management help to decrease the amount of impurities that are added during storage and make sure that the product is stable throughout its shelf life.

3.5 Types of Impurities

Pharmaceutical impurities can generally be divided into two types: the source of the impurities and the nature of the impurities. Good classification can aid in identifying the impurities, evaluating and controlling these in the pharmaceutical development and production processes. Generally, the impurities are classified as organic, inorganic impurities and residual solvents as per ICH guidelines. This classification is shown in Figure 3.2. The different challenges are encountered in each of the classes of pharmaceutical quality control, and analytical methods are needed for detection and quantification. Thus, it is essential to be knowledgeable about the various impurities if effective impurity control strategies are to be designed, and regulatory requirements fulfilled.

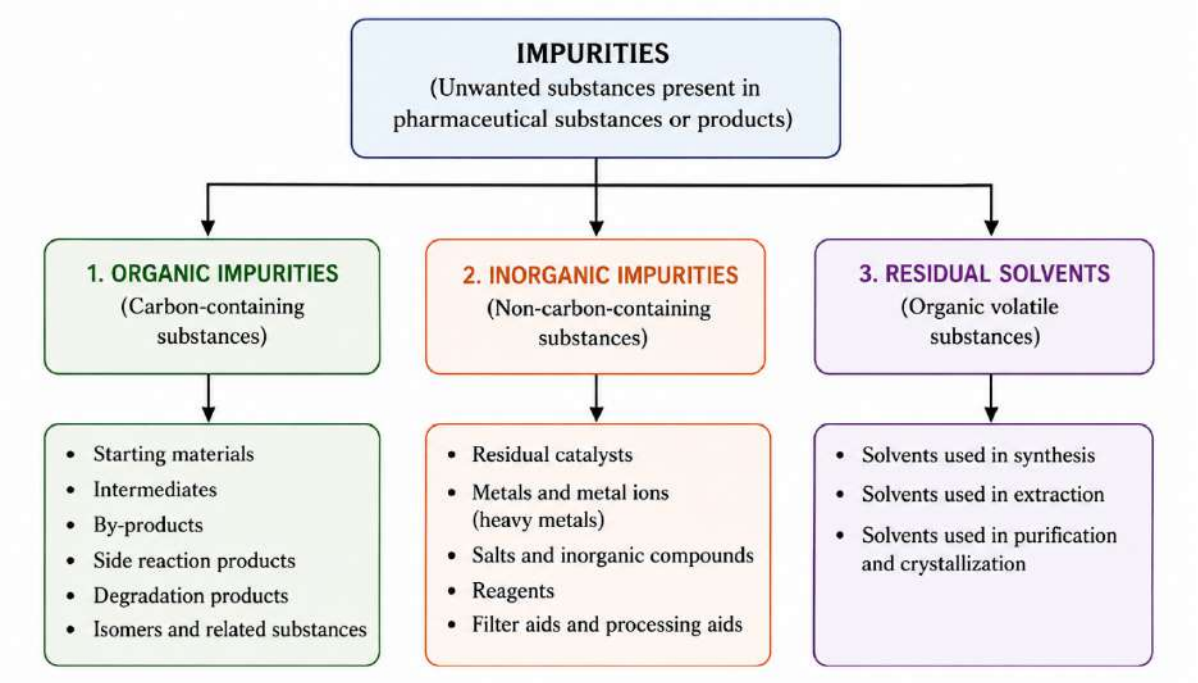


Figure 3.2: Classification of Pharmaceutical Impurities

Organic Impurities

Organic impurities are any carbon-based substance which may occur during the synthesis, manufacturing or degradation of pharmaceutical products. The impurities can be starting material, intermediate, by-products, degradation products or compounds formed during the reaction. Impurities that may be present are organic impurities that may be due to incomplete reaction, side reaction or instability of the API. May impact product potencies, stability and safety. Using analytical techniques like HPLC, GC and mass spectrometry is commonplace in the identification and quantification of the organic impurities that are very similar to the drug substance. For organic impurities, complete characterisation and control of these impurities for product quality and patient safety is necessary.

Inorganic Impurities

Impurities that are generated during the manufacturing process by inorganic materials (excluding carbon) can become part of the process or are a consequence of the raw materials and process equipment. The contaminants may be residual catalysts, heavy metals, filter aids, reagents, salts or inorganic contaminants. Impurities may be introduced during manufacturing, i.e., hot water used in manufacturing, processing equipment and packaging materials. At certain low levels of exposure, some inorganic contaminants can have significant health impacts. Thus, the limits of inorganic impurities are prescribed in the specifications of the pharmacopoeia of the pharmaceutical product. Atomic absorption and inductively coupled plasma spectroscopy are often used for their determination. It is important to have good control of inorganic impurities to ensure the safety and compliance of the product.

Residual Solvents

Residual solvents are VOCs that remain as a byproduct of a pharmaceutical manufacturing and/or purification process. These are widely used in the synthesis of pharmaceuticals, in extraction, crystallisation, and purification processes. While residual solvents are not designed to end up in the final product, some traces of them will be left in the product after processing. Residual solvents are divided into various categories based on ICH guidelines, depending on their toxicity. Some solvents can have harmful health effects because they are toxic, carcinogenic or because they have harmful environmental effects, particularly at high concentrations. Therefore, there are guidelines for the residual solvents that are accepted, and it is important to have monitoring done on a regular basis. GC is the most widely used method of all analytical methods for the detection and determination of residual solvents in pharmaceutical products.

3.6 Limit Tests

A semi-quantitative analysis method used for testing and controlling trace amounts of certain impurities in pharmaceutical materials is called a limit test. The tests are used to check if the level of a specific impurity is in excess of the pharmacopoeial limit. A limit test is not a quantitative one, but rather is a test that compares the intensity of the colour, turbidity or precipitate formed by the test solution to the colour, turbidity or precipitate formed by a standard solution containing a known amount of the impurity. The detection of impurities such as chloride, sulphate, iron, arsenic, lead and heavy metals is a typical test for which limit tests are employed. These impurities can impact the quality, stability, efficacy and safety of the pharmaceutical product if present at concentrations higher than these limits. In Pharmacopoeias like the Indian Pharmacopoeia(IP), British Pharmacopoeia(BP), and United States Pharmacopoeia(USP), some of the methods and acceptance criteria have been mentioned for the limit tests. These tests are particularly important for the quality control/quality assurance of the pharmaceutical industry.

Principle of Limit Tests

The colour, turbidity or precipitate produced by the impurity in the test solution is compared with the colour, turbidity or precipitate produced by the impurity in the standard solution, which contains a known amount of impurity. If it is at or below the standard's intensity, the sample complies with the standard's intensity. Other chemical reactions occur to make the impurities form coloured complexes, precipitates or suspensions which can be compared visually. The conditions used in all experiments should be the same as those used for both the test and standard solutions to obtain an accurate test. Because of their nature, they are not quantitative tests; limit tests are easily and cheaply performed checks for the presence of contaminants. They can be used regularly to be sure the pharmaceutical products are sufficiently pure to be used as a therapeutic and safe for use.

General Requirements

To successfully perform the limit tests, the tests must be carried out under certain pharmacopoeial conditions. The reagents used should be free from interfering impurities and of analytical grade. To avoid contamination, apparatus and glassware should be cleaned. The volumes of reagents to be used for test and standard solutions should be the same as prescribed. The same lighting conditions must be used to make an accurate comparison of turbidity and/or colour intensity. Fresh reagent is preferable to give accurate results. In order to exclude the presence of any unnecessary impurities, distilled or deionised water can be used in the procedure. The reaction time and observation conditions are important and must be carefully observed by the analysts as these may change and affect the test results. The requirements make the outcome of the limit test more reliable, repeatable and accurate in pharmaceutical analysis.

3.7 Limit Test for Chloride

The limit test for chloride is used to check if the amount of chloride in a pharmaceutical substance is within the accepted limits as per the pharmacopoeial requirements. Sources of chloride contamination can be found in the raw materials, production methods, reagents or storage conditions. When the levels of chlorides are too high, it may be an indication of inadequate cleaning during production or may affect product quality. This test is therefore frequently carried out in the pharmaceutical quality control process.

Principle

In this test, chloride ions react with silver nitrate in the presence of dilute nitric acid. The silver nitrate and chloride ions combine in solution to produce the microcrystalline white precipitate of silver chloride, and the turbidity of the solution increases. The turbidity of the test solution is semicqualitatively compared with the turbidity of a standard solution of known turbidity made up with a known amount to known volume.

Procedure

The sample (the quantity specified) is dissolved in water and then acidified with a little dilute nitric acid. After adding silver nitrate solution, it is then diluted to the required volume. At the same time, a standard solution is prepared that has a known amount of chloride impurity. The two solutions are then allowed to sit for the number of minutes indicated, and compared.

Observation

The turbidity of the test solution should not be more than that of the standard solution. If the turbidity is less than or equal to the turbidity of the standard, then the turbidimetric sample is suitable for the chloride limit test.

3.8 Modified limit test for chloride

When such substances are present that might interfere with the normal chloride limit test procedure, then the modified limit test for chloride is applied. Steps are taken to remove any coloured solution or insoluble matter or anything which interferes with the formation of turbidity. The principle is the same as the formation of turbidity of silver chloride by reacting chloride ions with silver nitrate. Other treatments such as filtration, clarification or pH adjustment may be performed prior to testing. The last comparison is done with the standard chloride solution under the same conditions. This is a simplified method that is more accurate and reliable in determining the level of chloride in a complex pharmaceutical product.

3.9 Limit Test for Sulphate

The limit test for sulphate is performed to check if there is any sulphate impurity in the pharmaceutical substance within the required limits. The raw materials, manufacturing reagents, water or processing equipment may all be a source of sulphate contamination. Excessive amounts of sulphates can affect the quality of the product and may be due to inadequate purification.

Principle

If an acid solution of sulphate ions is treated with barium chloride, then precipitate of barium sulphate will be formed, which is fine white in colour. The turbidity that will be produced will be directly proportional to the sulphate present and will be compared to a standard solution of sulphate by visual comparison.

Procedure

The solution to be tested is made by dissolving the sample in hydrochloric acid and water. After addition of the reagent (barium chloride), the solution is left to stand for a while. Another sample of a standard sulphate solution is prepared and used as a control sample.

Observation

The turbidity of the test solution should not be greater than the turbidity of the standard solution. If the turbidity is equal to or below the standard, then the sample has passed the sulphate limit test

.3.10 Modified Limit Test for Sulphate

The modified limit test for sulphate is used when the normal limit test for sulphate is interfered with by coloured material, insoluble material or other components, and it can be used. The principle is still the same: the barium ions react with the sulphate ions to form the turbidity of barium sulphate. Materials which interfere with the treatment process are removed by other treatment processes such as filtration, clarification, dilution or pH adjustment. The turbidity formed is compared to a standard

sulphate solution similarly prepared. It is the modified procedure that is used, and in the case of pharmaceutical substances that could not be analysed by the conventional procedure, for the accurate determination of the presence of sulphate impurities.

2.11 Limit Test for Iron

The limit test for iron is applied to identify the contamination of Iron in pharmaceutical products at low levels. The iron contamination may come from the raw materials, manufacturing equipment, storage vessels, or from water used during manufacturing.

Principle

Ferrous thioglycolate complex reacts with iron ions in the presence of ammonia to give a pink to purple colored compound using thioglycolic acid. The amount of colour produced is proportional to the amount of iron present and is compared to a standard iron solution.

Procedure

Solution derived from the sample is treated with citric acid, thioglycolic acid and ammonia solution as prescribed in the Pharmacopoeia. At the same time, a normal solution of iron is prepared which has the same content of iron. Both solutions are exposed to the same conditions in terms of development of colour.

Observation

The colour of the test solution should not be more than the colour of the standard solution. Compliance is when the amount of iron impurity is within the acceptable limits.

3.12 Limit Test for Arsenic

The limit test for arsenic is conducted as it is one of the most highly toxic impurities which can be found in pharmaceutical products due to the presence in raw materials or the manufacturing process.

Principle

Zinc and acid generate nascent hydrogen and the products formed will be arsine gas and arsenic compounds. The arsine gas causes mercuric chloride paper to turn yellow to brown. This is compared with the intensity of the stain made from a standard solution of arsenic.

Procedure

The sample is treated with hydrochloric acid, potassium iodide, stannous chloride and zinc which has been freed from arsenic. The arsine gas produced in the reaction comes in contact with mercuric chloride paper. At the same time and under the same conditions, a standard arsenic solution is treated.

Observation

A darker stain will not form on the mercuric chloride paper from the test solution than will occur with the standard solution.

3.13, Limit Test forLead

Limit test to determine the presence of small amount of lead in pharmaceutical products. Lead is a toxic, heavy metal which may be found in raw materials, equipment, water or the environment.

Principle

If lead ions are added to dithizone reagent, then coloured complex of lead-dithizonate will be formed. The colour obtained is compared with that of a standard lead solution that has a known amount of lead in it.

Procedure

Pharmacopoeial procedures are used to prepare and treat the sample solution. Dithizone reagent is added, and the coloured complex formed is extracted into an organic solvent. The standard solution of lead is treated simultaneously under the same conditions.

Observation

The colour intensity of the test solution should not be greater than that of the standard solution. Compliance is defined as lead levels being at an acceptable level.

3.14 Limit Test for Heavy Metals

Heavy metal limit test is a test used to detect toxic metal contaminants such as lead, mercury, bismuth, copper and other heavy metals in pharmaceuticals.

Principle

In an acid solution, the heavy metal ions will react with hydrogen sulphide or sulphide ions to produce coloured metal sulphides. The colour produced is compared to the colour of a standard lead solution that represents the standard concentration of the heavy metal.

Procedure

A sample solution is made and pH adjusted. The colour is developed by adding thioacetamide reagent or hydrogen sulphide reagent. A standard solution of lead is treated in the same manner as the other solutions under the same conditions and compared.

Observation

The colour of the test solution should not be more intense than the standard solution. If the colour intensity is equal to or less than the standard, the sample passes the heavy metal limit test.

3.15 Comparative Overview of Limit Tests

Limit tests are very important tests in the quality control process to ensure that the range of impurities is maintained as per the Pharmacopoeial standard. Each test involves some reaction with a chemical agent and causes a colour change, turbidity, precipitates or stains which can be seen and compared with a standard. Chloride and sulphate tests are based on turbidity formation, while iron, lead, and heavy metal tests are based on colour development. The arsenic test is unique because it will form arsine gas and stains on mercuric chloride paper. Instruments are more sensitive and accurate, and limit tests are still used today as they are simple, inexpensive and applicable to routine QC. These tests are essential to provide the purity and safety of the product and meet the regulatory requirements.

Pharmaceutical Applications

Limit tests are extensively used in a pharmaceutical Quality Control Laboratory for determining the purity of raw material, active pharmaceutical ingredient, excipients or finished pharmaceutical dosage forms. They contribute to the detection and control of undesirable or toxic impurities that can have a potential impact on the safety, efficacy, and stability of pharmaceutical products. Limit testing is necessary in all major pharmacopoeias and is frequently used in raw material testing, process validation, stability testing and batch release testing. They help to meet regulations and to maintain constant product quality. In the realm of patient safety and pharmaceutical quality assurance, limit tests are essential for ensuring that the pharmaceutical product is devoid of excessive amounts of harmful impurities.

Chapter Summary

Impurities are unwanted substances that, if they are present in pharmaceutical products, can affect the quality, safety, efficacy and stability of the product. They can be derived from raw materials, production, packaging materials, and storage. To satisfy regulatory agencies such as ICH and USP and keep products safe and of high quality, impurities need to be controlled and monitored. Pharmaceutical impurities can be considered in the general categories of organic impurities, inorganic impurities, or residual solvents. Limit tests are semi-quantitative analytical methods that are employed to detect and control the presence of trace quantities of impurities that may be found in pharmaceutical substances. Common pharmacopoeial limit tests include those for chloride, sulphate, iron, arsenic, lead and heavy metals. The tests are conducted by comparing the turbidity, colour, precipitate or stain produced by the test solution with that of the standard solution. Although instrumental methods are increasingly common for impurities, limit tests are still useful because they are easy to perform and are economical, and they are appropriate for routine pharmaceutical quality

control testing. The greatest priority to ensure patient safety and regulatory compliance is effective control of impurities.

Key Points

- Impurities are unwanted substances present in pharmaceutical products.
- Impurities may affect drug safety, efficacy, quality, and stability.
- Regulatory authorities prescribe permissible limits for pharmaceutical impurities.
- Major sources of impurities include raw materials, manufacturing processes, packaging materials, and storage conditions.
- Pharmaceutical impurities are classified as organic impurities, inorganic impurities, and residual solvents.
- Limit tests are semi-quantitative methods used to control impurities.
- The chloride limit test is based on the formation of silver chloride turbidity.
- The sulphate limit test is based on the formation of barium sulphate turbidity.
- The iron limit test involves formation of a coloured ferrous thioglycolate complex.
- The arsenic limit test is based on arsine gas generation and stain formation.
- The lead limit test involves the formation of a coloured lead-dithizonate complex.
- The heavy metal limit test is based on the formation of coloured metal sulphides.
- Limit tests help ensure compliance with pharmacopoeial standards.
- Impurity control plays a crucial role in pharmaceutical quality assurance and patient safety.

Review Questions

Short Answer Questions

1. Define pharmaceutical impurities.
2. Why is impurity control important in pharmaceuticals?
3. Explain the regulatory importance of impurities.
4. List the major sources of pharmaceutical impurities.
5. Classify pharmaceutical impurities.
6. What are organic impurities?

7. What are inorganic impurities?
8. Define residual solvents.
9. What is a limit test?
10. State the principle of the chloride limit test.
11. State the principle of the sulphate limit test.
12. What is the purpose of the iron limit test?
13. Explain the principle of the arsenic limit test.
14. Why is lead considered a hazardous impurity?
15. State the principle of the heavy metal limit test.

Long Answer Questions

1. Discuss the sources of pharmaceutical impurities in detail.
2. Explain the classification of pharmaceutical impurities with suitable examples.
3. Describe the regulatory importance of impurity control in pharmaceuticals.
4. Explain the principle, procedure, and observation of the chloride limit test.
5. Explain the principle, procedure, and observation of the sulphate limit test.
6. Describe the limit test for iron.
7. Explain the principle and procedure of the arsenic limit test.
8. Discuss the limit test for lead.
9. Explain the principle and pharmaceutical significance of the heavy metal limit test.
10. Compare various pharmacopoeial limit tests used in pharmaceutical analysis.

Multiple Choice Questions (MCQs)

1. An impurity is defined as:

A. Active pharmaceutical ingredient

B. Therapeutic agent

C. Unwanted substance present in a pharmaceutical product

D. Pharmaceutical excipient

Answer: C

2. Which organization has established impurity guidelines such as Q3A and Q3B?

A. WHO

B. ICH

C. CDSCO

D. FDA

Answer: B

3. Which of the following is a source of pharmaceutical impurities?

A. Raw materials

B. Manufacturing process

C. Storage conditions

D. All of the above

Answer: D

4. Residual solvents are classified as:

A. Organic impurities

B. Inorganic impurities

C. Volatile organic chemicals remaining after manufacturing

D. Heavy metals

Answer: C

5. The chloride limit test is based on the formation of:

A. Barium sulphate

B. Silver chloride

C. Lead sulphide

D. Ferric chloride

Answer: B

6. The sulphate limit test uses which reagent?

A. Silver nitrate

B. Potassium iodide

C. Barium chloride

D. Thioglycolic acid

Answer: C

7. The iron limit test employs:

A. Dithizone

B. Thioglycolic acid

C. Mercuric chloride

D. Hydrogen sulphide

Answer: B

8. The arsenic limit test is based on the formation of:

A. Hydrogen sulphide gas

B. Chlorine gas

C. Arsine gas

D. Ammonia gas

Answer: C

9. Lead is detected in the limit test using:

A. Dithizone reagent

B. Barium chloride

C. Silver nitrate

D. Potassium chromate

Answer: A

10. Heavy metal limit tests are generally based on the formation of:

A. Metal oxides

B. Metal chlorides

C. Metal sulphides

D. Metal nitrates

Answer: C

11. Which impurity category includes catalysts and metal ions?

A. Organic impurities

B. Residual solvents

C. Inorganic impurities

D. Volatile impurities

Answer: C

12. Which of the following is a toxic heavy metal impurity?

A. Sodium

B. Potassium

C. Lead

D. Calcium

Answer: C

13. Limit tests are generally:

A. Quantitative tests

B. Semi-quantitative tests

C. Biological tests

D. Microbiological tests

Answer: B

14. The modified limit tests are used when:

A. The sample is pure

B. There is no impurity present

C. Interfering substances affect the normal test procedure

D. Quantitative analysis is required

Answer: C

15. The primary purpose of limit tests is to:

A. Identify unknown drugs

B. Determine exact concentration of impurities

C. Ensure impurities are within permissible limits

D. Measure dissolution rate

Answer: C

UNIT II

ACID–BASE CHEMISTRY AND BUFFER SYSTEMS IN PHARMACY

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Chapter 4: Acid–Base Chemistry and Buffer Systems

Learning Objectives

After studying this chapter, the student will be able to:

- Define acids, bases, buffers, and pH.
- Classify acids and bases based on their properties.
- Explain the pharmaceutical importance of acids and bases.
- Describe the mechanism and classification of buffer systems.
- Discuss the significance of pH in pharmaceutical preparations.
- Apply acid–base concepts in pharmaceutical formulation and analysis.

4.1 Introduction

One of the most important and essential areas of the pharmaceutical sciences is acid–base chemistry, and it is one of the most important bases of many pharmaceutical processes. The concepts of acids, bases, buffers and pH are very important for understanding drug behaviour, excipient behaviour, and biological system behaviour. There are several pharmaceutical products with acidic or basic characteristics that would impact the solubility, stability, absorption, distribution and therapeutic activity of those products. Control of the acid–base properties is necessary during the formulation development, manufacturing, storage and administration of pharmaceuticals. The buffers are mainly used to maintain the pH and to prevent degradation of the drug molecule. Buffer systems used in pharmaceutical formulations are of many types as given in Figure 4.1.

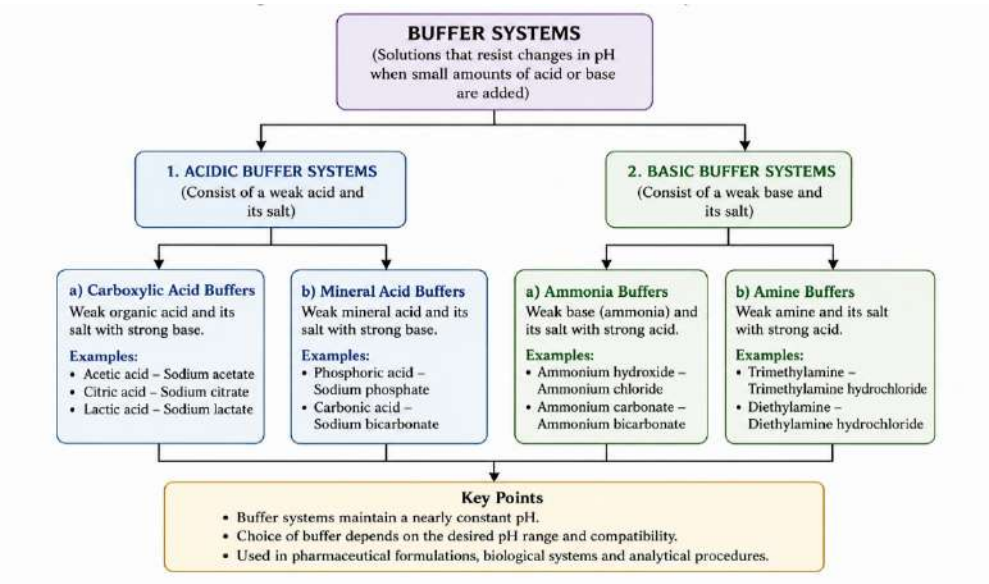


Figure 4.1: Classification of Buffer Systems

Titrimetric procedures are used in the pharmaceutical sciences for pharmaceutical assay and quality control, which are significant aspects of acid–base chemistry. Thus, it is essential to understand the acid–base principles to ensure the quality, safety, efficacy and stability of the pharmaceutical products.

4.2 Acids

Acids are used in many important and extensive ways in pharmaceutical formulations, analytical chemistry and physiology. They play an important role in drug stability, drug dissolution, bioavailability, and drug pharmacological activities. Acids are used in various pharmaceutical formulations as active ingredients, excipients, preservatives, acidifying agents, buffering agents and other applications. Acids will also affect the ionisation of drugs and distribution/absorption in the body. They are also involved in many biochemical and metabolic pathways that are necessary for normal physiological functions. There are several theories to explain the acidity of substances, such as Arrhenius theory, Brønsted–Lowry theory and Lewis theory. Some properties of acids are: They have a sour taste, they are proton donors, and they neutralise bases. They are used in several other applications in the pharmaceutical industry, such as formulation development, analytical testing and QC. The knowledge of the properties and classification of acids is crucial in choosing the appropriate ingredients and for the efficacy of pharmaceutical formulations.

Definition of Acids

An acid is a substance that will give up hydrogen ions (H+) in solution or a proton in a chemical reaction. According to the Arrhenius theory, an acid produces more hydrogen ions in water.

According to the Brønsted–Lowry theory, acids are proton donors, while the Lewis theory considers acids as electron pair acceptors.

Classification of Acids

Acids can be strong or weak, according to the extent of ionisation. Strong acids are 100% dissociated in water; weak acids are partially dissociated. They can also be classified into two categories, namely organic acids and inorganic acids.

Pharmaceutical Examples of Acids

Hydrochloric acid, citric acid, acetic acid, boric acid, phosphoric acid, tartaric acid and ascorbic acid are some of the commonly used pharmaceutical acids. The acids are extensively applied in pharmaceutical formulation as acidifying agents, preservatives, antioxidants, and buffers.

4.3 Bases

Bases are chemical compounds which neutralize acids and are very important in pharmacology. The basic properties of many pharmaceutical compounds impact their chemical activity, stability, solubility and therapeutic activity. Bases are used in a wide variety of applications such as antacids, buffering agents, pharmaceutical excipients and as alkalizing agents. They play a crucial role in the physiological regulation of acid–base balance, and participate in several biochemical reactions. The bases are commonly used in the pharmaceutical industry in different applications such as pH adjustment, formulation development, and analytical procedures. There are some theories developed for the basic behaviour: Arrhenius theory, Brønsted–Lowry theory and Lewis theory. Bases possess properties that are typical of them; they are slippery, taste bitter and turn red litmus paper blue. The knowledge of bases is essential for the development of a safe & effective dosage form, wherein the classification of bases and their pharmaceutical applications are studied. Basic knowledge of compounds is also beneficial for Analytical Testing and Quality Control activities.

Definition of Bases

Bases are substances that give off hydroxyl ions (OH-) in solution or take up protons in a chemical reaction. According to the Arrhenius theory, bases increase the concentration of hydroxyl ions in water, and according to the Brønsted–Lowry theory, bases are proton acceptors.

Classification of Bases

Depending on the degree of ionisation, bases can be strong or weak bases. Strong bases are 100% dissociated in a water solution; weak bases are only partially dissociated. Bases can also be classified as organic or inorganic bases.

Examples of bases in pharmaceuticals include:

Sodium hydroxide, potassium hydroxide, magnesium hydroxide, aluminium hydroxide, calcium hydroxide and ammonium hydroxide are examples. They are employed for pharmaceutical industry processes, pH adjustment and formulation of antacids.

4.4 Buffers

Buffers are solutions that resist changes in pH when small amounts of acid or alkali are added. They have a vital part to play in pharmaceutical formulations where there are many drugs with a pH window of stability. To maintain a constant hydrogen ion concentration and to avoid changes in pharmaceutical products' pH during manufacturing, storage, and administration, buffer systems are employed. They can be used in injections, ophthalmic solutions, oral fluid, pharmaceutical (biological drugs) and analytical solutions. Physiologically, buffer systems also have an important role with regard to maintaining the blood and tissue pH within the normal range. The pH change of a solution due to buffers is exhibited in Figure 4.2. The benefits of using the correct buffer system are that the drug is more stable, more soluble, less irritating and has the correct therapeutic effect. So, a buffer is one of the most crucial excipients in the pharmaceutical formulation and quality control area.

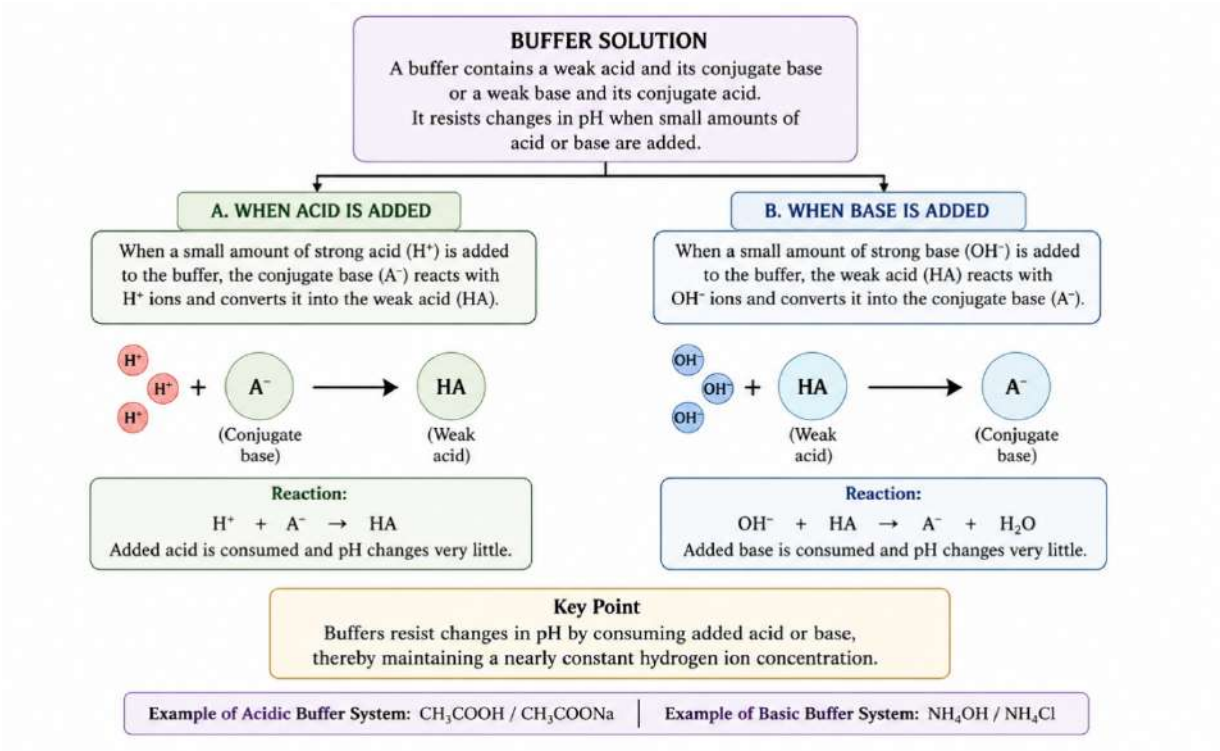


Figure 4.2: Mechanism of Buffer Action

Definition of Buffers

A buffer is a solution that does not undergo appreciable change in its pH value when a small amount of acid or alkali is added to it. Is observed in the regular reaction of weak acids and their conjugate base or weak bases and their conjugate acids.

Types of Buffer Systems

Buffers are two types – Acidic buffers and basic buffers. Buffers are composed of a weak acid (acidic buffers) or a weak base (basic buffers) and its salt.

Understand the significance of buffers in the field of Pharmacy.

The role of buffers is to stabilise the drug, to enhance the solubility of the drug, to increase the effect of a preservative, to decrease the irritating effect on tissues, and to make the pharmaceutical products physiologically compatible.

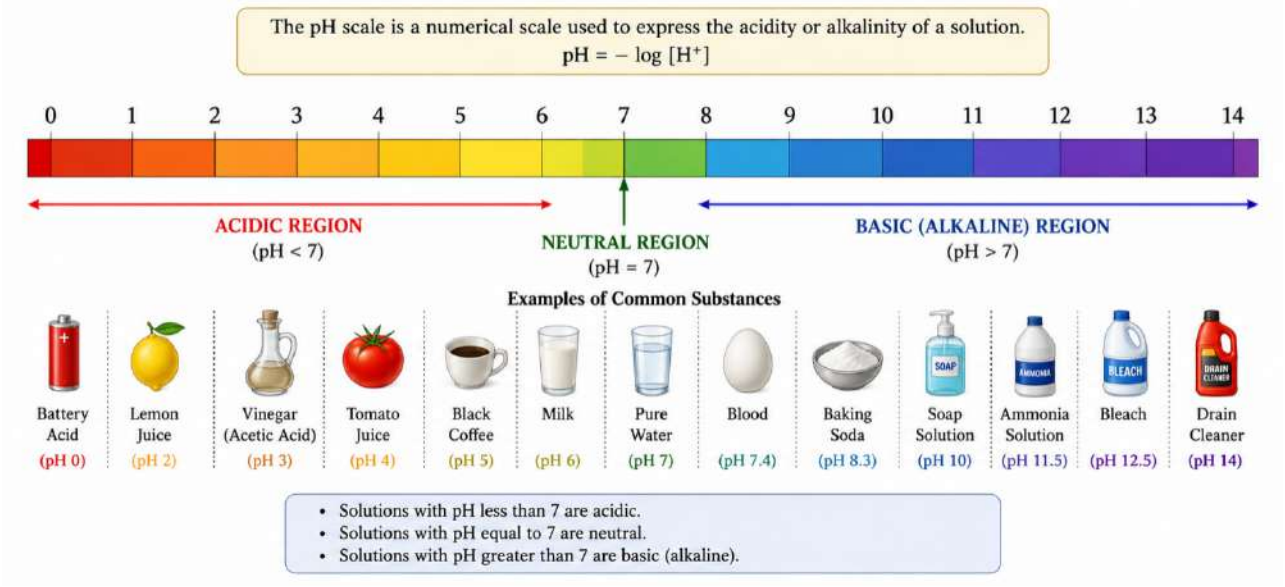
4.5 pH Scale

pH scale is a numerical scale that measures the acidity and alkalinity of a solution. It is one of the most important parameters in pharmaceutical science and it plays an important role in influencing the stability, solubility, absorption, therapeutic activity of the drug and the efficacy of preservatives. Normally, the pH scale ranges from 0 to 14, and anything below 7 is acidic, above 7 is alkaline, and at 7 is neutral. The acidic, neutral and basic areas are indicated on the pH distribution map (Figure 4.3). It is very crucial to maintain the correct pH of a pharmaceutical formulation for its quality, safety and efficiency. Table 4.1 contains some of the common pharmaceutical buffer systems and their optimum pH. Therefore, pH measurement and control are essential components of the pharmaceutical formulation development, manufacturing and quality control processes.

Table 4.1 Common Pharmaceutical Buffers and Their pH Range

Buffer System	**Composition**	**Buffer Type**	**Effective pH Range**	**Pharmaceutical Applications**
Acetate Buffer	Acetic Acid + Sodium Acetate	Acidic Buffer	3.8 – 5.8	Oral liquids, topical formulations, analytical solutions
Citrate Buffer	Citric Acid + Sodium Citrate	Acidic Buffer	3.0 – 6.2	Syrups, injections, biological preparations
Phosphate	Sodium Dihydrogen Phosphate +	Neutral	5.8 – 8.0	Ophthalmic

Buffer	Disodium Hydrogen Phosphate	Buffer		solutions, injections, tablets, biological products
Borate Buffer	Boric Acid + Sodium Borate	Basic Buffer	7.6 – 9.2	Ophthalmic preparations and antiseptic solutions
Ammonia Buffer	Ammonium Hydroxide + Ammonium Chloride	Basic Buffer	8.2 – 10.2	Pharmaceutical analysis and laboratory applications
Carbonate Buffer	Sodium Bicarbonate + Sodium Carbonate	Basic Buffer	9.2 – 10.8	Antacid preparations and analytical procedures
Tris Buffer	Tris(hydroxymethyl)aminomethane + Hydrochloric Acid	Basic Buffer	7.0 – 9.0	Biotechnology, protein formulations, biological studies
Lactate Buffer	Lactic Acid + Sodium Lactate	Acidic Buffer	3.0 – 5.0	Parenteral preparations and physiological solutions



Definition of pH

The pH is the negative log of the concentration of H+ in a solution.

$pH = -\log [H^+]$

It tells us the strength of an acid or base solution in a quantitative manner.

pH Scale and Its Significance

The pH scale is a range from 0 to 14 that is used to describe a solution as being acidic, neutral, or basic. It offers insights into the reactivity, stability, and biological usability of chemicals.

Importance of pH in Pharmaceutical Preparations

The pH influencesdrugs' stability, solubility, absorption, preservative activity, and patient comfort. Correct pH levels protect against degradation, optimise therapeutic activity, and promote compatibility with the physiological systems.

4.6 Buffer Equation

A mathematical relationship that describes the relationship between the pH of a buffer solution and the concentrations of the buffer's acidic and basic components is called the buffer equation. Pharmaceutical sciences make use of buffer equations for the prediction and control of the pH of pharmaceutical formulations. The calculated buffer pH is important when developing the drug formulation, as many drugs are found to be the most stable, soluble and effective at a specific pH. When pharmaceutical scientists are in buffer selection and preparation, they can use buffer equations to select appropriate buffer systems and find the concentration of buffer components required to get the desired pH. The Henderson–Hasselbalch equation is the most common buffer equation used, relating the pH of a buffer to the dissociation constant of the weak acid and the ratio of the concentration of the salt to the concentration of the acid. The equation listed above can be used to prepare buffer solutions of a desired pH. In pharmaceutical analysis, formulation development and quality control testing in biological systems, buffer equations find a broad range of applications. Thus, buffer equations play a vital role in the stability and efficacy of pharmaceutical products, and it is crucial to understand them.

Henderson–Hasselbalch Equation

The Henderson–Hasselbalch equation is the most commonly used equation for determining the pH of buffer solutions. It is based on the dissociation equilibrium of the weak acid and its conjugate base. The equation relates the pH, the acid dissociation constant (pKa), and the ratio of salt concentration to acid concentration.

For acidic buffers:

[pH = pK_a + \log \frac{[Salt]}{[Acid]}]

Where:

- **pH** = Hydrogen ion concentration expressed logarithmically
- **pKa** = Negative logarithm of the acid dissociation constant
- **[Salt]** = Concentration of conjugate base or salt
- **[Acid]** = Concentration of weak acid

For basic buffers, the equation may be expressed as:

[pOH = pK_b + \log \frac{[Salt]}{[Base]}]

The Henderson–Hasselbalch equation enables accurate estimation of buffer pH and is extensively used in pharmaceutical calculations.

Applications of Buffer Equation

The buffer equation has a wide variety of applications in pharmaceutical sciences and in analytical chemistry. It is used to determine the pH of a buffer solution, to prepare pharmaceutical products or to optimise the stability of the drug. The equation is used by pharmaceutical scientists to choose the right buffer system and concentration of buffer components. Furthermore, the equation is used in the formulation of injection, ophthalmic solution, oral liquid and biological products, which require strict control of pH. It is used in the pharmaceutical analysis to estimate the change of pH during titration and in the preparation of buffer. In addition, the equation is useful for the investigation of physiological buffer systems like blood and intracellular fluids. In pharmaceutical quality, efficacy and patient safety, the Henderson-Hasselbalch equation is important in that it can be used to precisely determine the pH.

4.7 Calculation of pH of Buffer Solutions

Calculation of buffer pH is an important aspect of pharmaceutical formulation and analytical chemistry. It is significant to determine the pH accurately as a low or high pH may have a significant impact on the stability, solubility, bioavailability or activity of the product. The Henderson-Hasselbalch equation is a commonly used equation to calculate the pH of a buffer solution. The concentration of the weak acid and its conjugate salt and the pKa of the weak acid is required to do the calculation. When the concentrations of acid and salt are the same, the pH of the buffer is equal to the pKa of the weak acid. The ratio of salt to acid will affect the pH of the solution because of the logarithmic relationship in the equation. Pharmaceutical scientists routinely use buffer pH calculations

in the formulation development, quality control and analytical procedures. The calculations are used to select buffers and for the control and maintenance of desired pH in pharmaceutical products.

Practice Problems

1. Calculate the pH of a buffer containing 0.05 M acetic acid and 0.05 M sodium acetate (pKa = 4.76).
2. Calculate the pH of a buffer containing 0.2 M acetic acid and 0.4 M sodium acetate (pKa = 4.76).
3. Calculate the pH of a phosphate buffer containing equal concentrations of sodium dihydrogen phosphate and disodium hydrogen phosphate (pKa = 7.2).
4. Calculate the pH of a buffer containing 0.1 M weak acid and 0.01 M salt when pKa = 5.0.
5. Calculate the pH of a buffer containing 0.5 M salt and 0.05 M acid when pKa = 4.5.

4.8 Pharmaceutical Applications of Buffers

Buffers are used widely in drug formulation, analytical and biological systems. They primarily serve to keep the pH of the product at a steady level throughout the manufacturing, storage and delivery of pharmaceutical products to avoid changing the acidity or alkalinity of the product. Buffers are generally used in injections to facilitate compatibility with body fluids and to reduce tissue irritation. In ophthalmic preparations, buffer systems are used to ensure comfort and to avoid damage to the tissues of the eye. The use of buffers in oral liquid formulations is to increase the stability, flavour, and preservative activity. Buffers are also used in biological products (e.g. vaccines), protein formulation and biotechnology applications for optimal biological activity. The uses of buffers in the pharmaceutical industry are: Chromatographic method, Dissolution study, Assay, and pH measurement. The body's physiological buffer systems are those that help to keep the acid–base balance maintained, such as the blood buffers. In a modern world of pharmaceutical sciences, buffers have an important role to play in maintaining the stability of the drug, the patient acceptability of the drug and the therapeutic efficacy.

Chapter Summary

The acid–base chemistry is very significant in pharmaceutical sciences, and it is important for the stability, solubility, absorption and therapeutic activity of drugs. Acids give protons, and bases take protons, or in solution, bases form hydroxyl ions. Materials that neutralise changes in pH and keep their hydrogen ion level stable. Buffers come in two types (acidic and basic) and are commonly used in pharmaceutical preparations. The pH scale will be used to measure both acidic and alkaline, and it is also a key factor in pharmaceutical product quality. Know how to compute the pH of buffer

solutions and be able to prepare appropriate buffer solutions by utilizing Henderson – Hasselbalch equation. Proper pH control is essential for the stability, effectiveness and safety of drugs. Buffers are very common in all the following applications: Injection, eye drops, oral solutions, biological drugs and analysis.

Key Points

- Acids donate protons, whereas bases accept protons.
- Buffer solutions resist changes in pH.
- Buffers are classified into acidic and basic buffers.
- pH is the negative logarithm of hydrogen ion concentration.
- The pH scale ranges from 0 to 14.
- The Henderson–Hasselbalch equation is used to calculate buffer pH.
- Buffer capacity depends on the concentration of buffer components.
- pH influences drug stability, solubility, and absorption.
- Buffers are widely used in pharmaceutical formulations.
- Proper pH control ensures product quality and therapeutic effectiveness.

Review Questions

Short Answer Questions

1. Define a buffer solution.
2. What is the Henderson–Hasselbalch equation?
3. Differentiate between acidic and basic buffers.
4. Define pH.
5. State the pH range of acidic solutions.
6. What is the importance of pH in pharmaceutical formulations?
7. Give two examples of pharmaceutical buffer systems.
8. Explain the mechanism of buffer action.
9. What is buffer capacity?
10. Why are buffers used in ophthalmic preparations?

Long Answer Questions

1. Discuss acid–base chemistry and its pharmaceutical importance.
2. Explain the classification of acids and bases with examples.
3. Describe buffer systems and their pharmaceutical applications.
4. Derive and explain the Henderson–Hasselbalch equation.
5. Explain the calculation of pH of buffer solutions with suitable examples.
6. Discuss the importance of pH control in pharmaceutical preparations.

Multiple Choice Questions (MCQs)

1. A buffer solution resists changes in:
    - A. Temperature
    - B. Pressure
    - C. pH
    - D. Density

Answer: C

2. The pH of a neutral solution is:
    - A. 0
    - B. 7
    - C. 10
    - D. 14

Answer: B

3. Which equation is used to calculate the pH of a buffer solution?
    - A. Arrhenius Equation
    - B. Nernst Equation
    - C. Henderson–Hasselbalch Equation
    - D. Beer–Lambert Equation

Answer: C

4. An acidic buffer consists of:
    - A. Strong acid and strong base
    - B. Weak acid and its salt
    - C. Weak base and its salt
    - D. Strong base and weak acid

Answer: B

5. Which of the following is an example of an acidic buffer?
    - A. NH_4OH/NH_4Cl
    - B. NaOH/HCl
    - C. CH_3COOH/CH_3COONa
    - D. KOH/KCl

Answer: C

6. Buffers are commonly used in:
    - A. Ophthalmic solutions
    - B. Injections
    - C. Oral liquids
    - D. All of the above

Answer: D

7. The pH scale ranges from:
    - A. 0–7
    - B. 1–10
    - C. 0–14
    - D. 2–12

Answer: C

8. When acid and salt concentrations are equal:
    - A. pH = 0

- B. pH = pKa
- C. pH = 14
- D. pH = pKb

Answer: B

9. Which buffer is commonly used in ophthalmic preparations?
    - A. Borate Buffer
    - B. Sulphate Buffer
    - C. Nitrate Buffer
    - D. Chloride Buffer

Answer: A

10. Buffer systems help maintain:

- A. Drug colour
- B. Drug odor
- C. Constant pH
- D. Drug density

Answer: C

Chapter 5: Isotonicity and Physiological Electrolytes

Learning Objectives

After studying this chapter, the student will be able to:

- Define isotonicity and its pharmaceutical significance.
- Differentiate between isotonic, hypotonic, and hypertonic solutions.
- Explain the applications of isotonic solutions in pharmacy.
- Describe major extracellular and intracellular electrolytes.
- Discuss the physiological functions of important electrolytes.
- Understand the role of electrolytes in maintaining fluid and acid–base balance.

5.1 Introduction to Isotonicity

The property of interaction of a biological fluid, for example, blood plasma, tears and intracellular fluid with the osmotic fluid is called isotonicity. It is based on osmosis - the movement of water from a solute concentration lower area to an area of higher solute concentration across a semipermeable membrane. A drug that contains the same amount of osmoles as the body fluids is called isotonic. Here, water flow is the same in both directions through cell membranes, and all cell functions and structures are normal. In the case of parenteral, ophthalmic, nasal and irrigation solutions, it is particularly important that they are isotonic, as they come in direct contact with sensitive tissues and biological fluids. Non-isotonic solutions can be uncomfortable, irritating, cause cell volume changes or cause tissue damage. Pharmaceutical scientists therefore make changes to their formulations to make them isotonic with the use of appropriate tonicity agents such as sodium chloride, dextrose or boric acid. A knowledge of isotonicity is crucial for the safety, efficacy and patient acceptance of pharmaceutical products. Isotonicity in biological systems is represented in Figure 5.3, which shows the basic mechanism of isotonicity in biological systems caused by tonicity, which involves the movement of water through the cell membrane.

5.2 Isotonic Solutions

Solutions that have the same osmotic pressure as the body fluid (such as blood plasma, tears or extracellular fluid) are called isotonic solutions. The rate of water movement into and out of the cell is equal — it's in equilibrium. This implies that there is no penetration of water in or out of cells, and cells remain healthy in their shape, size and function. In pharmaceutical and clinical applications, isotonic solutions are very significant as they will not damage cells and will not cause any discomfort in the patient. Isotonic solutions that are available include 0.9% sodium chloride injection (normal

saline), 5% dextrose injection, and Ringer's solution. These are generally given intravenously to replace fluids, for electrolyte replacement, for drug delivery or for overall fluid balance. Also prepared is an isotonic ophthalmic preparation which causes minimum irritation and is more patient-friendly. The comparative properties of isotonic, hypotonic and hypertonic solutions are shown in figure 5.1. The proper isotonicity is crucial for the compatibility with the physiological tissues and in the safety and efficacy of the pharmaceutical formulations.

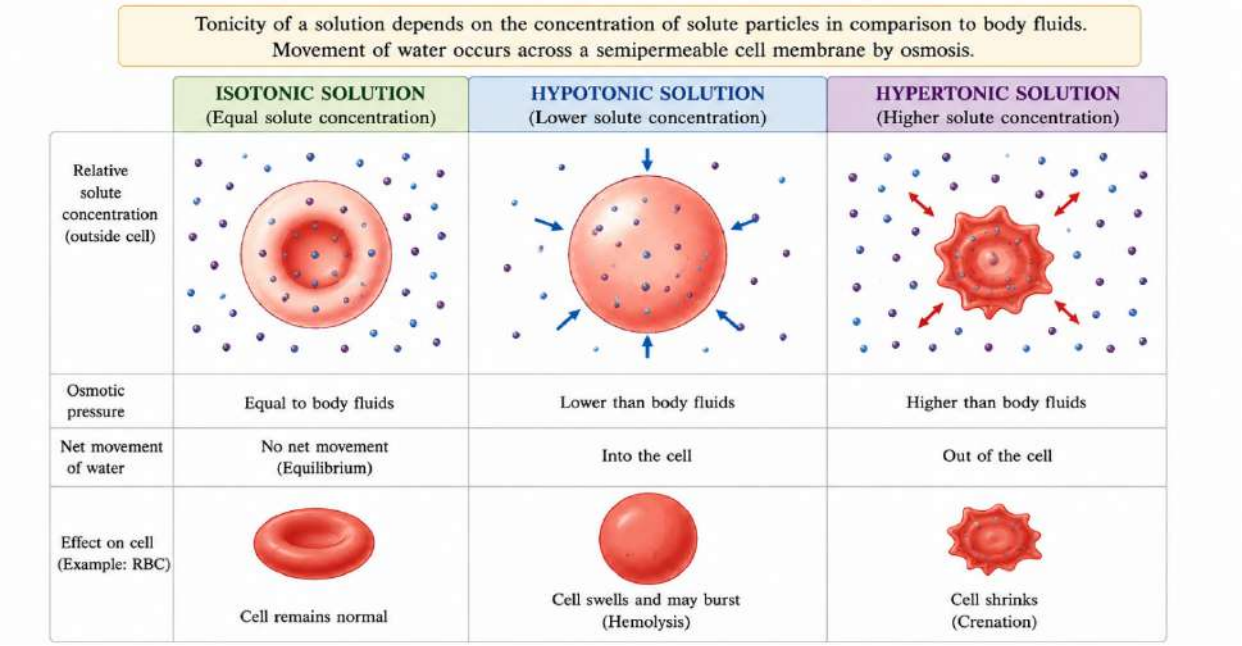


Figure 5.1: Isotonic, Hypotonic and Hypertonic Solutions

5.3 Hypotonic Solutions

A solution that has a lower osmotic pressure (more dilute) than the body fluids; has fewer dissolved particles of solute than the intracellular fluid is a hypotonic solution. In a hypotonic solution it is obvious that the concentration of solutes inside the cells is higher than the surrounding solution and water will move towards the cells by osmosis. The water moves inwards into the cells, causing them to expand into larger cells. A better than normal absorption of water can break the cell membranes. This same process is called “hemolysis” in the red blood cells. Hypotonic solutions should not be routinely administered intravenously because of possible serious physiologic consequences. But in controlled medical conditions, hypotonic solutions can be used to correct intracellular dehydration and some electrolyte imbalances. When the glucose is exhausted it is a weak solution of sodium chloride or some dextrose solutions. The medical practitioners and the pharmaceutical scientists must therefore know how the hypotonic solution functions in order to prevent any damage to the tissues, dysfunction of cells and any undesirable clinical effects due to its improper usage. Thus, the tonicity of the solution should be taken into account in preparation and/or use.

5.4 Hypertonic Solutions

Hypertonic solutions of higher osmotic pressure and higher number of dissolved particles than body fluids and intracellular fluid are present. In hypertonic solution water will passively move out of the cells into the more concentrated solution by osmosis. As the water molecules in the cells evaporate, they get smaller and lose volume. In red cells it is known as crenation. Hypertonic solutions have a number of therapeutic uses and are commonly used to treat severe hyponatremia, cerebral oedema and raised ICP. These can be hypertonic saline solution (sodium chloride > 0.9%). These solutions are focused on the primary goal of draining water from the tissues, into the bloodstream and reducing swelling while also restoring water balance. Hypertonic solutions are clinically useful, but should be used with caution because if not used properly, these solutions can cause excessive dehydration of cells. Treatment and monitoring for electrolyte levels should be monitored carefully. Therefore, it is crucial to know about hypertonicity in the formulation, clinical pharmacology and patient care of pharmaceuticals in order to prevent harm and/or improve efficacy.

5.5 Applications of Isotonicity

Isotonicity is not only a concept that is applied in formulation of pharmaceutical products, but also in clinical situations. If a pharmaceutical preparation comes in contact with body tissue or biological fluids, it must be isotonic so as to not cause discomfort, irritation or damage to body tissues. The importance of isotonicity adjustment in parenteral solutions, ophthalmic preparations, nasal formulations and irrigation solutions. Some of the common substances used in the pharmaceutical sciences to provide the desired tonicity include the use of weighting agents such as sodium chloride, dextrose, boric acid, and potassium chloride. Maintaining isotonicity will ensure the patient's comfort and improve the therapeutic effect, while reducing the risk of complications. May be painful, inflammatory, toxic or may decrease absorption of the drugs if not kept isotonic. Hence, one of the most significant quality attributes of many pharmaceutical products is the isotonicity. In the case of use safety, it is required to ensure the compatibility of physiological fluids, in the preparation of intravenous fluids or ophthalmic solutions.

Intravenous Fluids

IV fluids are infused into the bloodstream (intravenous) so they need to be very similar to the osmotic pressures of blood plasma. Intravenous solutions must be isotonic and can't hemolyze, crenate or cause osmotic stress to blood cells. Common intravenous fluids include 5% dextrose injection, normal saline and Ringer's lactate solution. These include the setting up of fluid, electrolyte, maintenance and administration of medication.

Ophthalmic Solutions

Isotonic (like tears) solutions are the least irritating and uncomfortable ophthalmic solutions. Non-isotonic preparations may cause excessive tearing, burning sensation, redness and non-compliance with the treatment. The isotonicity adjustment for patient comfort and best delivery of therapeutic agents to the ocular tissues.

5.6 Major Physiological Electrolytes

Substances that become ionized in water and are required for normal physiological functions are called electrolytes, e.g., Na^+, K^+, Ca^{2+}, Cl^-. They regulate osmotic pressure, transmission of nerve impulses, muscle contraction, enzyme activity, acid–base balance, fluid balance and metabolism of the cell. The distribution of electrolytes between the extracellular and the intracellular fluids is regulated by their biological functions. The most important electrolytes in the physiology are the sodium, potassium, chloride, bicarbonate, magnesium and phosphate ions. The electrolyte effects include dehydration, cardiac effects, neuromuscular effects, metabolic effects and life threatening effects. Hence, homeostasis of electrolytes is essential for good health and survival. Electrolytes are commonly used in a number of clinical electrolyte solutions such as intravenously administered fluids, oral rehydration and replacement solutions. The distribution of major electrolytes in various compartments of the body is shown in Figure 5.2, and their important physiological functions are summarized in Table 5.1. Physiological electrolytes are of utmost importance for the pharmaceutical scientists, clinicians and health care professionals for patient care and formulation development.

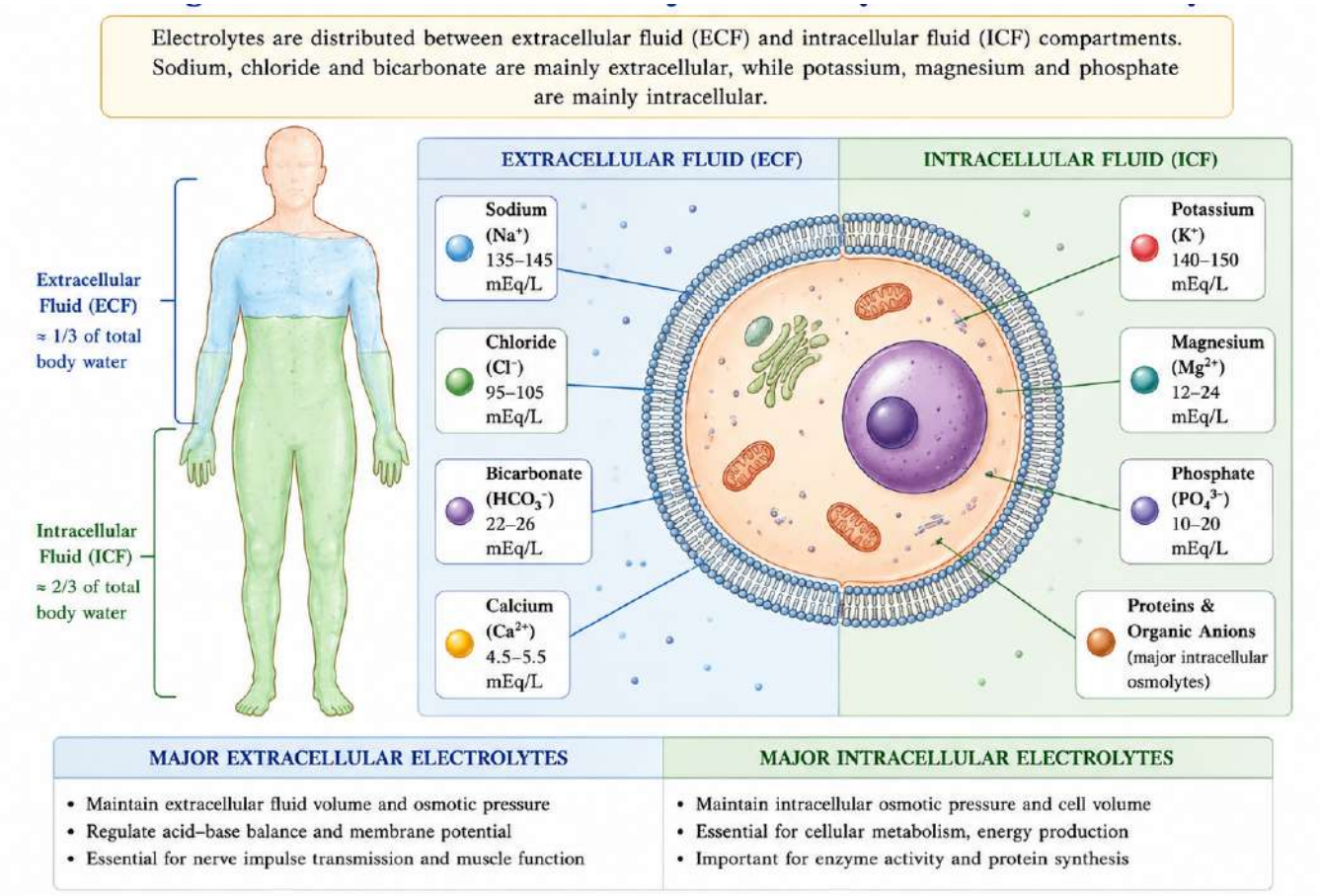


Figure 5.2: Distribution of Major Electrolytes in the Human Body

Table 5.1 Major Physiological Electrolytes and Their Functions

Electrolyte	Symbol	Major Location	Primary Functions	Clinical Significance
Sodium	Na^+	Extracellular Fluid (ECF)	Maintains extracellular fluid volume, osmotic pressure, nerve impulse transmission, and muscle contraction	Imbalance may cause dehydration, edema, hypertension, or neurological disorders
Chloride	Cl^-	Extracellular Fluid (ECF)	Maintains osmotic balance, electrical neutrality, and acid–base balance; component of gastric hydrochloric acid	Abnormal levels affect fluid balance and acid–base homeostasis
Bicarbonate	HCO_3^-	Extracellular Fluid (ECF)	Major buffer ion responsible for maintaining blood pH and	Deficiency may lead to metabolic acidosis

			acid–base equilibrium	
Potassium	K^+	Intracellular Fluid (ICF)	Maintains intracellular osmotic pressure, nerve conduction, muscle contraction, and cardiac function	Imbalance may cause arrhythmias and muscle weakness
Magnesium	Mg^{2+}	Intracellular Fluid (ICF)	Cofactor for enzymatic reactions, protein synthesis, energy metabolism, and neuromuscular function	Deficiency may cause neuromuscular and cardiovascular disorders
Phosphate	PO_4^{3-}	Intracellular Fluid (ICF)	Energy storage (ATP), bone formation, nucleic acid synthesis, and cellular signaling	Essential for metabolism and skeletal health
Calcium	Ca^{2+}	Mainly Extracellular Fluid and Bone	Blood coagulation, muscle contraction, nerve transmission, and bone mineralization	Deficiency may result in tetany and bone disorders

Extracellular Electrolytes

The electrolytes that are found in the extracellular fluid are, in the majority, found in blood plasma and interstitial fluid. They control osmotic pressure, acid–base balance and electrical neutrality, as well as fluid balance. Sodium, chloride and bicarbonate ions are the primary extracellular electrolytes that are critical to homeostasis.

Sodium Ion (Na^+)

Sodium is the major extracellular cation and plays a role in the regulation of the volume of ECF, osmotic pressure, blood pressure and transmission of nerve impulses. It is also associated with a range of processes associated with muscle contraction and the movement of nutrients across cell membranes. High and low sodium levels can cause dehydration and edema, confusion, seizures and cardiovascular effects.

Chloride Ion (Cl^-)

The main extracellular anion present in the body is chloride, which plays a role in osmotic balance, maintaining electrical neutrality and regulating acid–base balance. It also plays an important role in the manufacture of hydrochloric acid in the stomach that is required for digestion.

Bicarbonate Ion (HCO_3^-)

The bicarbonate buffer is one of the major buffers of the body and plays a crucial role in the acid-base balance regulation. Eliminates excess acids and keeps the physiological pH normal for normal metabolic functions.

Intracellular Electrolytes

Intracellular electrolytes are primarily located within the cell, and are essential to cellular metabolism, energy production, protein synthesis and electrical activity. The chief electrolytes of the intracellular fluid are potassium ions, magnesium ions, and phosphate ions.

Potassium Ion (K^+)

The most abundant cation within the cells is potassium and it is also very important in the conduction of nerve impulses, muscle contraction, cardiac rhythm, protein synthesis and maintaining the osmotic pressure of the intracellular environment. Potassium balance disturbances may have a major impact on cardiac and neuromuscular functions.

Magnesium Ion (Mg^{2+})

Mg2+ is a cofactor for many enzymes which need it for energy metabolism, nucleic acid synthesis and protein production. It also helps to facilitate normal neuromuscular transmission and to keep normal cardiac function.

Phosphate Ion (PO_4^{3-})

The main intracellular anion is phosphate, which plays a role in energy storage, in cell signalling and for nucleic acid and bone mineralization. It is part of adenosine triphosphate (ATP) that furnishes the cells with energy required to do work.

5.7 Functions of Major Physiological Ions

Physiological ions are ions that are electrically charged particles which are necessary for the normal functioning of the body. These ions are found in body fluids and tissues and act to control the body's fluid balance, osmotic pressure, acid–base balance, nerve impulse transmission, muscle contraction, enzyme activity and cellular metabolism. Physiological ions are ions that play a role in the physiology of the body, e.g. sodium, potassium, chloride, bicarbonate, calcium, magnesium and phosphate ions. Sodium and chloride mainly play a role in maintaining the extracellular fluid volume and osmotic

pressure while potassium plays a role in maintaining the extracellular fluid balance in the body and plays a role in the neuromuscular functions of the body. Bicarbonate is a major buffer ion which helps to keep blood pH within normal physiological limits. Calcium is required to help muscles contract, blood clot, transmit nerve signals and build bones. Magnesium is a cofactor of numerous enzymes, and is a part of energy metabolism. Phosphate is an essential component of ATP, nucleic acids and cell signaling. These ions need to be maintained at the correct levels to maintain homeostasis and normal functioning. Abnormal levels of ions can result in serious metabolic, cardiovascular disorders, neurological and muscular disorders. Thus, knowledge about the role of physiological ions should be gained in the field of pharmaceutical sciences and in clinical practice.

5.8 Electrolytes of replacement therapy

Electrolyte replacement therapy (ERT): intravenous fluids that have the proper electrolyte to correct the electrolyte disturbance in a patient who is dehydrated (fluid loss) or who has an electrolyte deficiency/metabolic imbalance. Electrolyte imbalance can be caused by diarrhea, vomiting, burns, kidney disease, surgery or severe illness. Replacement therapy is used to restore fluid volume, normal cell function, osmotic balance and to avoid life threatening complications. All the common electrolyte replacement medicines contain sodium chloride, potassium chloride, calcium chloride or oral rehydration salts (ORS). They come in different forms such as injection, liquid for oral ingestion, tablets or powder to be reconstituted. The electrolyte therapy given will depend on the clinical condition and the kind of electrolyte deficiency. Electrolyte replacement therapy is an important aspect of emergency medicine, critical care, pediatrics and general medicine. With good administration physiological equilibrium will be restored, patients will recover and complications caused by electrolyte disturbances will be prevented.

Sodium Chloride

Category

Sodium chloride is a fluid replenisher, electrolyte replenisher and isotonicity adjusting agent. One of the most commonly used pharmaceutical electrolytes and a key part of the extracellular fluid.

Properties

Sodium chloride is a white crystalline powder or colourless crystals (also called salt) that tastes salty. Clear solution that is soluble in water. Stable in most pharmaceutical formulations and under normal storage conditions with respect to chemical changes. Sodium chloride plays a major role in the osmotic pressure and fluid balance in the body.

Uses

For electrolyte replacement, isotonic and preparation solutions, irrigation solutions and parenterals. It is used typically to prevent dehydration, shock, electrolyte imbalance and as an intravenous solution when giving intravenous drugs, and is a 0.9% sodium chloride injection (normal saline). It's also a tonicity adjusting agent in ophthalmics and parenterals.

Potassium Chloride

Category

Potassium chloride belongs to a class of drugs known as potassium salts: potassium supplements and electrolyte replenisher to correct a potassium deficiency and restore the normal electrolyte balance inside the cells.

Properties

Potassium chlorine is a white, crystal powder or colourless crystal. Lacks have no smell, have a salty taste and are very soluble in water. Chemically stable and readily ionizes to potassium and chloride in water. IC (intracellular) cation which is essential for cell function is potassium.

Uses

Treat and prevent hypokalemia (or any other hypo?) with potassium chloride, especially if there is too much fluid loss or prolonged IV therapy or if diuretics are used. It can also be found in electrolyte replacement fluids and in IV solutions. Potassium is necessary for a healthy heart rhythm, muscle and nerve function.

Calcium Chloride

Category

Calcium chloride is a type of medicine known as calcium salts and electrolyte replacements which replace calcium in people who are low in calcium in their body or who do not have enough calcium in their body.

Properties

Calcium chloride is a salt that is very soluble and white, or colourless, and crystalline. It is hygroscopic and easily absorbs moisture from the air. It releases calcium ions in the solution, necessary for the functioning of a number of physiological processes, including blood coagulation, muscle contraction.

Uses

The calcium chloride is used in treating hypocalcemia, cardiac resuscitation, electrolyte replacement and calcium deficiency disorders. It can also be used in emergency medicine to treat some of the toxic

effects of hyperkalemia and magnesium toxicity. The calcium chloride can be used to quickly correct calcium in patients in critical condition.

Oral Rehydration Salt (ORS):

Composition

Oral Rehydration Salt (ORS) is a special formulation of electrolytes and glucose, which can be used to replace both water and electrolytes lost due to diarrhoea, vomiting and dehydration. WHO recommends ORS to be made up of sodium chloride, potassium chloride, trisodium citrate dihydrate and glucose anhydrous in water.

Mechanism of Action

The mechanism of ORS is the same as the sodium-glucose co-transport mechanism present in the intestinal mucosa. The glucose is used to carry in the sodium ions and water enters by osmosis. This process will rehydrate and restore electrolyte balance in an efficient manner. The potassium and citrate also helps correct the electrolyte deficiencies and metabolic acidosis which can be seen in dehydration.

Therapeutic Uses

The use of ORS is high in the treatment and prevention of dehydration caused by high fluid requirements of acute diarrhoea, gastroenteritis and cholera. It is one of the most cost effective and most effective treatment of morbidity and mortality from dehydration particularly in children and old people.

5.9 Physiological Acid–Base Balance

Physiological acid–base balance is the regulation and maintenance of the hydrogen ion concentration in a narrow range that is necessary for normal cellular and metabolic functions. The normal PH of arterial blood is 7.35 to 7.45. Any deviation from this range will affect the activity of enzymes, metabolism of cells and activity of organs. The regulation of acid–base balance is achieved by the regulation of the buffer system, respiratory system, and kidneys working together. The buffers confer instant resistance to pH changes and the lungs control carbon dioxide level, while the kidneys control the excretion or retention of hydrogen and bicarbonate ions. The appropriate acid–base balance is imperative for physiological stability, normal biochemical reactions and a healthy lifestyle. If the acid–base imbalance is not corrected, it may result in either acidosis or alkalosis with potentially important clinical implications.

Importance of Acid–Base Balance

To ensure normal function of enzymes, metabolic reactions, distribution of electrolytes, transport of oxygen and normal cell function, the acid–base balance must be maintained. In an ideal pH, the optimum physiological function will occur without causing an injury to the tissues because of excessive pH of the environment created by the too low or excessive pH.

Regulation of Blood pH.

Blood pH regulation by buffers, respiratory mechanisms and renal mechanisms is a complex process. CO2 concentration is regulated by the respiratory system and hydrogen ions are secreted by the kidneys and bicarbonate is reabsorbed. All these mechanisms are interrelated and work together to keep the pH of the blood within the normal physiological range.

Role of Buffer Systems.

The initial line of defense against changes in pH is buffer systems. There are three major physiological buffers, bicarbonate buffer system, phosphate buffer system and protein buffer system. These systems are able to neutralise excess acids or bases and maintain the acid–base balance of the body.

5.10 Clinical Significance of Electrolyte Imbalance

An electrolyte imbalance occurs due to the change in the amount of one or more electrolytes from the normal range in the body. These disturbances may result in serious cell dysfunction, and have a significant impact on clinical outcomes. The altered sodium level may result in neurological dysfunction and/or seizures in hyponatremia and dehydration in hypernatremia. The imbalance of potassium is of particular importance, because it may have a direct effect on the cardiac function: Hypokalemia may lead to muscle weakness and arrhythmias while hyperkalemia can induce life-threatening cardiac arrest. Abnormal calcium levels can cause tetany, muscle spasm, bone disease and heart problems. Dysfunctions in magnesium and phosphates also affect enzyme functions, energy metabolism and neuromuscular functions. Electrolyte abnormalities can occur due to dehydration or renal disease, endocrine disorders, gastrointestinal losses, burns, medication or prolonged illness. The timely diagnosis and timely replacement therapy is crucial in preventing complications. This creates clinical implications that allows health care providers to provide an appropriate treatment and physiological balance in the case of electrolyte balance.

Chapter Summary

One of the important pharmaceutical properties is isotonicity which is the compatibility of the pharmaceutical preparations with body fluids. Cells are normal in size when using isotonic solutions, they will swell when using hypo tonic solutions and they will shrink when using hypertonic solutions. The functions of electrolytes are fluid balance, osmotic pressure, nerve conduction, enzyme activity,

muscle contraction and acid–base regulation. Sodium, chloride and bicarbonate ions are the main extracellular electrolytes and potassium, magnesium and phosphate ions are the major intracellular electrolytes. The electrolyte replacement therapy is the use of electrolyte solutions such as sodium chloride, potassium chloride, calcium chloride and oral rehydration salts that restore the physiological balance. Regulation of acid–base balance by buffer system, respiratory function and renal regulation. Clinically, electrolyte disorders can have a severe impact, and should be rapidly diagnosed and treated.

Key Points

- Isotonic solutions possess the same osmotic pressure as body fluids.
- Hypotonic solutions cause cellular swelling.
- Hypertonic solutions cause cellular shrinkage.
- Sodium is the principal extracellular cation.
- Potassium is the principal intracellular cation.
- Bicarbonate is the major physiological buffer ion.
- Sodium chloride is widely used in electrolyte replacement therapy.
- ORS prevents and treats dehydration effectively.
- Blood pH is normally maintained between 7.35 and 7.45.
- Buffer systems, lungs, and kidneys regulate acid–base balance.
- Electrolyte imbalance may cause serious physiological disorders.

Review Questions

Short Answer Questions

1. Define isotonicity.
2. Differentiate between isotonic, hypotonic, and hypertonic solutions.
3. What are physiological electrolytes?
4. State the functions of sodium ions.
5. Write the uses of potassium chloride.
6. What is ORS?
7. Mention the composition of ORS.

8. Define acid–base balance.
9. Name the major physiological buffer systems.
10. What is electrolyte replacement therapy?

Long Answer Questions

1. Explain isotonicity and its pharmaceutical significance.
2. Discuss major physiological electrolytes and their functions.
3. Describe sodium chloride, potassium chloride, and calcium chloride.
4. Explain the composition, mechanism, and uses of ORS.
5. Discuss physiological acid–base balance and its regulation.
6. Explain the clinical significance of electrolyte imbalance.

Multiple Choice Questions (MCQs)

1. Normal saline contains:
   a) 0.45% NaCl
   b) 0.9% NaCl
   c) 1.5% NaCl
   d) 5% NaCl
   Answer: b

2. The principal intracellular cation is:
   a) Sodium
   b) Calcium
   c) Potassium
   d) Chloride
   Answer: c

3. ORS is primarily used for:
   a) Hypertension
   b) Dehydration
   c) Diabetes
   d) Anemia
   Answer: b

4. Normal blood pH is:
   a) 6.8–7.0

b) 7.35–7.45

c) 7.8–8.0

d) 8.2–8.5

Answer: b

5. The major extracellular cation is:

a) Potassium

b) Magnesium

c) Sodium

d) Calcium

Answer: c

6. Which electrolyte is important for cardiac rhythm?

a) Chloride

b) Potassium

c) Phosphate

d) Bicarbonate

Answer: b

7. Which system provides immediate resistance to pH changes?

a) Respiratory system

b) Renal system

c) Buffer system

d) Nervous system

Answer: c

8. Calcium chloride is used in the treatment of:

a) Hypocalcemia

b) Hyperglycemia

c) Hypertension

d) Hyperlipidemia

Answer: a

9. Bicarbonate primarily helps maintain:

a) Blood pressure

b) Acid–base balance

c) Bone density

d) Vision

Answer: b

10. Excessive potassium levels may cause:

    a) Anemia

    b) Cardiac arrhythmias

    c) Cataracts

    d) Osteoporosis

    Answer: b

UNIT III

VOLUMETRIC ANALYSIS

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Chapter 6: Acid–Base Titrations

Learning Objectives

After studying this chapter, the student will be able to:

- Define acid–base titrations and explain their pharmaceutical importance.
- Describe acid–base indicators and their characteristics.
- Explain the theories of acid–base indicators.
- Classify acid–base titrations based on the strength of acids and bases.
- Select suitable indicators for different titrations.
- Apply acid–base titration principles in pharmaceutical analysis.

6.1 Introduction to Acid–Base Titrations

One of the most important and widely used methods used in volumetric analysis is acid–base titration. Based on the quantitative neutralisation reaction between an acid and a base to form a salt and water. It is a method that is widely used in pharmaceutical laboratories for quantifying, purifying, and verifying the strength of pharmaceutical substances. In a titration, the known concentration solution is slowly added to the solution of the analyte until the reaction is complete. Equivalence point is the point where there are equal amounts of acid and base present. The completion of the reaction is determined by an indicator or by an instrumental method; the point at which the reaction is completed is called the endpoint of the practical analysis. Acid–base titrations are extensively used for the assay of pharmaceutical compounds, standardization of reagents, quality control testing, and

pharmacopoeial analysis. Their popularity is due to their simplicity, accuracy, precision, and low cost. The titration curve of different acid-base systems varies with the strengths of the reactants. The different types of acid–base titrations are listed in Table 6.1. Pharmaceutical workers must have a good knowledge of the principles of acid-base titration since the techniques are fundamental to many analytical assays employed in the manufacturing, research, and quality assurance of pharmaceuticals.

Table 6.1 Common Acid–Base Indicators and Their pH Range

Indicator	Type	Color in Acidic Medium	Color in Alkaline Medium	pH Transition Range	Common Applications
Methyl Orange	Weak Organic Acid	Red	Yellow	3.1 – 4.4	Strong acid–weak base titrations
Methyl Red	Weak Organic Acid	Red	Yellow	4.4 – 6.2	Strong acid–weak base titrations
Bromocresol Green	Weak Organic Acid	Yellow	Blue	3.8 – 5.4	Acidic titrations and pharmaceutical assays
Bromothymol Blue	Weak Organic Acid	Yellow	Blue	6.0 – 7.6	Strong acid–strong base titrations
Phenol Red	Weak Organic Acid	Yellow	Red	6.8 – 8.4	Neutralization reactions and biological systems
Phenolphthalein	Weak Organic Acid	Colorless	Pink	8.2 – 10.0	Weak acid–strong base titrations
Thymol Blue (1st Transition)	Weak Organic Acid	Red	Yellow	1.2 – 2.8	Highly acidic solutions
Thymol Blue (2nd	Weak Organic	Yellow	Blue	8.0 – 9.6	Alkaline titrations

Transition)	Acid				
Thymolphthalein	Weak Organic Acid	Colorless	Blue	9.3 – 10.5	Strongly alkaline titrations
Litmus	Natural Indicator	Red	Blue	4.5 – 8.3	General acid–base identification

6.2 Acid–Base Indicators

Acid-Base Indicators are organic compounds that change colour in a certain range of pH and are utilised to discover the endpoint of an acid-base titration. Usually, these are weak acids or bases, whose non-ionised and ionised forms are of different colours. These forms are in equilibrium and as hydrogen ions are changed in a titration, there is a characteristic colour change. The choice of indicator is important because the indicator will change colour as close as possible to the equivalence point of the titration. Depending on the type of titration being performed, each indicator would have a different pH range where the indicator would change colour in the titration. Pharmaceutical analysis involves the use of indicators such as methyl orange, methyl red, bromothymol blue, phenolphthalein and thymolphthalein. The pH ranges and colour change of the pH indicator used in the lab are listed in Table 6.1, and the colour change of the indicator in acid and alkaline media is shown in Figure 6.1. Acid-base indicators are important in the fields of pharmaceutical quality control and analytical chemistry because they can give a simple and accurate endpoint determination method for a titration. Appropriate choice and use of them greatly enhance the accuracy and repeatability of volumetric

analytical methods.

Indicator	pH Transition Range	Color at Different pH						
		pH 2	pH 4	pH 6	pH 7	pH 9	pH 11	pH 12
Methyl Orange	3.1 – 4.4							
Methyl Red	4.4 – 6.2							
Bromothymol Blue	6.0 – 7.6							
Phenol Red	6.8 – 8.4							
Phenolphthalein	8.2 – 10.0							
Thymol Blue (1st Transition)	1.2 – 2.8							
Thymol Blue (2nd Transition)	8.0 – 9.6							
Thymolphthalein	9.3 – 10.5							
Litmus	4.5 – 8.3							

Figure 6.1: Colour Change of Acid–Base Indicators

Definition

Acid-base indicator: A chemical substance that changes colour at the point where the acid–base reaction takes place and is either a weak organic acid or a weak organic base.

Characteristics of Ideal Indicators

Ideal properties of an acid-base indicator: It changes colour over a sharp range of pH. The colour change should be clearly noticeable but not everlasting and should not be light and temperature-sensitive. Should have no chemical reaction with the reactant (analyte) or the titrant, and should be performed on a small scale. Stability, sensitivity and rapidity of colour change are other important properties of an ideal indicator.

6.3 Theories of Acid–Base Indicators

There are several theories that account for the colour change of an acid–base indicator. The most important and accepted of them are the Ostwald Theory and the Quinonoid Theory. Theories have been provided to explain the change in indicator colour during a titration that occurs when the pH changes. The colour change of the indicators is due to the change in the molecular structure or degree of ionisation of the indicators with the change in hydrogen ion concentration. These changes in pH during the neutralisation process result in shifting of the molecular equilibrium between the different molecular forms of the indicator, which accounts for the changes in colour observed. The knowledge

of indicator theories helps the analyst to select the proper indicator for the particular titration and to accurately determine the endpoint. In each theory, there are different views of indicators, and each of these theories gives a complete picture of the work of indicators. Acid-Base Indicators Theory is of special importance in pharmaceutical analysis, as the exact determination of the end-point is necessary to get a consistent result in the assay performed. Theories of Indicators will continue to play an important role in volumetric analysis and in analytical chemistry**.**

Ostwald Theory

Ostwald's theory holds that any acid–base indicator is a weak acid or weak base that is in equilibrium between an ionised form and a unionised form. These forms are in various hues. If the solution is a weak acid indicator:

$HIn \rightleftharpoons H^+ + In^-$

The unionised form appears in one colour, the ionised form in another colour. The equilibrium shifts to the unionised form in an acidic medium and towards the ionised form in an alkaline medium. This change in colour is observed during titration as a result of this shift.

Quinonoid Theory

According to the Quinonoid Theory, the change of colour of an indicator is accounted for by changes in the structure between benzenoid and quinonoid forms. The benzenoid structure is colored with one colour, and the quinonoid structure is colored with another colour. The change in pH turns one into the other, creating the characteristic pH change. One of the classic examples is phenolphthalein, which is colourless in an acidic solution and pink in an alkaline solution.

6.4 Classification of Acid–Base Titrations

The titrations are classified based on the strengths of the acids and bases used for the neutralization reaction in acid–base titrations. The form of the titration curve, the pH at the equivalence point and the choice of indicator depend on the strength of the reacting species. By choosing the right titration conditions and the accurate analytical result via appropriate classification, the analyst can choose the right conditions. There are essentially four types of acid base titrations: strong acid–strong base titrations, weak acid–strong base titrations, strong acid–weak base titrations and weak acid–weak base titrations. In each category, the conditions for neutralisation vary, and the indicators for determining the endpoint vary. The titrations are very common in pharmaceutical analysis for determination of assay, standardisation of reagents, purity testing, and evaluation of quality. The knowledge of the classification of acid–base titrations is very crucial as it is the basis for choosing an appropriate analytical procedure and interpreting the titration results accurately. There are also different types of

titrations with different curves of neutralization and buffer regions, which will impact the precision of the analysis and the point at which the endpoint will occur summarized in Figure 6.2.

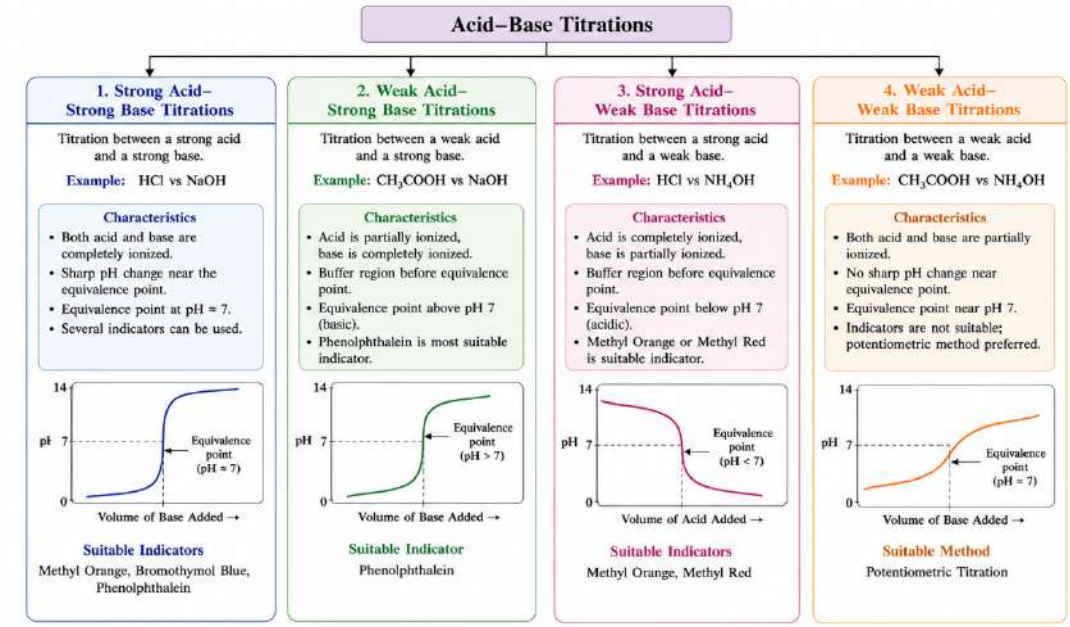

Figure 6.2: Classification of Acid–Base Titrations

Strong Acid–Strong Base Titrations

Strong acid – strong base titrations are titrations where the acid and the base are strong. They may include hydrochloric acid, sodium hydroxide, sulphuric acid and potassium hydroxide. The region of the equivalence point of these titrations is approximately at the neutral pH (7), and the change in pH at the equivalence point is significant. The pH shift is quite large, which means that several indicators can be successfully used. There is a large pH change that can be used for a number of indicators.

Weak Acid–Strong Base Titrations

In weak acid–strong base titrations, the acid is only 50% ionised, while the base is completely ionized. It can be done by titrating acetic acid with NaOH. Salt hydrolysis results in the equivalence point being higher than pH7. Phenolphthalein has a similar pH range to the alkaline endpoint and is used very extensively.

Strong Acid–Weak Base Titrations

These titrations are between a strong acid and a weak base, e.g., hydrochloric acid and ammonium hydroxide. The equivalence point is below 7 since the salt formed is hydrolysed. Typically, methyl orange and methyl red are good indicators for such titrations.

Weak acid–weak base titrations.

The titrations of partially ionised acid – base pairs are called weak acid – weak base titrations. The pH change is not abrupt; there is not much difference between the pH at the equivalence point and the pH at the point being approached, and this will cause problems in detecting a visual endpoint. Usually, instrumental methods are preferred rather than the use of conventional indicators, and potentiometric titration is a common example of such a method.

6.5 Preparation of Hydrochloric Acid Solution

One of the most frequently used standard reagents in acid–base titrations and pharmaceutical analysis is hydrochloric acid. The concentrated hydrochloric acid may be available in a more concentrated form; therefore, it is important to carefully dilute the acid to the proper normality or molarity. Hydrochloric acid is a secondary standard because it is volatile, and it would not be possible to weigh it directly to prepare a solution of known concentration. The solution prepared should then be standardised with the help of a primary standard substance. The concentrated hydrochloric acid is added to a measured quantity of the volumetric flask containing distilled water. The solution is well mixed and then adjusted to the correct volume. Safety precautions should be taken since hydrochloric acid is corrosive and emits irritating fumes. It is always important to add the acid to water and not water to the acid, to avoid excessive heat generation or splashing. After preparation, the solution is kept in well-closed glass containers to minimise evaporation, leading to concentration changes. Hence, Hydrochloric acid solutions are used in most of the laboratory in pharmaceutical industry for neutralisation titration, in the assay and for standardisation of alkaline solutions. The key to the correct preparation of a hydrochloric acid solution is that any error produced during the preparation will directly affect the analytical result and the quality control process in pharmaceuticals.

6.6 Standardisation of Hydrochloric Acid

The process of measuring the concentration of a solution in an accurate manner, using the known concentration of another pure substance, is called standardisation. Hydrochloric acid is made up from secondary standards as it cannot be prepared to a precisely known concentration; it has to be standardised first before using it in analytical procedures. Sodium carbonate is very pure, stable, non-hygroscopic and readily available, and therefore it is used as a primary standard for the standardisation of hydrochloric acid. The quantity of the sodium carbonate sample is known, is dissolved in distilled water and is then standardised and titrated against the hydrochloric acid solution using the indicator methyl orange. The endpoint is indicated by a change of colour from yellow to orange-pink. To find the exact concentration of hydrochloric acid, the amount of hydrochloric acid required for complete reaction is measured, and the principles of volumetric analysis are used to find the actual concentration. The adoption of standardisation has helped ensure accuracy and

dependability in pharmaceutical testing, quality control and research applications. The procedure will be repeated several times if it is necessary to get the concordant reading and to minimise the error in the experiment. This is important, as any difference in concentration will cause a false reading of the assay and will impact an assay of a pharmaceutical product. Thus, solutions of hydrochloric acid can be used as titrants in many acid–base analyses.

6.7 Preparation of Sodium Hydroxide Solution

Sodium hydroxide solution is the common titrant used in volumetric analysis to determine the amount of acidic pharmaceutical material and is also used in acid–base volumetric analysis. NaOH is very hygroscopic and absorbs CO_2 available in the air to form sodium carbonate. So, NaOH is not a primary standard and has to be prepared in a particular manner before it can be standardised. An estimated quantity of sodium hydroxide pellets is dissolved in freshly boiled and cooled distilled water to make up the solution. Desired water is free of carbon dioxide; otherwise, the carbon dioxide will react with the sodium hydroxide, and the concentration of the water will change. Once completely dissolved, the solution is moved to a volumetric flask and water is added to make up to the volume. The solution is prepared and kept in tightly closed polyethene bottles so that it will not absorb CO2 from the atmosphere. Sodium hydroxide solutions are widely used in the laboratories for titration of acidic compounds, in assay of the ingredients of pharmaceuticals and also in the standardisation of acidic solutions. The actual concentration that is achieved in the preparation cannot be guaranteed so the solution needs to be standardized prior to analysis. The sodium hydroxide solutions should be carefully prepared and stored so as to ensure their accuracy, stability and reliability in the pharmaceutical analysis.

6.8 Standardization of Sodium Hydroxide

For quantitative analysis, the concentration of sodium hydroxide solution is a definite amount after standardisation. Most often a primary standard acid, like oxalic acid, potassium hydrogen phthalate (KHP) or benzoic acid, is used for the standardization. Oxalic acid is often used for a variety of reasons: it is available to a high degree of purity, it has a known composition and it is easily weighed. In the process, a certain amount of the primary standard compound is dissolved in distilled water and then titrated against sodium hydroxide solution with phenolphthalein as an indicator. When the permanent pale pink colour is observed and remains unchanged, the endpoint is reached, and the process should be repeated until it reaches the endpoint. Using a titration to measure the amount of NaOH required to neutralise is used to determine the exact concentration of NaOH needed for the neutralisation. The titration is repeated to obtain concordant results to improve the accuracy. Sodium hydroxide solutions are commonly used as a standard in quality control, research or routine assay. Systematic errors are minimized, resulting in reliable analytical results, by accurate standardization.

Moreover, the process is essential in pharmaceutical laboratories for accurate concentration determination, which is crucial for regulatory compliance and product assessment.

6.9 Theory of Neutralization Reactions

The basis of Volumetric analysis and acid/alkali titration is a type of chemistry called a neutralization reaction. A neutralization reaction that is quantitative is the reaction between an acid and a base to form salt and water. According to the Arrhenius concept, acids donate a hydrogen ion (H^+) and bases donate a hydroxyl ion (OH^-). The hydrogen ions neutralise the hydroxyl ions to form water molecules as indicated:

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

The reaction is fast and goes to completion and is therefore suitable for analytical purposes. The equivalence point occurs when the quantity of acid and base are equivalent. This is a point which can be determined in the titration of an acid-base reaction using an appropriate indicator or by instrumental techniques. Neutralisation reactions are reactions in which the pH will change when titrating. The extent of the change in pH will depend on the relative strengths of the acid and base. The solution formed by a strong acid/strong base reaction will be neutral at the equivalence point and the solution formed by reaction of a weak acid/strong base or vice versa will be acidic/alkaline at the equivalence point due to hydrolysis effects. Neutralization reaction is a general reaction that is used for assay of drugs, in standardization of solutions, purity determination and quality control testing. The neutralization theory is an important theory for the interpretation of the titration results and choice of analytical method.

6.10 Neutralization Curves

The curve that plots the change in pH in an acid–base titration is referred to as a neutralization curve. Curves provide important information about the process of titration, such as the buffer regions, equivalence points and indicators. The shape of the neutralization curve is dependent on the strength of the acid and base of the reaction. The neutrality curve is an important tool in pharmaceutical analysis as it helps the analyst to understand the titration behaviour and to accurately determine the end point. Every acid base system has its own pH change to acid and base ratio which in turn dictates the acid base indicator and analyses to be employed.

Strong Acid–Strong Base

Strong acid–strong base titrations are ones in which both the acid and the base are completely ionized in solution. The pH changes slowly at the beginning of the equivalence point and rapidly at the end of the equivalence point. Equivalence point occurs at around pH 7 since the salt produced does not

undergo hydrolysis. Due to the abrupt change in pH, a few indicators can be used, such as: methyl orange, bromothymol blue, phenolphthalein.

Weak Acid–Strong Base

If the first species is a WEAK ACID (WEAK BASE) then there will be a weak acid (WEAK BASE) component to the titration because the titration will have a buffer region before the equivalence point. This equivalence point is at pH>7.0 because the salt formed is hydrolysed. Usually phenolphthalein is the most suitable indicator for these titrations.

Strong Acid–Weak Base

The pH at the equivalence point of a strong acid–weak base titration will be less than 7 if the salt being formed is acidic. The change in the colour of the indicator is not as distinct as in the strong acid–strong base titration. Methyl orange, and methyl red are common indicators used.

Very Weak Acids and Bases:

The pH changes in the titration of a very weak acid and very weak base are very gradual and the equivalence point is not clearly defined. The end point is rarely readily observed by visual inspection and there are no conventional end points. Normally, a chemical's accurate analysis would be carried out by instrumental methods such as potentiometric titration.**6.11 Assay of Ammonium Hydroxide**

The usual method for assaying ammonium hydroxide is by titration with a standardised hydrochloric acid solution. Ammonium hydroxide is a weak base, and will react quantitatively with hydrochloric acid in the following reaction:

$NH_4OH + HCl \rightarrow NH_4Cl + H_2O$

An accurately measured quantity of ammonium hydroxide solution is then placed in a conical flask and made up to volume with distilled water. Indicator that is often used is methyl red which gives a sharp endpoint in the acidic pH range suitable for weak base titrations. This solution is then titrated using a standard hydrochloric acid solution (colour change). The quantity of hydrochloric acid used is measured then the ratio of strength and percentage purity of ammonium hydroxide is worked out. The assay is carried out in a controlled laboratory environment, minimizing the experimental error and obtaining repeatability. This is the typical approach taken in the pharmaceutical industry and quality testing laboratories to verify ammonium hydroxide preparations. For the purposes of compliance to the pharmacopoeial specifications, product quality maintenance and verification of concentration of pharmaceutical preparations that contain ammonium hydroxide, accurate assay results are crucial.**Numerical Problems**

1. Calculate the normality of hydrochloric acid if 25 mL of HCl neutralizes 20 mL of 0.1 N sodium carbonate solution.
2. A 0.1 N sodium hydroxide solution requires 18.5 mL to neutralize 20 mL of oxalic acid solution. Calculate the normality of oxalic acid.
3. Calculate the strength (g/L) of a 0.5 N hydrochloric acid solution.
4. Determine the percentage purity of ammonium hydroxide if 20 mL of sample requires 24.5 mL of 0.1 N HCl.
5. Calculate the volume of 0.1 N NaOH required to neutralize 25 mL of 0.2 N HCl.

Chapter Summary

One of the important volumetric analysis methods, such as Acid–base titrations, is the neutralization of acids and bases. Common titrants are hydrochloric acid and sodium hydroxide that are not primary standards and should be standardised. The neutralization reaction forms salt and water and is utilized to find out the strength of acids and bases using acid base titrations. A graph which gives the change in pH at each stage of a titration is called a neutralization curve and is used to select an appropriate indicator. The equivalence points will vary with the relative strengths of the various systems of acids and bases. The assay of ammonium hydroxide is carried out by standardised hydrochloric acid, it is a very common procedure in pharmaceutical analysis. The acid–base titrations are still of significance in the present day in the quality control, preparation and determination of pharmaceuticals.

Key Points

- Acid–base titrations are based on neutralization reactions.
- Hydrochloric acid and sodium hydroxide are secondary standards.
- Standardization ensures accurate concentration determination.
- Neutralization produces salt and water.
- Neutralization curves aid endpoint detection.
- Equivalence points vary according to acid and base strength.
- Indicators must be selected according to titration type.
- Ammonium hydroxide is assayed using standardized hydrochloric acid.
- Acid–base titrations are widely used in pharmaceutical analysis.
- Accurate titration improves reliability of analytical results.

Review Questions

Short Answer Questions

1. Define acid–base titration.
2. What is the principle of acid–base titration?
3. Define acid–base indicator.
4. State any four characteristics of an ideal acid–base indicator.
5. Explain the Ostwald theory of indicators.
6. What is the Quinonoid theory?
7. Classify acid–base titrations.
8. Give two examples of strong acid–strong base titrations.
9. Why is hydrochloric acid considered a secondary standard?
10. Why is sodium hydroxide solution not used as a primary standard?
11. Name the primary standard used for standardization of hydrochloric acid.
12. Name the indicator commonly used in the standardization of hydrochloric acid.
13. Name the primary standard used for standardization of sodium hydroxide.
14. What is the equivalence point in a titration?
15. What is meant by the end point of a titration?
16. Define neutralization reaction.
17. What is a neutralization curve?
18. Which indicator is commonly used in weak acid–strong base titrations?
19. Why are indicators unsuitable for weak acid–weak base titrations?
20. Write the reaction involved in the assay of ammonium hydroxide.

Long Answer Questions

1. Discuss the principle, advantages, and pharmaceutical applications of acid–base titrations.
2. Explain acid–base indicators and describe the characteristics of an ideal indicator.
3. Discuss the Ostwald and Quinonoid theories of acid–base indicators.

4. Classify acid–base titrations with suitable examples.
5. Describe the preparation and standardization of hydrochloric acid solution.
6. Explain the preparation and standardization of sodium hydroxide solution.
7. Discuss the theory of neutralization reactions in detail.
8. Explain the neutralization curve of strong acid–strong base titration.
9. Describe the neutralization curve of weak acid–strong base titration.
10. Explain the neutralization curve of strong acid–weak base titration.
11. Why are weak acid–weak base titrations difficult to perform using indicators?
12. Describe the assay procedure of ammonium hydroxide with principle and reaction.
13. Compare equivalence point and end point in acid–base titrations.
14. Discuss the importance of acid–base titrations in pharmaceutical analysis.
15. Explain the factors affecting the selection of indicators in acid–base titrations.

Multiple Choice Questions (MCQs)

1. Acid–base titration is based on:

a) Oxidation reaction
b) Reduction reaction
c) Neutralization reaction
d) Precipitation reaction

Answer: c) Neutralization reaction

2. The product formed during a neutralization reaction is:

a) Salt and water
b) Acid and water
c) Base and water
d) Salt only

Answer: a) Salt and water

3. Which of the following is a secondary standard?

a) Sodium carbonate
b) Oxalic acid

c) Potassium hydrogen phthalate

d) Hydrochloric acid

Answer: d) Hydrochloric acid

4. Hydrochloric acid is commonly standardized against:

a) Sodium carbonate

b) Sodium chloride

c) Potassium chloride

d) Ammonium chloride

Answer: a) Sodium carbonate

5. Sodium hydroxide is standardized using:

a) Sodium carbonate

b) Oxalic acid

c) Sodium chloride

d) Potassium bromide

Answer: b) Oxalic acid

6. Which indicator is commonly used in the standardization of sodium hydroxide?

a) Methyl orange

b) Methyl red

c) Phenolphthalein

d) Bromothymol blue

Answer: c) Phenolphthalein

7. According to Ostwald theory, indicators are:

a) Strong acids and strong bases

b) Weak acids or weak bases

c) Neutral compounds

d) Salts

Answer: b) Weak acids or weak bases

8. Quinonoid theory explains indicator action based on:

a) Oxidation

b) Reduction

c) Structural change

d) Precipitation

Answer: c) Structural change

9. The equivalence point of a strong acid–strong base titration occurs at:

a) pH 3

b) pH 5

c) pH 7

d) pH 10

Answer: c) pH 7

10. Which indicator is most suitable for weak acid–strong base titrations?

a) Methyl orange

b) Phenolphthalein

c) Methyl red

d) Litmus

Answer: b) Phenolphthalein

11. The equivalence point of a strong acid–weak base titration is:

a) Above pH 7

b) At pH 7

c) Below pH 7

d) At pH 14

Answer: c) Below pH 7

12. Which indicator is suitable for strong acid–weak base titrations?

a) Phenolphthalein

b) Methyl orange

c) Thymolphthalein

d) Phenol red

Answer: b) Methyl orange

13. Weak acid–weak base titrations are generally performed using:

a) Methyl orange

b) Phenolphthalein

c) Litmus

d) Potentiometric methods

Answer: d) Potentiometric methods

14. Sodium hydroxide absorbs which gas from the atmosphere?

a) Oxygen

b) Nitrogen

c) Carbon dioxide

d) Hydrogen

Answer: c) Carbon dioxide

15. Which indicator changes from colorless to pink in alkaline medium?

a) Methyl orange

b) Methyl red

c) Phenolphthalein

d) Bromothymol blue

Answer: c) Phenolphthalein

16. The reaction between HCl and NaOH produces:

a) NaCl and H_2O

b) Na_2CO_3 and H_2O

c) NH_4Cl and H_2O

d) NaCl only

Answer: a) NaCl and H_2O

17. The assay of ammonium hydroxide is carried out using:

a) Sodium hydroxide

b) Sulphuric acid

c) Hydrochloric acid

d) Nitric acid

Answer: c) Hydrochloric acid

18. Which indicator is generally used in the assay of ammonium hydroxide?

a) Phenolphthalein

b) Methyl red

c) Bromothymol blue

d) Litmus

Answer: b) Methyl red

19. The point at which chemically equivalent quantities react is called:

a) End point

b) Equivalence point

c) Neutral point

d) Buffer point

Answer: b) Equivalence point

20. Acid–base titrations are extensively used in:

a) Pharmaceutical analysis

b) Quality control

c) Assay determination

d) All of the above

Answer: d) All of the above

Chapter 7

Non-Aqueous Titrations

Learning Objectives

After studying this chapter, the student will be able to:

- Define non-aqueous titration and explain its importance in pharmaceutical analysis.
- Describe the principles involved in non-aqueous acid–base titrations.
- Explain the limitations of aqueous titrations.
- Discuss the advantages of non-aqueous titration methods.
- Classify non-aqueous solvents used in titrimetric analysis.
- Select suitable solvents and indicators for pharmaceutical assays.
- Apply non-aqueous titrations in the estimation of weakly acidic and weakly basic pharmaceutical substances.

7.1 Introduction

Volumetric analysis that uses a solvent other than water for the titration process is known as non-aqueous titration. This is particularly useful for the assay of pharmaceutical products which are weakly acidic or weakly basic but would not be ideally suited for analysis in water because of poor endpoints or because they are not completely ionized in water. Use of appropriate non-aqueous solvents, increases the acidic or basic characteristics of the analyte, which gives sharper and more distinct endpoints and increases the accuracy, precision and reliability of the analysis. With the advent of new pharmaceuticals, non-aqueous titration is becoming important in pharmaceutical chemistry since many of the pharmaceuticals like alkaloids, antihistamines, sulphonamides, local anaesthetic, barbiturates and some antibiotics are weak acids or weak bases. The non-aqueous solvents used are usually glacial acetic acid, acetic anhydride, methanol, ethanol, dimethylformamide and pyridine. As per the type of the analyte either acidimetric or alkalimetric titration can be resorted to the use of the appropriate indicator and titrant. The non-aqueous titration has several advantages over aqueous titration: (1) the analytes are more soluble in the non-aqueous solvent; (2) the end point can be detected more easily in the non-aqueous solvent; (3) less hydrolysis of the analyte; (4) greater completion of the reaction; (5) greater sensitivity of the analysis. The advantages of non-aqueous titration have been exploited in pharmacopoeial assays, in pharmaceutical quality control, in research laboratories and in industrial analytical methods for the accurate determination of weakly acidic and weakly basic pharmaceutical products.

7.2 Requirements for Non-Aqueous Titrations

When aqueous titration method cannot provide accurate, precise and reproducible analytical results, the non-aqueous titration method is used. There are many pharmaceutical compounds that are only weakly acidic or weakly basic and only slightly ionize in water. These substances are frequently encountered which have incomplete ionization and give cloudy endpoints and faulty assay values with conventional aqueous titration methods. Also some drugs are not water soluble, or the drug will be hydrolysed in water and it will be difficult or impossible to analyse. Non-aqueous solvents have the advantage of increasing the acidity or basicity of the analyte thus increasing ionization and the extent of reaction. This leads to better resolution of the endpoints and analytical sensitivity. In some instances, the non-aqueous titration method can be used specifically for assay of a few weakly acidic or basic pharmaceuticals, e.g., alkaloids, antihistamine compounds, sulfonamides, barbiturates, local anesthetics and a few others. Furthermore, the techniques are not as water sensitive and can be applied to the study of compounds that are not stable in aqueous phase. Acids and Bases that are weak use the following solvents as shown in Figure 7.1. Non-aqueous titrations possess high level of accuracy, endpoint detection and wide applications, which are essential in the pharmaceutical quality control laboratory and pharmacopoeial and industrial research laboratories.

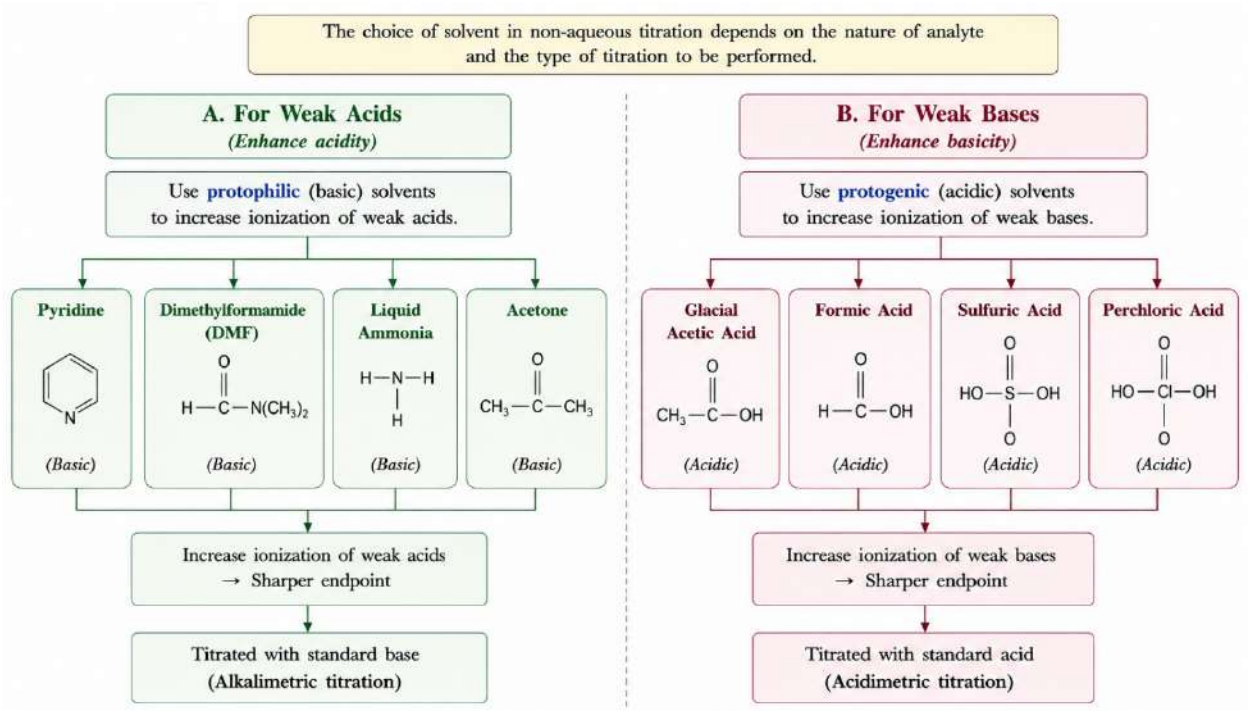

Figure 7.1: Selection of Solvents for Weak Acids and Weak Bases

7.3 Types of Solvents Used in Non-Aqueous Titrations

The use of a solvent is one of the most crucial steps in the use of a non-aqueous titration. The degree of ionization, rate of reaction, the position of the end point and the accuracy of the titration process

depends on the nature of the solvent. Non-aqueous solvents can be tentatively classified into 4 types based on their proton donating and proton accepting capabilities. A few of these are protogenic, protophilic, amphiprotic and aprotic solvents.

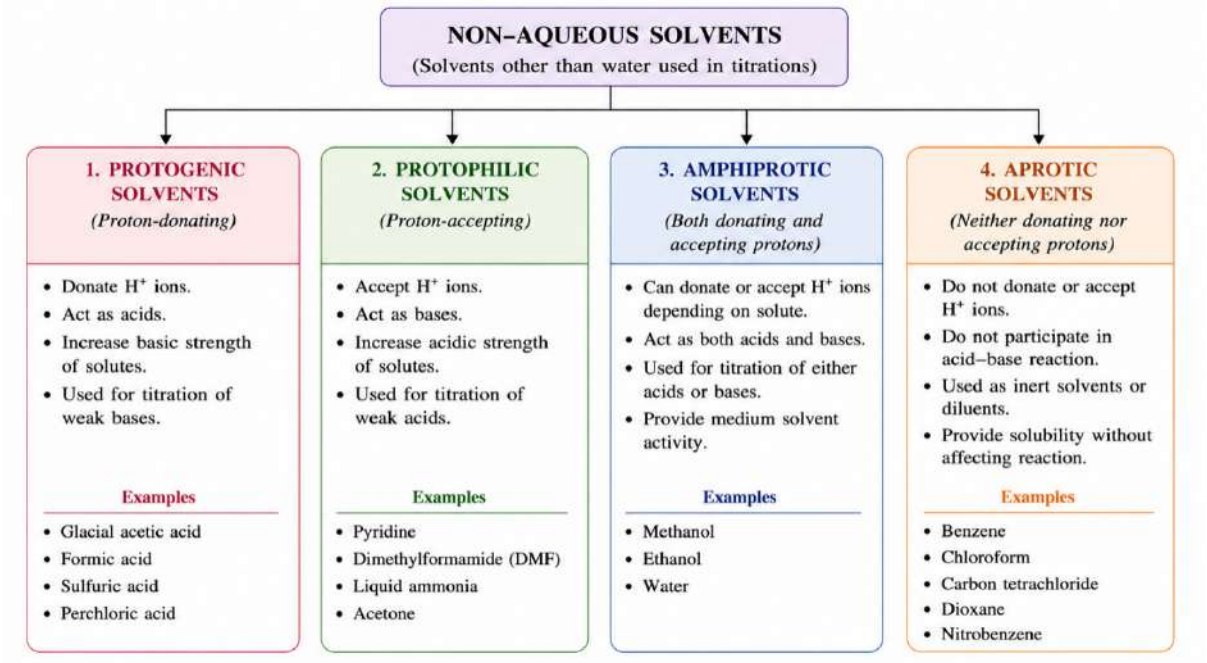

Figure 7.2: Types of Non-Aqueous Solvents

The classes have different physicochemical characteristics, which can be used for certain analyses. Appropriate selection of the solvent will produce a more acidic or basic medium in which the analyte is present, which will further ensure complete neutralisation reactions. Four main types of solvents can be used in non-aqueous titrations, which are represented in Figure 7.2. These qualities of the knowledge of these solvent systems are crucial in choosing the most suitable analytical condition and to be able to achieve accurate pharma assays.

Protogenic Solvents

Solvents that tend to lose hydrogen ions readily (acidic properties) are called protogenic solvents. Such solvents enhance the basic strength of the weak bases that are dissolved in them, by facilitating protonation. They are particularly useful for the assay of less basic pharmaceuticals. These contain glacial acetic acid, formic acid, sulfuric acid and perchloric acid. As a protogenic solvent, it is used most commonly in pharmaceutical analysis, because of its good solvent properties and compatibility with many drug substances, as glacial acetic acid. The solvents give a very acidic reaction medium to ensure that the reaction is complete with the standard acid titrants and give sharp endpoints.

Protophilic Solvents

Protophilic solvents: solvents which can accept a proton, act as base and will attract the proton of a dissolved substance. These solvents make weak acids more acidic, thus enhancing their titration characteristics. These are pyridine, dimethylformamide (DMF), liquid ammonia and acetone. Protophilic solvents have a broad range of applications for the analysis of weakly acid pharmaceutical compounds as they enhance the degree of ionization and promote complete neutralization reactions.

Amphiprotic Solvents

Amphiprotic solvents can donate or accept protons, depending on the substance that is dissolved in the solvent. These solvents can thus act as acids or bases. They include such things as methanol, ethanol and water. They can be used in many analytical applications because of their dual nature as versatile solvents. Often requires moderate solvent activity and a large range of solubility, sometimes amphiprotic solvents are used.

Aprotic Solvents

Aprotic solvents cannot donate or accept protons to a significant extent, and are therefore not involved directly in acidic–base reactions. Their primary function is to dissolve analytes and solvents to minimize solvents' interference. Examples are benzene, chloroform, carbon tetrachloride or dioxane. Table 7.1 categorizes the various types of solvents.

Table 7.1 Classification of Non-Aqueous Solvents

Class of Solvent	Definition	Characteristics	Common Examples	Pharmaceutical Application
Protogenic Solvents	Solvents that donate protons (H^+ ions)	Act as acids; increase the basic strength of solutes; promote protonation	Glacial acetic acid, Formic acid, Sulfuric acid, Perchloric acid	Used for titration of weak bases in acidimetric non-aqueous titrations
Protophilic Solvents	Solvents that accept protons (H^+ ions)	Act as bases; increase the acidic strength of solutes; promote ionization of weak acids	Pyridine, Dimethylformamide (DMF), Acetone, Liquid ammonia	Used for titration of weak acids in alkalimetric non-aqueous titrations
Amphiprotic Solvents	Solvents capable of both donating and	Can act as acids or bases depending on the reaction conditions	Methanol, Ethanol, Water	Used in various acid–base reactions due to versatile solvent properties

	accepting protons			
Aprotic Solvents	Solvents that neither donate nor accept protons	Chemically inert toward proton-transfer reactions; mainly act as diluents	Benzene, Chloroform, Carbon tetrachloride, Dioxane, Nitrobenzene	Used as inert media or co-solvents in non-aqueous titrations

7.4 Acidimetric Titrations in Non-Aqueous Media

If the substance to be determined is a weak base then the titration is called acidimetric titration in non-aqueous medium. In the pharmaceutical industry, titration is of significance since many pharmaceutical products have weak basic character which cannot be titrated in water. A non-aqueous acidimetric titration uses the solvent glacial acetic acid and the analyte is dissolved in it to make it more basic, which ensures complete reaction with the titrant. The most commonly used titrant is perchloric acid in glacial acetic acid for its strong acidity, endpoint and stability. The indicator substances that are commonly used in endpoint detection are: crystal violet, malachite green and quinaldine red. Acidimetric non-aqueous titrations are extensively used in the assay of alkaloids, antihistamines, local anesthetics, atropine, ephedrine, diphenhydramine and many other pharmaceutical compounds that are of a weakly basic nature. Such determinations are to be performed by an overall apparatus and an overall arrangement which will be shown in figure 7.3. The following are the advantage of the above mentioned titrations: They are more soluble; They are more ionized; They are more sensitive for detecting the endpoint in titration; They have sharper endpoint when detected. Acidimetric titrations in non-aqueous media are extensively used in the pharmacopoeial methods and pharmaceutical quality control for quantitative estimation of weakly basic drugs because

of these benefits.

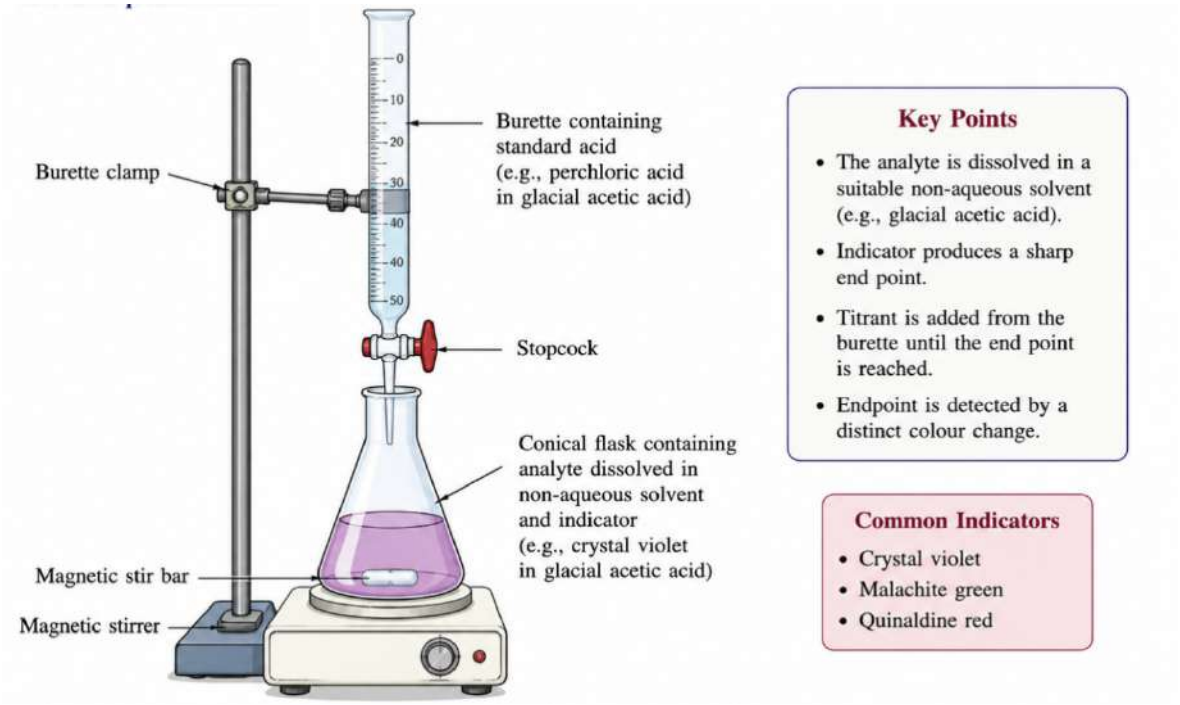

Figure 7.3: Non-Aqueous Titration Setup

7.5 Alkalimetric Titrations in Non-Aqueous Media

The amount of weak acids are determined in non-aqueous titration by titrating the acids with a standard solution of an alkali in a suitable non-aqueous solvent. Weak acids like barbiturates, sulphonamides, phenols and organic acids are difficult to titrate, are not well ionised in water and have poorly defined endpoints in water. The compounds become more acid in the appropriate non-aqueous solvents and reactions of complete neutralization can be more easily accomplished. Non-aqueous alkalimetry uses solvents to help to ionize weak acids like dimethylformamide (DMF), pyridine, methanol and liquid ammonia. Commonly used standard solutions are sodium methoxide, potassium methoxide or tetrabutylammonium hydroxide. Depending on the nature of the analyte and solvent system, suitable indicator like thymol blue, azo violet, thymolphthalein is selected. The benefits of non-aqueous alkalimetric titrations over aqueous titrations are that the endpoints are more distinct, the sensitivity of the titrations is greater and titrations are more accurate. These have been widely used to measure the weakly acidic drugs and pharmaceuticals in the pharmacopoeial assays and in the pharmaceutical quality control laboratories.

7.6 Preparation of Acidic Titrants

Acidic titrants for non-aqueous titrations are solutions of a strong acid which are dissolved in a suitable non-aqueous solvent. The acidic titrant used the most is glacial acetic acid with perchloric acid. Perchloric acid is employed due to its properties of being a strong acid in non-aqueous solvents,

and the reliable and repeatable titration result. Perchloric acid is isotropically added to glacial acetic acid, stirring as it is added. Acetic anhydride is usually used to eliminate traces of water which can affect the titration process. The mixture is transferred to a clean, dry reagent bottle and stored in such a way that the solution is not affected by moisture from the air. The concentration of the titrant used to prepare it may vary and thus must be standardized before use for analysis. The acidic titrants thus made are used extensively for the determination of weakly basic drugs like local anesthetics, antihistamines and alkaloids in pharmaceutical preparations. Proper preparation and storage are important for stability and strength, while for pharmaceutical analysis, the accuracy and precision of the titrant used is critical.

7.7 Standardization of Acidic Titrants

Acidic titrants must be standardised so that they can be used in an analytical process with the exact concentration. Glacial acetic acid is used to make perchloric acid solutions, which are typically standardized with potassium hydrogen phthalate (KHP). The dissolving of the correct amount of the primary standard is done in a suitable non-aqueous solvent and the titration is performed using the acidic titrant. Endpoint can be done with suitable indicators, like crystal violet, or potentiometric methods. The volume of titrant used is recorded and then, the exact concentration is calculated by using the principle of volumetric analysis. The use of standardization makes the results of non-aqueous titration accurate, reliable and reproducible. Usually, several titrations are repeated so that concordant readings can be obtained and any errors in the experiment minimized. The standardization of acidic titrants is very important for pharmaceutical quality control and conformance to the pharmacopoeias as many weakly basic pharmaceuticals are often analysed with acidic titrants. Acidic titrants which are properly standardized give reliable analytical results and play an important part in the evaluation of pharmaceutical products.

7.8 Preparation of Basic Titrants

Non-aqueous titrants are usually made up of strong bases in a suitable alcohol-based solvent. The most frequently used basic titrants are used for the alkalimetric non-aqueous titration. Sodium methoxide in anhydrous methanol may be prepared by controlled dissolution of the sodium in the anhydrous methanol. Sodium methoxide and hydrogen gas are the products of the reaction; care needs to be taken in the preparation procedures of these products. KOH is made in a similar manner to NaOH, using potassium instead of sodium. These are highly reactive solutions, sensitive to moisture and carbon dioxide and should be made up using dry reagents and stored in screw capped containers. Moisture in the atmosphere and the analytical error that may be caused by the concentration of the titrant may vary. They are solutions which cannot be made to an exact concentration, and which need to be standardized before use. Basic titrants are commonly used in the assay of weakly-acidic pharmaceutical materials, and are also used to provide a sharp endpoint in non-aqueous media. For

pharmaceutical analysis, these titrants need to be well prepared and stored to maintain the stability and performance needed for the analysis.

7.9 Standardization of Basic Titrants

The basic titrants are standardized to determine the exact concentration, and to obtain consistency in the analytical result. Sodium methoxide or potassium methoxide solutions are usually standardized with a primary standard: an acidic compound like phthalic Acid (KHP) or benzoic acid. During the procedure the amount of the primary standard is carefully measured and added to an appropriate non-aqueous solvent. An indicator, such as thymol blue or thymolphthalein, is then used to titrate the solution out, using the basic titrant. An endpoint is detected by either a colour change or potentiometrically. Using the stoichiometric relation, the volume of titrant used is measured and the titrant is known as basic titrant. Standardization will remove any errors that might be due to varying concentrations of the reagents and will give accurate assay results. The basic titrants are extremely prone to moisture and carbon-di-oxide in the air and periodic re-standardisation might be necessary. Standardisation is an important step in quality assurance in pharmaceutical analysis and necessary for the performance of non-aqueous titrimetric methods to get reproducible and reliable results.

7.10 Estimation of Weakly Acidic Substances

The alkalimetric titration for the estimation of many pharmaceutical substances is done non-aqueously as they are weak acids. Titration is not very accurate for many organic acids, barbiturates, sulfonamides, and phenols since they are only partially ionized in an aqueous solution. Complete ionization of these compounds is increased by using protophilic solvents such as dimethylformamide, pyridine and liquid ammonia. This is because the analyte is dissolved in the solvent of choice and then titrated by a standardised basic titrant, sodium methoxide or potassium methoxide. The indicators are selected based on the endpoint pH and solvent. Non-aqueous alkalimetric titrations provide better end points and sensitivity than do aqueous titrations. These approaches are widely used in the assay of the weakly acidic drugs and pharmaceutical intermediates of pharmaceutical quality control. The method is very precise, accurate and reproducible and plays a valuable role in the analytical methods used in the pharmaceutical industries and research laboratories. The use of correct solvent and standardization of titrant is required to assure correct assay.

7.11 Estimation of Weakly Basic Substances

The non-aqueous acidimetric titration method is normally employed to estimate pharmaceutical substances which have weak basic properties. Some antibiotics, local anesthetics, anti-histamines and alkaloids, which have poor basicity in water, have rather shaky endpoints. In order to overcome these limitations, the analyte is dissolved in a protogenic solvent, like glacial acetic acid, in order to exhibit better basic properties and complete neutralization. The titrant used is the standardised perchloric

acid. The endpoint is determined by the use of indicators like crystal violet, malachite green and quinaldine red. The amount of titrant needed to reach the end point is determined and then the concentration or purity of the titrand (analyte) is found. The non-aqueous acidimetric titration is more sensitive, more accurate and more gives sharper endpoints than the aqueous titration. Hence, it is extensively employed in the assay of weak basic drug substances in pharmacopoeial assay and pharmaceutical quality control laboratory.

7.12 Assay of Sodium Benzoate

One of the more common techniques for the assay of sodium benzoate is non-aqueous alkalimetric titration (in suitable non-aqueous media, it is a weakly-acidic substance). Substance-solution A (sodium benzoate) is titrated with a standard basic titrant in a proper solvent system. A known mass of sodium benzoate is added to an appropriate non-aqueous solvent, e.g. dimethylformamide or methanol. The solution obtained is then titrated with a standard base (sodium methoxide solution) with thymol blue or suitable indicator. Clear and permanent colour change at the end point. The percentage purity and assay value of sodium benzoate is determined by the amount of titrant used. The use of non-aqueous titration will give accurate and repeatable results since the solvent will increase the degree of ionization and allow the reaction to go to completion. The method of assaying is typically adapted in the quality control laboratory of a pharmaceutical company and for pharmacopoeial analysis. Sodium benzoate is extensively applied as a preservative in pharmaceutical products, food products, cosmetics etc., so the accurate determination of sodium benzoate is important.

Chapter Summary

Non-aqueous titrations are very important for the analysis of weakly acidic and weakly basic pharmaceuticals. Different types of non-aqueous solvents are used such as protogenic or protophilic, amphiprotic or aprotic solvents with the type of the analyte. Actually the titrants employed are acidic (perchloric acid in glacial acetic acid) or basic (sodium methoxide). The preparation and standardization of titrants are very important in obtaining reliable analytical results. The methods of titration do not involve water are more sensitive, have more distinct endpoint and are more accurate than aqueous titrations. Such methods are broadly used in pharmacopoeial assays and the quality control operations in pharmaceuticals.**Key Points**

- Non-aqueous titrations are used for weak acids and weak bases.
- Acidimetric titrations employ acidic titrants such as perchloric acid.
- Alkalimetric titrations use basic titrants such as sodium methoxide.
- Proper solvent selection is critical for accurate analysis.

- Protogenic solvents enhance basicity of analytes.
- Protophilic solvents enhance acidity of analytes.
- Titrants must be standardized before use.
- Non-aqueous titrations provide sharper endpoints than aqueous titrations.
- Weakly acidic and weakly basic drugs are commonly analyzed by this method.
- Sodium benzoate can be assayed by non-aqueous titration.

Review Questions

Short Answer Questions

1. Define alkalimetric titration in non-aqueous media.
2. What are basic titrants?
3. Why is perchloric acid used in non-aqueous titrations?
4. Name two commonly used basic titrants.
5. What is the role of glacial acetic acid in non-aqueous titration?
6. Define weakly acidic substances.
7. Define weakly basic substances.
8. Why is standardization necessary for non-aqueous titrants?
9. Name the indicators used in acidimetric non-aqueous titrations.
10. Write the principle of sodium benzoate assay.

Long Answer Questions

1. Discuss alkalimetric titrations in non-aqueous media.
2. Explain the preparation and standardization of acidic titrants.
3. Describe the preparation and standardization of basic titrants.
4. Explain the estimation of weakly acidic substances by non-aqueous titration.
5. Discuss the estimation of weakly basic substances by non-aqueous titration.
6. Describe the assay of sodium benzoate with principle and procedure.

MCQs

1. Non-aqueous alkalimetry is used for:
   a) Strong acids
   b) Weak acids
   c) Strong bases
   d) Neutral salts

Answer: b

2. Common acidic titrant used in non-aqueous titration is:
   a) HCl
   b) H_2SO_4
   c) Perchloric acid
   d) Nitric acid

Answer: c

3. Sodium methoxide is used as:
   a) Indicator
   b) Solvent
   c) Basic titrant
   d) Primary standard

Answer: c

4. Glacial acetic acid is classified as:
   a) Protogenic solvent
   b) Protophilic solvent
   c) Aprotic solvent
   d) Neutral solvent

Answer: a

5. Crystal violet is commonly used in:
   a) Acidimetric non-aqueous titration
   b) Gravimetry
   c) Redox titration
   d) Complexometry

Answer: a

6. Weakly basic drugs are commonly assayed using:
   a) Sodium methoxide

b) Potassium chloride

c) Perchloric acid

d) EDTA

Answer: c

7. Sodium benzoate is generally assayed by:

a) Gravimetry

b) Non-aqueous titration

c) Redox titration

d) Precipitation titration

Answer: b

8. DMF stands for:

a) Dimethylformamide

b) Dimethyl fluoride

c) Diethyl formate

d) Dimethyl formalin

Answer: a

9. Which solvent enhances acidity of weak acids?

a) Protogenic solvent

b) Protophilic solvent

c) Aprotic solvent

d) Neutral solvent

Answer: b

10. Non-aqueous titrations are widely used in:

a) Pharmaceutical analysis

b) Quality control

c) Pharmacopoeial assays

d) All of the above

Answer: d

Chapter 8

Precipitation Titrations and Gravimetric Analysis

After completing this chapter, students will be able to:

1. Explain the principles of precipitation titrations and gravimetric analysis, including solubility, precipitation equilibrium, and stoichiometric relationships.
2. Describe the major steps of gravimetric analysis—precipitation, digestion, filtration, washing, drying, ignition, and weighing—and explain their importance in obtaining accurate results.
3. Differentiate between Mohr's, Volhard's, modified Volhard's, and Fajans methods with respect to their principles, indicators, endpoint detection, applications, and limitations.
4. Apply precipitation and gravimetric principles to the quantitative estimation of analytes, including the determination of sulphate as barium sulphate ($BaSO_4$), and perform relevant analytical calculations.

8.1 Introduction

The quantitative chemical analysis of precipitation is one of the classical analytical methods which is still in use due to its simplicity, well defined stoichiometry, and due to the fact that many inorganic ions can be analyzed by this method. The principle is that if conditions are right, then two or more species, when dissolved in water, will form a sparingly soluble compound. When the amount of precipitate formed is directly proportional to the amount of analyte, the reaction can be used for analytical determination. Precipitation gravimetry and precipitation titrimetry are known as the methods of precipitation. Gravimetric Analysis: This method is used to determine the quantity of an analyte by converting it to an insoluble solid precipitate that can be isolated from the solution, purified, dried or heated to a stable form for weighing. Precipitation titration is the process of titrating the analyte with a standard solution until the endpoint is reached, or very close to it, as it is detected in the experiment. Silver nitrate is employed in precipitation titrations and is particularly important in the precipitation of the chloride, bromide and iodide ions.

There are three most commonly used argentometric methods, such as Mohr's method, Volhard's method and Fajans' method. In the Mohr procedure, directly titrated with standardized silver nitrate in the presence of chromate indicator. The endpoint is related to the first appearance of red-brown silver chromate when the halide has been greatly precipitated. The conversion of the silver nitrate into excess and the subsequent back titration of the excess amount with a standard solution of potassium thiocyanate and Fe3+ as indicator is done as in Volhard method. Another direct titration procedure, called the Fajans titration uses an adsorption indicator whose colour changes as a result of the change

in electrical character of the precipitate surface at the equivalent point. The methods are based on the same basic precipitation chemistry, but vary in endpoint mechanism and conditions.

Precipitation chemistry is another process and gravimetric analysis is another type of precipitation chemistry, but in this instance the analytical signal is the mass of precipitate formed and not the amount of titrant. The physical and chemical characteristics of the precipitate are important in the success of a gravimetric determination. The preferred size is generally large, crystalline particles which are easier to filter, wash and purify than highly dispersed particles. The addition of control of temperature, reagent concentration, pH, stirring, and addition rate may affect the crystal formation and/or reduce coprecipitation. So, precipitation analysis is an important link between chemical equilibrium and quantitative measurement. The chapter starts out gradually, first with gravimetric principles and operations, and builds the theory and practical procedures of precipitation titrations, before ending with an important gravimetric application of barium sulphate.

8.2 Principle of Gravimetric Analysis

Gravimetric analysis is quantitative analysis, whereby the amount of analyte(s) is determined by measuring the mass of the substance with which it is chemically related. Precipitation gravimetry is a method where the analyte is converted to a sparingly soluble product using an appropriate precipitating reagent. This results in the solid remaining that is washed off of the solution to remove soluble impurities, dried or ignited to ensure uniform chemical content, cooled, and weighed. The mass measured is then used to calculate the amount of analyte, through the use of stoichiometric relationships. The method is thus reliant on complete or nearly complete conversion of the analyte, quantitative collection of the precipitate, minimal contaminations, and great accuracy in measuring the final weighing form.

For gravimetric analysis, the precipitates should have very low solubility, definite and reproducible composition, high purity and have physical properties that allow efficient separation. Preferably composed of relatively larger as well as faster settling particles, which can be easily filtered. Very small particles can have a large surface area that can attract dissolved impurities in the mother liquor. They also may go through the filter or be difficult to rinse. The precipitation conditions are therefore important. The rate of addition of reagent, temperature, good stirring, pH and reagent concentration can be controlled to minimize excessive supersaturation and crystal growth.

Precipitation gravimetry is a process that is fundamental to solubility product. The equilibrium reaction for a sparingly soluble salt whose formula is AB is $AB(s) \rightleftharpoons A^+ + B^-$, and the solubility-product constant is Ksp. If the ionic product is greater than that at equilibrium then it precipitates. In addition to being affected by the state of equilibrium, the complete analytical precipitation is also affected by the factors of particle formation and kinetic factors. Complex formation/competing

reactions may make more of the analyte in solution, while common-ion effects may make it less soluble, causing more of the analyte to precipitate.

Coprecipitation is another significant feature which involves substances other than the desired analyte being included in the precipitate. Typical mechanisms are adsorption, occlusion, inclusion and post-precipitation. Some of these effects can be reduced by digestion and by using a highly controlled process of precipitation. Recprecipitation can be used for particularly high purity. The measured mass has to be one for which the composition of the compound is known. Gravimetric analysis is therefore more than just a means of forming a precipitate; it is a series of chemical and physical steps which can be controlled and standardized to convert an analyte into a suitable weighing form. The whole procedure is condensed into Figure 8.1, which presents steps within the digestion, filtration, washing, drying/ignition, cooling, weighing and final stoichiometric calculation steps that are associated with the precipitation process.

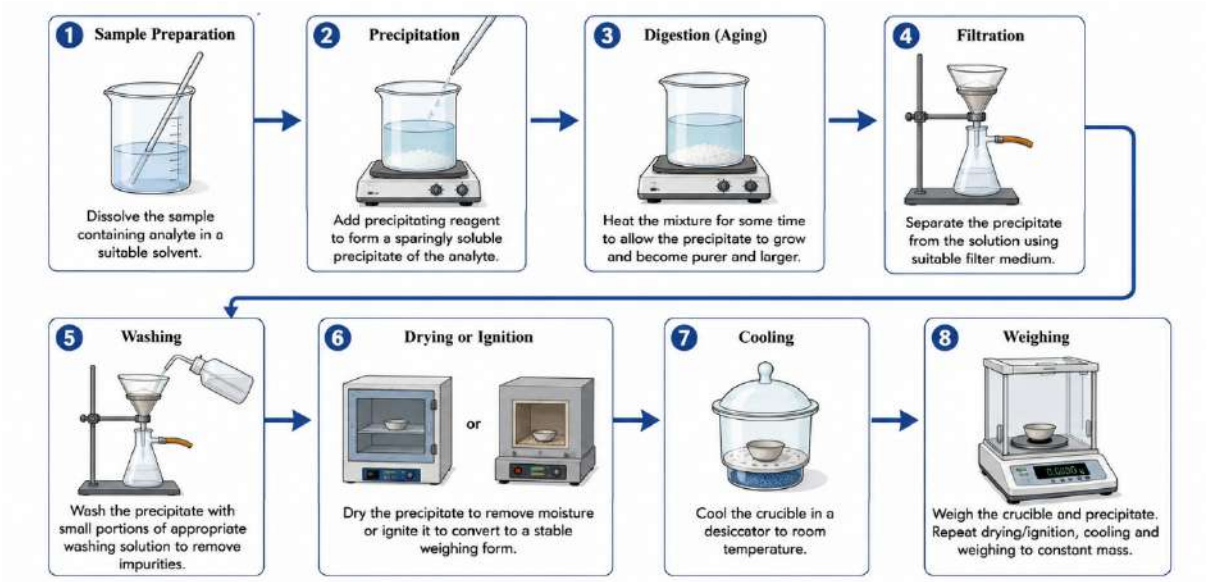

Figure 8.1. Steps in Gravimetric Analysis

The sequence shown in **Figure 8.1** emphasizes that gravimetric analysis is a connected analytical process. Successful determination requires quantitative precipitation followed by careful isolation, purification, conversion to a stable weighing form, and accurate mass measurement.

8.3 Steps Involved in Gravimetric Analysis

Because the accuracy of gravimetric analysis depends on the accuracy of the entire procedure, it must be carefully carried out in a sequence of operations. These principal stages are precipitation, digestion, filtration, washing, drying, ignition (if necessary), cooling and weighing. The sample is typically dissolved or otherwise treated before precipitation in such a way as to make sure that the analyte is present in a proper chemical form. The precipitating reagent is then slowly added in a controlled

manner to precipitates the desired insoluble product. Once formed, the precipitate can be left to digest, increasing the size of the crystals. Then it is filtered off and washed to wash off soluble impurities. Isolated material is then either dried or ignited depending on the nature of the precipitate to obtain a stable weighing form. Lastly, it is cooled and weighed several times until a constant mass is reached.

Precipitation

The process of transforming the dissolved analyte to a sparingly soluble solid is called precipitation. The precipitating reagent must be highly specific and must precipitate a compound with a well-known composition. The reagent is normally added slowly with continuous stirring, and experimental conditions such as pH and temperature are controlled to promote formation of a pure and easily filterable precipitate. The rapid addition of reagent in concentrated form may lead to very high supersaturation and very fine particles, while a controlled addition of reagent will allow the slow growth of particles.

Digestion

Digestion is the process of leaving the newly formed precipitate in contact with the mother liquor, sometimes at a high temperature. Small particles partially dissolve and material is deposited on larger particles. This is because it decreases the surface area, increases the crystal size and, in general, increases the filterability. Some forms of surface adsorption may be decreased by digestion, which also may increase the purity of the precipitates.

Filtration

Filtration is used to remove the solid from the mother liquor. The filter medium should not cause a slow filter rate if it is to remove the precipitate. This is because any precipitate not transferred to the vessel or lost through the filter is a negative error.

Washing

Washing will wash soluble impurities and mother liquor. The washing liquid should not greatly dissolve or react with the precipitate. Use several small wash parts rather than a single large part of wash, since this will remove impurities effectively, but will minimize analyte loss.

Drying

Drying is the process that removes the moisture physically bound to the product, and does not necessarily alter the chemical composition of the precipitate, and the dried product is obtained in a dry state and weighing form. The drying temperature should be high enough to dry the moisture out, but not so high as to cause decomposition or volatilization.

Ignition

In the ignition process, stronger heating is applied, in order to transform the precipitate into a stable compound of known composition. Can remove organic material, water, carbon dioxide or other volatiles. If filter paper is used, it is especially crucial to control the ignition because if it burns too quickly, it may cause mechanical loss of precipitate.

Weighing

The material is then dried/ignited, and then cooled, usually in a desiccator, and weighed accurately. Repeatedly heated and cooled and weighed until the mass remains constant. The mass of the final compound is then determined by the use of stoichiometry to determine the amount of analyte present. It is therefore necessary that each step be accomplished: if the precipitation is not complete, if digestion is not complete, if mechanical loss in the filter, if washing is not sufficient, if the drying is not performed well, or if the weighing is not stable.

Table 8.1. Comparison of Precipitation Titration Methods

Feature	**Mohr's Method**	**Volhard's Method**	**Fajans Method**
Basic type	Direct titration	Back-titration	Direct titration
Principal titrant	Standard $AgNO_3$	Standard KSCN or NH_4SCN	Standard $AgNO_3$
Main application	Chloride and selected halides	Halides and related silver determinations	Halides, particularly chloride
Indicator	K_2CrO_4	Fe^{3+}	Adsorption indicator
Endpoint	Formation of red-brown Ag_2CrO_4	Formation of red Fe–SCN complex	Colour change due to indicator adsorption
Typical medium	Approximately neutral	Acidic	Controlled pH
Main advantage	Simple direct procedure	Useful in acidic medium and adaptable to back-titration	Sharp endpoint under suitable surface conditions
Major limitation	pH and chromate requirements	More complex because of back-titration	Sensitive to precipitate surface and indicator conditions

8.4 Precipitation Titrations

Precipitation Titrations are volumetric analytical techniques where a sparingly soluble compound is precipitated by reacting it with a titrant. Measurement of the concentration of the analyte is made by the volume of standardized titrant needed to reach the equivalence point. For a simple reaction (one with the same number of molecules on each side of the equation and one mole of chloride to one mole of silver ion at the equivalence point) the number of moles of chloride is equal to the number of moles of silver ion delivered at the equivalence point for the reaction $AgCl(s) \rightarrow Ag^{+} + Cl^{-}$. In reality, it is not possible to observe the equivalence point directly, though. An indicator or instrumental method is thus needed to detect an endpoint which is as close as possible to the theoretical equivalence point.

The value of the equilibrium constant for the precipitation reaction and the ability to detect a sharp change near the equivalence point are important factors which affect the effectiveness of a precipitation titration. A reaction will be analytically useful if the precipitate is very sparingly soluble, and the concentration change in the immediate neighbourhood of the equivalence point is large. The shape of the titration curve is dependent on the solubility product, concentration of the titrant, the concentration of the analyte and the composition of the solution. Systematic errors can occur due to side reactions such as complex, acid-base reaction, precipitation.

Precipitation titrations are most significant in classical pharmaceutical and analytical chemistry, and are called argentometric titrations. They are often used to precipitate chloride, bromide and iodide and the precipitating reagent is silver nitrate. There are three classical methods. Mohr's method, Volhard's method and Fajans method. Their only difference is that they are endpoint detections. Mohr's method is a method used to recover the second precipitate when the analyte is used up, in the presence of chromate. Excess of silver ion is determined by back titration with the help of Fe3+ and Volhard's method is used for this purpose. The adsorption indicator changes colour with the change of surface charge of the precipitate around the equivalence point, thus working on the Fajans method.

There are some conditions to be met in precipitation titration. The concentration of the indicator should be enough to indicate, but not to significantly disrupt the precipitation equilibrium. The PH should be suitable for the indicator and precipitation reaction. The precipitate should be held in good dispersion for an endpoint to be detected, and there should be vigorous but controlled mixing. There should be no interfering ions which react with the titrant or indicator that interfere, or that can be removed. The proper standardization of titrant is also necessary.

Precipitation titrations are particularly useful because they can be performed quickly, cheaply and easily in the laboratory. They require, however, more control than a simple acid-base titration, because precipitation equilibria which influence the endpoint and, in some cases, the properties of the precipitate are present. These are so important that it is important to understand them with regard to obtaining accurate analytical results.

8.5 Mohr's Method

The argentometric precipitation titration method is a direct titration method which is mainly used to determine chloride and other halide ions, under proper conditions, in Mohr's method. Potassium chromate is the indicator standardised silver nitrate solution is used to titrate the analyte solution. Precipitation reactions are the simplest type of reactions in which precipitates of AgCl(s) (white) form from the mixing of Ag^+ and Cl^-. The added silver ions will be preferentially consumed in the formation of silver chloride since the concentration of chloride is relatively high, so long as chloride is in solution. When almost all the chloride had precipitated the concentration of silver ions increases to allow for some reaction with the chromate ions. The chromate gives a red-brown precipitate of silver chromate ($Ag_2CrO_4(s)$) which is the first colour to form and is considered the endpoint: $2Ag^+ + CrO_4^{2-} \rightarrow Ag_2CrO_4(s)$.

The experimental setup is a burette containing the standard solution of AgNO3, a conical flask containing the sample and a potassium chromate indicator and a suitable mixing system. The procedure is shown in figure 8.2 in which the formation of the silver chloride before equivalence and silver chromate at the endpoint is shown in a schematic way. The end point needs to be carefully considered as a local excess of silver nitrate is lost and a transient colour can be developed. Therefore, the best endpoint color for the persistent colour is a reddish brown color throughout the suspension.

One of the most crucial conditions of the Mohr method is pH control. Typically the solution should be near neutral. There will be a larger concentration of protonated forms of chromate in the strongly acidic solution which will reduce the concentration of chromate and hence the amount of silver chromate formed. Silver can undergo reaction with other compounds in strongly alkaline solution which can interfere the detection of the endpoint. The amount of the chromate indicator should also be controlled because if too much is added, it will also cause endpoint error to the precipitation reaction.There are several benefits to using Mohr's. It is a direct procedure, is relatively simple and has a visually obvious endpoint. It is especially useful for routine chloride determinations in the presence of interferences in the sample matrix. It is not as good for very acidic or alkaline samples, however, and ions that are capable of producing an insoluble silver salt may interfere with it. This step will be optimal if the composition of the sample is appropriate for the precipitation and indicator equilibria, and the pH of the sample is appropriate for the indicator.equilibria.

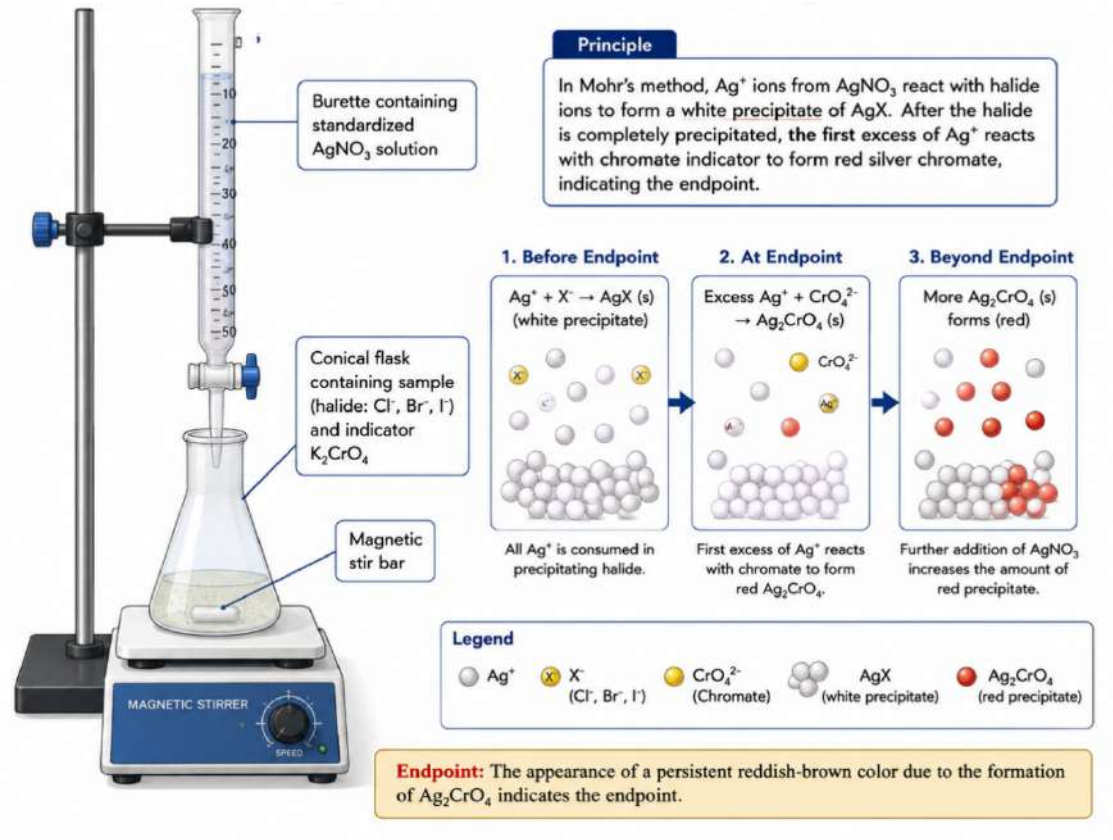

Figure 8.2. Mohr's Method Setup: Burette containing standardized $AgNO_3$ solution → conical flask containing the chloride sample and potassium chromate indicator → continuous mixing during titration → formation of AgCl precipitate → endpoint indicated by persistent reddish-brown Ag_2CrO_4 formation.

8.6 Volhard's Method

Usually, Volhard's method is based on back titration, and is an argentometric method. Especially convenient for halides and under conditions requiring acidic conditions. The known amount of excess silver nitrate is added to the sample of halide in standard procedure. The solid forms are called precipitates and in this case the precipitates are the silver halide salts such as AgCl (chloride). The amount of the remaining silver ion in solution is then determined by titration with a standard solution of potassium or ammonium thiocyanate. Ferric (Fe3+) ion is used as an indicator. When the first small excess of thiocyanate is added it will react with Fe^{3+} to give a red soluble complex Fe–SCN, which is the endpoint.

The method can be subdivided into 3 main reactions. When the silver ion reacts with the analyte (X) to form precipitate of silver ion compound (X), the reaction would be: $Ag^+ + X^- \rightarrow AgX(s)$ The second reaction that takes place is: Excessive amounts of silver ion react with thiocyanate to produce silver thiocyanate.The other reaction which takes place is: Excess of silver ion reacts with thiocyanate to give silver thiosulfate. Lastly, when all the silver ions have been used up, the first excess

thiocyanate will react with the ferric ion to produce a coloured complex: $Fe^{3+} + SCN^- \rightleftharpoons [FeSCN]^{2+}$. So the initial concentration of the silver ion is known; after the reaction the concentration of the silver ion is found by the thiocyanate titre. The difference is due to the silver ion which reacted with analyte.

The advantage of Volhard method is that this titration can be carried out in an acidic solution. There are a few interference reactions that have been eliminated and the Fe(III) indicator is satisfactory under acidic conditions. But the process is more complex than a direct titration as it involves using an excess reagent and a second titration. In determining chloride the reaction likely to take place is the reaction of silver chloride and the thiocyanate. In some cases thiocyanate can react with silver chloride, this could be a problem. The established procedures may, therefore, need to be filtered or adapted to avoid this secondary reaction affecting the endpoint.

The endpoint is the first appearance of the iron-thiocyanate complex, which is a reddish colour. After mixing, the colour should be maintained throughout the mixture, and not just in the area where the titrant was added. It is important that silver nitrate and thiocyanate solutions be properly standardized. The chemical environment (environmental difference) created by using the method differs from that created by the Mohr procedure; this is the reason why the method is valuable.

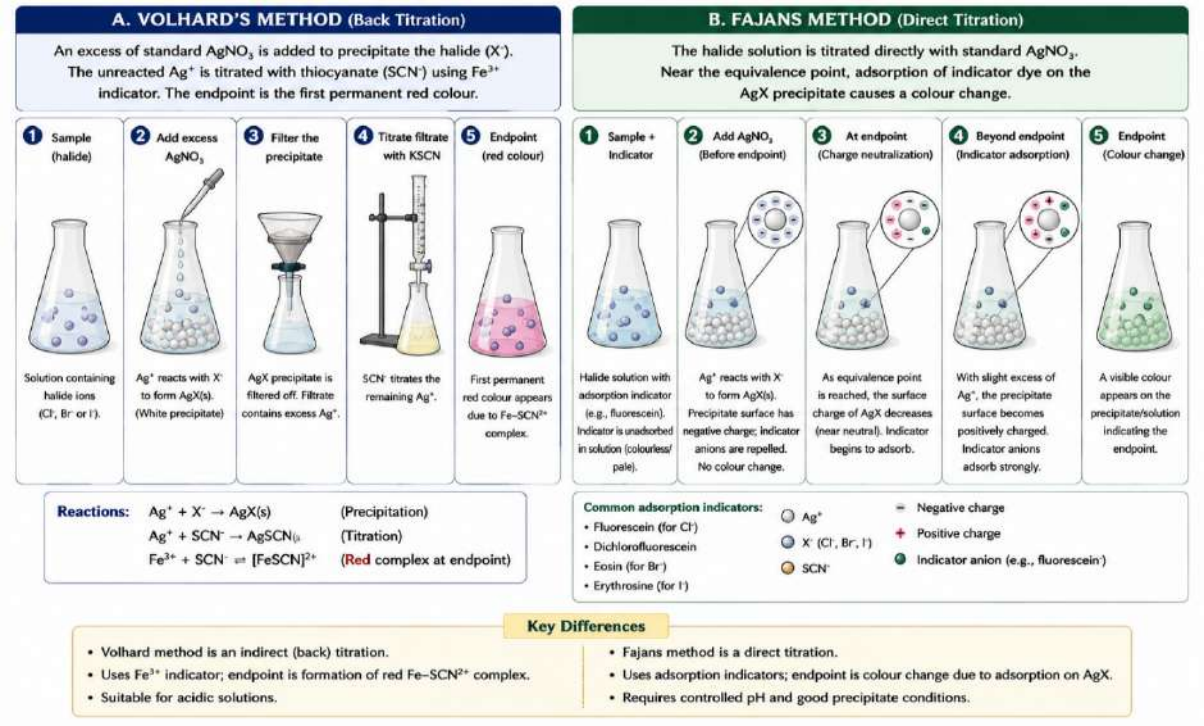

Figure 8.3. Volhard's and Fajans Method Overview: **Volhard** Sample containing halide → add excess $AgNO_3$ → precipitate AgX → determine remaining Ag^+ by titration with KSCN/NH_4SCN → Fe^{3+} indicator → persistent red iron–thiocyanate complex at endpoint.

8.7 Modified Volhard's Method

An adaptation of the original Volhard method to overcome practical difficulties of original back titration in improving determination of halide ion is modified Volhard. The principle is the same: Excess of standard silver nitrate is added to the analyte and the excess of silver ion is then measured against a standard solution of thiocyanate with the help of an indicator, ferric ion. The amount of the analyte is then calculated by subtracting the amount of silver nitrate present in the solution after back-titration (residual silver nitrate) from the amount of silver nitrate originally added to the solution. The main concerns of the modification are the method of handling the silver halide precipitate, and the minimisation of secondary reactions between the precipitate and the thiocyanate.

The silver chloride and thiocyanate will react with each other in the chloride determination because silver thiocyanate is less soluble under the conditions of the chloride determination. The measured titre may be affected by some conversion of AgCl, or other effect, if any, of the precipitated AgCl is present during the back-titration with the thiocyanate. This may lead to an analytical error as thiocyanate might react with the excess silver ion in solution, but also with silver ions on the precipitate also. The physical separation of the precipitate is therefore often carried out, and other conditions are chosen that will minimise the secondary reaction, resulting in the modified procedure. The specific technique will be selected based on the analyte and the analytical method selected.

The main advantages of the Volhard system are achieved with the modified approach. The titration can be conducted in acidic media which is beneficial for the samples where Mohr method is not applicable. A visual endpoint can be obtained with ferric ion by the formation of the coloured Fe–SCN complex. The back-titration principle may be employed to determine species which cannot be readily titrated by a normal endpoint of precipitation.

The accuracy is dependent on a number of procedural factors. The amount of the excess silver ion must be accurately measured, the silver nitrate must be correctly standardized and the excess silver ion must be accurately titrated. All of the analyte must be precipitated, otherwise any analyte that was left would react with the silver, and lead to an incorrect estimate. The precipitate should be treated as the modification has been chosen and endpoint should be determined only after the precipitate has been well mixed. Sometimes, silver or thiocyanate will come from the reagents or the experimental system and blank correction is needed.

Therefore it is not necessary to consider the modified Volhard method as an altogether other principle of analysis. Rather, it's the potential of the Volhard back-titration thought, improved. It is of particular importance as it demonstrates how the fundamental concept of the determination, stoichiometry, can be modified to control the precipitation equilibria, secondary reactions and physical separation problems.

8.8 Fajans Method

The argentometric precipitation titration is called as Fajans method, which is the precipitation titration at the end point using adsorption indicator. It is used for titration of halide ions, such as chloride with standardized solution of silver nitrate. The primary precipitation reaction is $Ag^+ + X^- \rightarrow AgX(s)$ where X^- can be Cl^-, Br^- or I^-. The second coloured precipitate as seen in the Mohr method is not seen in the endpoint. It is, however, base on the variation of electrical charge on the surface of the precipitate in the vicinity of the equivalence point.

Prior to the equivalence point, there are more precept ions than halide ions. These ions may be selectively absorbed onto the surface of the particles of silver halide and impart a surface charge of minus sign to the particles. The solution contains positively charged species which can create a counter-ion layer around the particles. The concentrations of the ions involved in the main precipitation are equal at equivalence point. As soon as there is a slight excess of silver ions, they are preferentially adsorbed at the surface of the precipitate and the surface charge becomes positive. The positive surface can then interact with an anionic adsorption indicator and from this colour change can be detected.

The indicators could be the following, depending on the experimental conditions and the analyte: Fluorescein, other dyes. Care needs to be taken to carefully control the concentration of the indicator. Too little indicator will lead to a weak endpoint, too much indicator will change the behaviour of the surface, and will impact the precipitation balance. The pH also plays a role because the form of the indicator that is ionized can affect its adsorption. The end point is related to adsorption phenomena and the precipitate particle size and surface area should be suitable.

There are a number of advantages to the Fajans procedure. It is a direct titration without the use of a chromate indicator, and can produce a very abrupt colour change, if chemical and physical conditions are carefully controlled. It is particularly useful when the surface of the precipitate is known to react with the adsorption indicator that has been selected. This method, however, requires the presence of substances which alter the surface charge or compete for adsorption. The sharpness of the endpoints may be reduced by the presence of inappropriate pH, organic compounds, and by excessive amounts of electrolytes and colloidal impurities.

The Fajans method, then, is an example of one of the significant aspects of analytical chemistry: the surface chemistry of a precipitate can affect the chemical equilibrium of a solution phase reaction. Control of precipitation conditions, indicator selection, pH, ionic environment and mixing are important to achieve successful application..

8.9 Comparison of Mohr’s, Volhard’s and Fajans Methods

The Mohr, Volhard and Fajans methods are classical argentometric methods, which are quite different in their endpoint mechanisms and experimental requirements. Mohr's method is a direct titration method which uses a standardized solution of silver nitrate containing potassium chromate and a sample containing a halide ion. End point is reached when a significant amount of the halide has been precipitated by the formation of the first permanent reddish-brown silver chromate. It is, therefore, based on the proportion of the precipitation reaction. The method is most effective if the solution is neutral, or nearly neutral, since it can upset the chromate equilibrium and/or create other silver species that will compete with the chromate.

The method of Volhard is a fundamentally different one as, in general, it is a back-titration. The sample is added to a solution containing a large excess of silver nitrate and the excess silver ion is then titrated using the excess of standard solution of thiocyanate with ferric ion as the indicator. At the end point, a red complex of Fe–thiocyanate is formed and persists. It's a great benefit that it can operate in an acid environment. However, it is necessary to take some precautions (or steps to prevent reaction) if the precipitated silver halide will be separated from the thiocyanate, or it is necessary to take steps for separation.

Fajans method is a direct titration similar to Mohr's method, but with the use of an adsorption indicator. The endpoint is based on the change in the surface charge of the precipitate of silver halide at the equivalence point. If there is a slight excess of silver ion present the indicator will be adsorbed on the positively charged surface of the precipitate and give a visible colour change. Requires more than the method can provide to give a good endpoint: particle size, surface area, indicator chemistry, ionic environment, pH.

Because of these differences, there are two methods to be chosen from. Mohr's method can be applied to a simple chloride without an acidic medium and is usefully applied for the analysis. If an appropriate adsorption indicator is available and has a sensitive endpoint then Fajans is preferred, if this is not the case then Volhard is favored. Always, interfering ions, type of matrix, and desired accuracy of the analysis must be taken into account. Hence, method selection should not only look into considerations of practicability but also those of suitability of the sample, equilibrium of precipitation and indicator system and experimental conditions.

8.10 Estimation of Barium Sulphate by Gravimetry

The gravimetry of barium sulphate is a classical method for quantitative determination of sulphate, which is illustrated by this method of precipitation analysis. It is a method in which the very sparingly soluble barium sulphate is precipitated by adding a soluble barium salt to a solution containing sulphate ions. The basic reaction is the following: $Ba^{2+} + SO_4^{2-} \rightarrow BaSO_4(s)$. The sulphate ion crystallises as barium sulphate and has a fixed chemical composition that is very low in its solubility

thus being very suitable for gravimetric determination. The $BaSO_4$ is filtered out, washed, dried or burned as necessary and then weighed after precipitation. The mass measured is converted to the number of sulphate ions, based on the ratio of $BaSO_4$ to SO_4^{2-} in the reaction.

The sample must be dissolved and the conditions adjusted to be correct before analysis. A solution of barium is added dropwise to the warm or hot sample solution, stirring constantly, the reagent used is generally barium chloride. Importance of controlled addition is that when added too quickly, very fine particles may be formed which may not be filterable, may pick up impurities. The precipitate is thus browned off and is commonly left for a prolonged time after its formation. Digestion encourages crystal growth and enhance filterability. Also can reduce surface area for soluble contaminants to be adsorbed.

The $BaSO_4$ precipitate is filtered out using an appropriate gravimetric filter. During washing soluble barium salts and chlorides etc. are removed. The washing operation should be adequate to ensure good purity of the precipitate, while minimizing mechanical losses. Then the filter and precipitate is dried or ignited based on the analysis method. If an ignition is wanted, the heating should be carefully controlled so that mechanical loss of fine particles of $BaSO_4$ does not occur. At the end, it will be dried in a dessicator and weighed until constant weight is reached.

It is based on the molar masses. If the number of moles of $SO_4$2 is equal to the number of moles of $BaSO_4$, then the number of moles of $SO_4$2 can be determined from the mass of $BaSO_4$.The mass of $BaSO_4$ can be used to calculate the number of moles of $SO_4$2- present in it as 1 mole of $BaSO_4$ contains 1 mole of $SO_4$2- Thus,

Mass of SO_4^{2-} = Mass of $BaSO_4$ × (Molar mass of SO_4^{2-} / Molar mass of $BaSO_4$).

If percentage sulphate is needed then the mass of the sulphate is divided by the mass of the sample and then multiplied by 100. To get the reliable result, one should get the complete precipitation, proper digestion, quantitative filtration, efficient washing and constant final mass. The gravimetric method of Barium sulphate gravimetry is therefore a good example of the whole gravimetric process and shows how a simple precipitation reaction can be made into a satisfactory quantitative analysis method.

Chapter Summary

The formation and behaviour of sparingly soluble compounds are important quantitative techniques, namely precipitation titrations and gravimetric analysis. Gravimetric analysis is used to determine the quantity of an analyte based on its mass of a pure and stable compound that contains a known quantity of the analyte. The key to precipitation gravimetry is to form a precipitate that is low in solubility, definite in composition, fairly pure, and has desirable physical properties. Precipitation is controlled to limit supersaturation from occurring and to promote the growth of larger particles. The crystal

growth and filterability have been improved by digestion, and by filtration, the solid has been removed from the mother liquor. The washing is done to remove soluble impurities, and drying/ignition is to get a stable weighing form. Repeated weighing to constant mass (after cooling in a desiccator) ensures repeatability of the final measurement.

Precipitation titrations are used to determine the volume of the standardized reagent used to reach end point. Silver nitrate can be used for Argentometric titrations, particularly for determining halides. The direct titration method using chromate as an indicator involves the formation of the silver chromate as an end-point indicator. In general, Volhard's method is a back titration method, the amount of excess silver ion is determined by titration with thiocyanate by using ferric ion as an indicator. The modified Volhard method consists of changes in the procedure to reduce secondary reactions with the precipitated silver halide. The Fajans method is a direct titration method which uses an adsorption indicator and relies on a change in the surface charge on the precipitate in the vicinity of the equivalence point.

The method selected will depend upon the nature of the sample, the pH, interfering substances, properties of precipitates, and the nature of the end point required. The method of Mohr requires suitable neutral conditions, Volhard's method is useful in acidic media and Fajans method can be made to give a sensitive endpoint under appropriate conditions of surface and indicator. The gravimetric estimation of sulphate as barium sulphate demonstrates the use of precipitation, digestion, filtration, washing, drying or ignition and weighing. They all illustrate how the chemistry of chemical equilibrium, precipitation, separation, indicator chemistry and stoichiometry are central to quantitative analytical chemistry.

Key Points

1. Precipitation analysis is based on formation of a sparingly soluble compound.
2. Gravimetric analysis determines analyte quantity from the mass of a chemically defined weighing form.
3. An ideal gravimetric precipitate should have low solubility, definite composition, high purity, and good filterability.
4. Controlled precipitation helps produce larger and purer particles.
5. Digestion promotes crystal growth and improves filterability.
6. Filtration must quantitatively retain the precipitate.
7. Washing removes soluble impurities without causing significant analyte loss.

8. Drying removes moisture, whereas ignition may convert a precipitate into a stable weighing form.
9. Constant mass is required for reliable gravimetric measurement.
10. Precipitation titrations use standardized reagents to determine analyte concentration from titrant volume.
11. Argentometric titrations commonly employ silver nitrate for halide determination.
12. Mohr's method uses potassium chromate and detects formation of silver chromate at the endpoint.
13. Volhard's method generally uses excess silver nitrate followed by thiocyanate back-titration.
14. Ferric ion is used as the indicator in the Volhard procedure.
15. Modified Volhard procedures reduce errors caused by interactions between silver halide and thiocyanate.
16. Fajans method uses adsorption indicators and depends on changes in precipitate surface charge.
17. pH and indicator selection strongly influence precipitation titration endpoints.
18. Interfering ions capable of precipitating with silver or interacting with indicators can cause analytical error.
19. Barium sulphate is an important gravimetric weighing form for sulphate determination.
20. Accurate quantitative analysis requires control of every operation from sample preparation through final calculation.

Review Questions

Short-Answer Questions

1. Define precipitation gravimetry and explain its fundamental principle.
2. What characteristics should an ideal gravimetric precipitate possess?
3. Explain the importance of digestion in gravimetric analysis.
4. What is coprecipitation? Name its major mechanisms.
5. Differentiate between drying and ignition.
6. Why is constant mass required in gravimetric analysis?

7. Define precipitation titration.
8. What is argentometric titration?
9. State the principle of Mohr's method.
10. Why is potassium chromate used in Mohr's method?
11. What is the endpoint reaction in Mohr's titration?
12. Explain the principle of Volhard's method.
13. Why is ferric ion used in the Volhard procedure?
14. What is meant by back-titration?
15. Explain the principle of the Fajans method.
16. What is an adsorption indicator?
17. Why is pH control important in precipitation titrations?
18. Mention two limitations of Mohr's method.
19. What is the purpose of modifying the Volhard procedure?
20. Explain the basis of gravimetric estimation of sulphate as $BaSO_4$.

Long-Answer Questions

1. Describe the complete procedure of precipitation gravimetry, explaining the purpose of each stage.
2. Discuss the factors controlling the formation, purity, and filterability of gravimetric precipitates.
3. Explain the principle, procedure, endpoint, advantages, and limitations of Mohr's method.
4. Describe Volhard's method with relevant chemical reactions and explain the role of the ferric indicator.
5. Discuss the modified Volhard method and explain why modification may be necessary in chloride determination.
6. Explain the theory and practical procedure of Fajans titration.
7. Compare Mohr's, Volhard's, and Fajans methods with respect to titrant, indicator, medium, endpoint, advantages, and limitations.

8. Describe the gravimetric estimation of sulphate as barium sulphate, including precipitation, digestion, filtration, washing, ignition, weighing, and calculation.
9. Explain the importance of solubility product and common-ion effects in precipitation analysis.
10. Discuss major sources of error in precipitation titrations and gravimetric analysis and describe measures for minimizing them.

Multiple-Choice Questions

1. Which property is most desirable for a gravimetric precipitate?

A. High solubility

B. Variable composition

C. Low solubility and definite composition

D. High volatility

Answer: C

2. The purpose of digestion of a precipitate is primarily to:

A. Increase its solubility

B. Promote crystal growth and improve filterability

C. Convert it into a gas

D. Increase the concentration of impurities

Answer: B

3. Which reagent is commonly used as the titrant in Mohr's method?

A. HCl

B. NaOH

C. $AgNO_3$

D. KSCN

Answer: C

4. The indicator used in Mohr's method is:

A. Methyl orange

B. Potassium chromate

C. Ferric chloride

D. Fluorescein only

Answer: B

5. The coloured compound responsible for the endpoint in Mohr's method is:

A. AgCl

B. AgBr

C. Ag_2CrO_4

D. $FeSCN^{2+}$

Answer: C

6. Volhard's method is generally classified as a:

A. Direct acid-base titration

B. Back-titration

C. Complexometric titration

D. Redox titration

Answer: B

7. The indicator used in the Volhard method is based on:

A. Fe^{3+}

B. CrO_4^{2-}

C. Eriochrome Black T

D. Starch

Answer: A

8. Fajans method uses:

A. An adsorption indicator

B. A redox indicator

C. A metal-ion indicator only

D. A gas indicator

Answer: A

9. In gravimetric sulphate determination, sulphate is commonly precipitated as:

A. $BaCl_2$

B. $BaSO_4$

C. Ag_2SO_4

D. Na_2SO_4

Answer: B

10. The final mass in gravimetric analysis should normally be obtained after:

A. One rapid weighing

B. Addition of excess solvent

C. Repeated treatment until constant mass

D. Dissolution of the precipitate

Answer: C

Chapter 9: Complexometric Titrations

Learning Objectives

Upon completion of this chapter, students will be able to: Describe the basic principles of complexometric titrations and explain how metal ions are quantitatively determined by the formation of a stable coordination complex with an appropriate ligand. The students will be able to understand the properties of complexometric titrants such as ethylenediaminetetraacetic acid (EDTA) including its chelating behaviour, its stoichiometric relation with the metal ions, conditional stability constant and its importance in chelating. They will be able to classify complexometric titrations as direct, back, displacement and indirect titrations and be able to recognize the analytical appropriateness of each. Students should also be able to describe the role of metallochromic indicators, describe the properties of a good metal-ion indicator and explain how a visible colour change occurs at the endpoint. The chapter also intends to give insight into masking and demasking techniques to enhance selectivity of the analysis when more than one metal ion is present in the same sample. Student should be able to differentiate between masking reagent and demasking reagent and its significance in selective sequential determination of metal ions. Special emphasis will be placed on the properties, preparation, standardization, and use of disodium EDTA in pharmaceutical and analytical determinations. Students will also learn how to describe the formation of metal–EDTA complexes, in general terms the reaction $M^{n+} + Y^{4-} \rightarrow MY^{(n-4)-}$, and will know that the reacting species of EDTA depends on the pH of the solution. The chapter will help students to understand how to set up the complexometric titration practically and why buffer, indicator, controlled pH and accurate endpoint detection is important. Lastly, analytical procedure for estimation of Magnesium sulphate and Calcium gluconate by Disodium EDTA, Stoichiometric calculations, Sources of analytical error and suitability of complexometric methods for pharmaceutical quality control and routine quantitative analysis will be discussed. The main advantage of complexometric titration is the ability to form a complex that is stable and soluble in water with many metal ions and have convenient and reproducible quantitative measurements under controlled conditions.

9.1 Introduction

Complexometric Titrations are volumetric analytical procedures, based on the formation of coordination complexes between metal ions and complexing agents. They are mostly used to quantify metal ions in pharmaceutical products, biological samples, environmental samples, water, food and industrial formulations. The amount of metal ion in the solution is typically determined by adding a standardized solution of the ligand to the solution of the metal ion until all the metal ion has been consumed. A known, stoichiometric quantity of the metal ion is then present, and the amount of

ligand used is correlated to the amount of metal ion present. There are several complexing agents which can be used but the most important titrant is EDTA which will form a stable complex with a wide range of metal ions and will generally react with the metal ions in 1:1 molar ratio regardless of the charge of the metal ion.

The EDTA ligand is a hexadentate ligand with 4 COO- and 2 N donor groups. These donor atoms allow EDTA to bind to a metal ion, and to form a very stable chelate ring system. The structure is of particular interest in so far as the complex stability is considerably greater than many of the simpler monodentate ligand complexes. In the aqueous solution, however, EDTA exists in a few different protonated forms, and the reactivity of a particular metal EDTA complex depends on the pH of the solution. Therefore, complexometric titrations are usually carried out in buffered solutions which have the optimal pH for ensuring the presence of proper species of EDTA in the solution and of the metal ion in a proper state that can react with EDTA. It is highly useful for analysis, as it has several donor sites and its molecular structure.

The other key element is the metal-ion indicator. The metallochromic indicators are used for the detection of metal ions forming colored complexes. When EDTA is titrated the metal ion will bind to EDTA rather than the indicator and at some point will remove the indicator since the metal-EDTA is more stable. The colour change provides a visual endpoint. The selectivity can be increased using other techniques like pH control, masking agents, selective precipitation or demasking techniques. The importance of these strategies is even greater if other metal ions are present, because EDTA cannot differentiate between any one metal ion. The complexometric analysis is therefore a combination of the coordinating chemistry, equilibrium chemistry and volumetric measure. It is of practical importance because it provides the potential for the development of relatively simple and convenient quantitative methods which are easily adapted to routine analytical practice from relatively complex metal ion equilibria.

9.2 Classification of Complexometric Titrations

There are two kinds of complexometric titrations depending on the method of adding the metal ion to complexing agent and the method by which the endpoint is determined. Titration can be done in four ways: direct, back, displacement and indirect. A buffer is used to maintain an appropriate pH for the sample and then the sample is titrated with a standard EDTA solution and a suitable metallochromic indicator. When there is a 1:1 EDTA:metal ratio, the amount of EDTA used is proportional to the amount of metal ion present. The most common direct method is the direct titration method which uses a fast reaction and an indicator that has a sudden colour change at the equivalence point.

If it is not possible to perform the direct titration, because the reaction between metal and EDTA is slow, the analyte precipitates during the course of the titration, or there is no suitable indicator, then

back titration is required. The excess amount of EDTA is added into the amount of analyte solution in this procedure. Time is given to allow the complex to form and then some EDTA is added to a standard solution containing a different metal ion to be titrated. The amount of EDTA reacted with the analyte is the difference between the EDTA added and EDTA that reacted. This method may be especially helpful for metal ions that form a slow complex or for those for which direct endpoint detection is not easily achievable.

The titration of the metal ion in the analyte with a pre-formed metal–EDTA complex is called displacement or replacement titration. If the complex that the analyte forms with EDTA is more stable than the metal complex EDTA originally formed, then the metal will be removed. Then the released metal ion is titrated with a suitable standard solution. This method can be used if there is no appropriate indicator present for the analyte. Certain anions or substances which do not react easily with EDTA are titrated indirectly. The sample is first treated with an appropriate metal ion and the concentration of the metal ion that has been used up or remained after the treatment is then determined by complexometric titration.

The type of titration that is used will depend on the reaction kinetics, stability of the complex, composition of sample, availability of indicators, pH of sample and interference from other ions. Complexometric titrations cannot thus be restricted to a single experimental method, but are a group of analytical methods that depends on the metal–ligand equilibria. Knowing the classification enables the analyst to select the method which will give an adequate reaction rate, a selective complex formation and a clear endpoint.

9.3 Metal Ion Indicators

Definition

A metal-ion indicator, or "metallochromic indicator", is an organic compound which can form a relatively weak reversible complex with a metal ion, which can change colour when titrated with a metal ion. In many instances the indicator is employed at the end of the titration and not as the titrant. When the titration is first started a small amount of metal ion will produce a coloured complex with the indicator. When addition of standardized EDTA is made, it will compete with the indicator for the metal ion. Therefore, the metal–EDTA complex is more stable with the selected conditions than the metal–indicator complex and thus the metal ion is displaced slowly from the indicator by the EDTA. Near the equivalence point most of the substance present (the metal) will have reacted with EDTA, leaving free indicator. The colour of the free indicator will be different from that of the metal complex, making the visible endpoint.

The overall process can be described as M + In ⇌MIn and then MIn + EDTA → MEDTA + In. Depending on the metal, indicator and pH, the specific chemical species will be determined. The

endpoint will be sharp only when the equilibrium between the metal–indicator and metal–EDTA complex is favourable. The metal–indicator complex should not be too stable to give a good initial colour, but more so than the metal–EDTA complex to allow the EDTA to displace the indicator near the equivalence point. If the indicator is too strongly attached to the metal, it may not be able to completely remove the metal at the equivalence point, resulting in a slow or inaccurate end point.

Metal–EDTA complexes are mostly colourless or almost colourless and hence the metal-ion indicators are more important. A suitable indicator will cause an otherwise invisible chemical equivalence point to produce a visible colour change. Many metallochromic indicators, however, are available in a variety of protonation states each of which has a different colour and metal-binding ability, making a great deal of the indicator's performance dependent upon its pH. In this case the range of pH values of the indicator should also be appropriate for its intended use and is normally used in the presence of an appropriate buffer. The concentration of the indicator should also be so small that a large percentage of the analyte is not used up. Therefore, the choice of the indicator is certainly one of the most crucial conditions that must be satisfied for a successful complexometric titration.

Characteristics

Ideally a metal-ion indicator should possess certain chemical and practical properties. First, it should have a definite and repeatable colour change between the metal bound and metal free form; endpoint detection is more difficult with a weak and/or slow colour change, and more difficult observer-dependent error exists. Second, the metal-indicator complex formed must be reasonably stable, but less stable than the metal-EDTA complex under the conditions of the titration. Because the relative constancy, it is possible to displace the indicator in the quantitative manner as the equivalence point is approached. Thirdly, the indicator should be selective for the metal ion that is being determined at the pH value(s) selected. The selectivity is not completely selective, but it may be greatly improved by the use of pH and masking controls.

The indicator should also be chemically stable in the media employed in the titration and should not undergo an unwanted oxidation/reduction, precipitation or decomposition reaction in this media. When used for this analytical process at the concentrations used it should maintain its colour intensity. Indicator should be soluble or dispersible in the medium in which it is used and should have minimum amount of interfering substances or metal ions. Other critical features include a suitable response to pH level. There are several protonation states of metallochromic indicators and each of the protonation states has different colour properties and metal binding properties that will change with pH. The indicator should therefore, have a useful colour contrast at the pH of the titration chosen.

An indicator should react to the sample to form a complex within an appropriate time frame to assure equilibrium prior to endpoint observation. A thermodynamic stable relation may be favourable, but a delay and/or unclear colour change may be achieved because of the kinetic limitations. The concentration of use of the indicator also needs to be appropriate. Excessive indicator can result in excessive analyte binding, which will result in variable end points, and insufficient indicator will result in a weak colour change. The quantity of indicator is thus precisely determined in a routine analysis.

The most common indicators are Eriochrome Black T, calmagite, murexide, xylenol orange and others of this type that are also metallochromic dyes. They can be used for various metals at various pH. Eriochrome Black T can be used especially for the determination of calcium and magnesium in the pH 10 range, where the colour of the free indicator is quite different from the colour of the metal–indicator complex. Ca titration in strongly alkaline solution is often associated with murexide. Xylenol orange may be used for a variety of metal ions at acidic or moderately acidic pH. Therefore, when choosing an indicator for a given metal make sure to use the indicator for the metal, pH, complex stability and expected endpoint contrast, not just the name of the indicator.

Examples

The complexometric analysis is used with various range of applications of metallochromic indicators. Eriochrome Black T (EBT) or Mordant Black 11 is one of the most popular indicators used for a magnesium and calcium determination. The EBT is coloured when mixed with magnesium/calcium (around pH 10), but it is different to the free indicator. In the EDTA titration EDTA complex will bind to the metal ion more strongly and release the indicator which will undergo a characteristic colour change. Thus, EBT has a high importance in the measurement of "total hardness of water" and in pharmaceutical substance which contains magnesium.

Calmagite is chemically similar to EBT and may be used to determine the alkaline-earth metals. In most of the applications, it is more stable or convenient to achieve the colour transition. The ammonium purpurate (murexide) is particularly suitable for the determination of calcium at high pH. If the media is alkaline, magnesium will be precipitated as magnesium hydroxide or it will not interfere and be suppressed in the analysis of calcium. The endpoint of the murexide is the change in color between the calcium–indicator complex and the free indicator.

Other important indicators are the metallochromic indicators; these are utilized in an appropriate controlled environment of acid or near neutral for various metals such as xylenol orange for lead, zinc and other multivalent ions. It is used with several EDTA titrations, all of which change colour differently in different media, according to the International Pharmacopoeia. Metallochromic

indicators are not confused with the adsorption indicators, fluorescein and similar, which have different endpoint behaviour.

The indicator used should be appropriate to the conditions of the titration. If none of the indicators mentioned will provide a satisfactory endpoint at the desired pH, a stable complex may be formed between EDTA and the metal, but the metal is not suitable for direct titration. Masking, back titration, displacement titration or instrumental endpoint detection may be suitable in such situations. The indicator should also be suitable for the matrix of the sample and should not be greatly affected by other metal ions which may occur in the sample. Examples of indicators: for a Mg^{2+}/Ca^{2+} system, EBT and calmagite are good examples; for a Ca^{2+} system, murexide is particularly useful; for several of the heavier metal ions, xylenol orange is useful. In complexometric analysis the choice of the indicator is very important.

9.4 Masking Reagents

Substances added to complexometric analysis to prevent the interfering metal ions from reacting with the titrant and/or indicator under the conditions of the analysis are known as masking reagents. Masking is used for this reason because EDTA is somewhat non-specific and will form a stable complex with many metal ions. Direct titration with EDTA may be used for more than one metal in the sample, in some instances, unless the interfering metal(s) is or are prevented from reacting. This is done by the use of a masking reagent which changes the interfering metal ion into one that does not significantly interfere in the EDTA titration. Masking may occur as a complex formation process, precipitation, pH control, oxidation-state control or any other selective chemical process.

One of the most popular masking mechanisms is complex formation. If the metal is incompatible with the EDTA, it can form a sufficiently stable complex with a suitable masking agent to block the reaction with EDTA. For instance, potassium cyanide has a high affinity to complex several transition and heavy metal ions, such as Zn^{2+}, Cd^{2+}, Cu^{2+}, etc. In such instances the metals are not lost when they are used to determine another ion and EDTA. But cyanide is extremely hazardous, and must be applied only in controlled laboratory environments with the use of proper safety precautions. Other masking agents used depending on the system of metal ions include triethanolamine, fluoride, citrate and tartrate.

Precipitation is another method of masking. During titration an interfering metal can be transformed to a sparingly soluble compound which can either be removed from the solution or made unavailable. Selective masking can also be accomplished using control of pH since the tendency of metal ions to hydrolyse, precipitate or form complexes changes with pH. For instance, magnesium can be separated or suppressed under strong alkaline conditions and calcium can be determined. Another benefit of the

oxidation-state control is that the complexation of the same element in different oxidation states can be quite different.

The masking procedure needs to be carefully designed. Masking reagent should be specific towards interfering ion, and should not react extensively with analyte or EDTA. Also, it should be able to withstand the titration conditions. Excess masking reagent may cause pH, ionic strength or response of indicator changes that can cause problems. If it can be properly masked, then a titration with EDTA can be a selective analytical procedure. It can be very useful in the presence of more than one metal ion in a solution, as masking and unmasking can be used to allow each individual ion to be determined without separating the solution physically.

9.5 Demasking Reagents

Substances that are used to liberate a metal ion that has been masked by another reagent, or the other chemical treatment, are called demasking reagents. It is important to demask the ion in the case of several metal ions present in the same sample, and they should be determined sequentially. Sometimes a masking reagent will be used to block the interference from one or more metals and allow the titrating of the analyte selectively. After that, a demasking reagent is added which breaks the masking complex or transforms it into another one that releases one of the metal ions that was previously masked. Then the newly formed ion can be titrated with EDTA or other appropriate reagent. This will enable selective analysis of various components while not requiring separation of the entire sample.

Note that there are multiple ways demasking can occur. For the new conditions, a demasking reagent might form a more stable complex with the masking reagent or with the metal ion that is masked, thus freeing the metal ion in a form that will react with EDTA. It has been reported that formaldehyde and chloral hydrate can be used to selectively demask zinc and cadmium under proper conditions in cyanide containing systems. Another way is to alter the pH to make the masking complex unstable as long as the metal to be titrated is present. It is also possible to remove the masking agent by selective precipitation or by the action of a solvent, or to change the chemical environment.

A good reagent for demasking should be sensitive to the desired metal ion, but not to the other ions present. It should not be an irreversible reaction with the metal that would interfere with the titration. The reaction should also occur rapidly in order to be convenient. Demasking is a process of equilibrium, so the results of demasking will depend on the relative formation constants and the chemical conditions created after adding the demasking reagent.

The technique of masking/demasking is very effective when combined with other techniques of multi-component analysis. For example, a mixture of several metal ions can be pretreated to mask the effect of some of the metal ions and then another ion can be titrated. A demasking agent is then used to

release the protected metal which can be determined during a subsequent titration. Selective complexometric studies have shown that such sequential methods are useful for the determination of mixtures of aluminium, lead and zinc. So, demasking is not only unmasking but also is a designed analytical process that can contribute selectivity to a process which has a wide complexing capacity of the titrant itself.

Table 9.1. Metal Ion Indicators, Masking and Demasking Reagents

Reagent/Indicator	**Principal application**	**Function**	**Typical metal ions**
Eriochrome Black T	Alkaline-earth titrations	Metallochromic indicator	Mg^{2+}, Ca^{2+}
Calmagite	Complexometric endpoint detection	Metallochromic indicator	Mg^{2+}, Ca^{2+}
Murexide	Calcium determination	Metallochromic indicator	Ca^{2+}
Xylenol orange	Acidic/near-neutral titrations	Metallochromic indicator	Pb^{2+}, Zn^{2+} and others
Potassium cyanide	Selective masking	Forms stable metal–cyanide complexes	Zn^{2+}, Cd^{2+}, Cu^{2+} and others
Triethanolamine	Selective masking	Complex formation	Fe^{3+}, Al^{3+}
Fluoride	Selective masking	Stable fluoride complex formation	Fe^{3+}, Al^{3+}
Chloral hydrate	Demasking	Releases selected masked ions	Zn^{2+}/Cd^{2+} systems
Formaldehyde–acetic acid mixture	Demasking	Breaks selected masking complexes	Zn^{2+}/Cd^{2+} systems

The major indicator, masking, and demasking reagents commonly encountered in complexometric analysis are summarised in **Table 9.1**, with their principal analytical functions and representative applications.

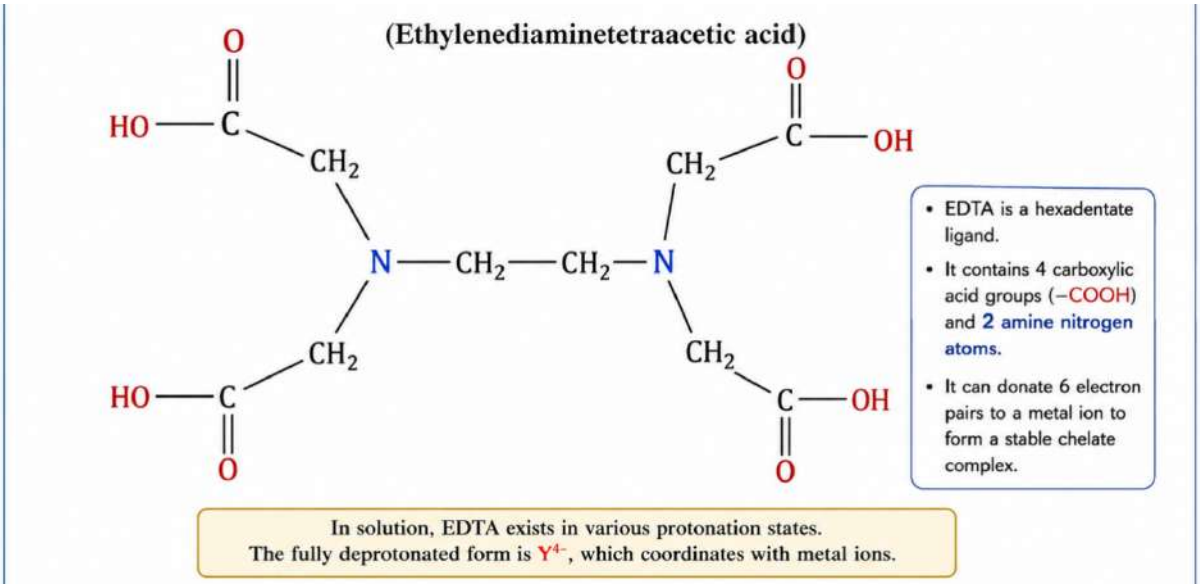

Figure 9.1. Structure of EDTA

EDTA has a total of 2 nitrogen atoms and four carboxylic acid groups, making a total of 6 donor atoms for the metal ion. EDTA, in its fully deprotonated state, can completely surround a metal ion, and a stable chelate complex is formed which makes it a broad application of EDTA as a complexometric titrant. The protonation state of EDTA varies with pH; therefore, the species present in the complexation reaction in an aqueous titration will depend on the buffering conditions.

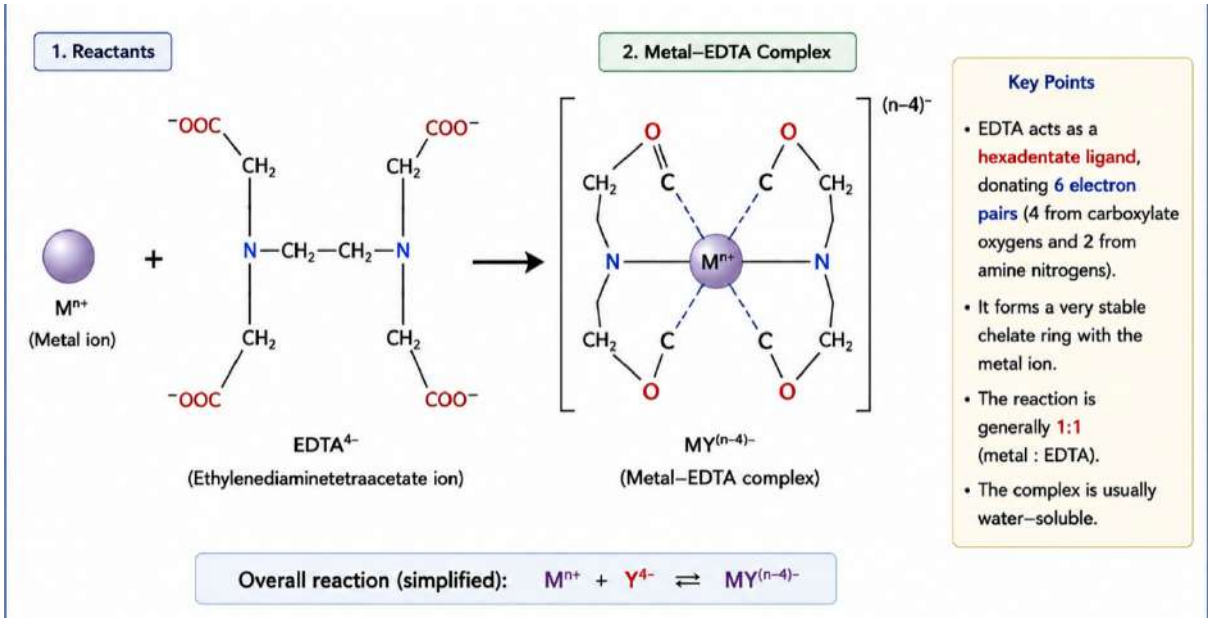

Figure 9.2. Metal–EDTA Complex Formation

The overall reaction is $M^{n+} + Y^{4-} \leftrightarrow MY^{\wedge}(n-4)-$, where the EDTA is generally protonated and gives up a proton upon reaction with the metal ion, when the reaction is conducted in an aqueous solution. Normally the complex formed between the metal ion and EDTA will be at a 1:1 ratio with one

molecule of EDTA to each molecule of metal ion, allowing the concentration of the metal ion to be determined by the amount of standardized EDTA used. The chemical basis of many metal–EDTA complexes is the chelate structure and the high stability of these complexes.

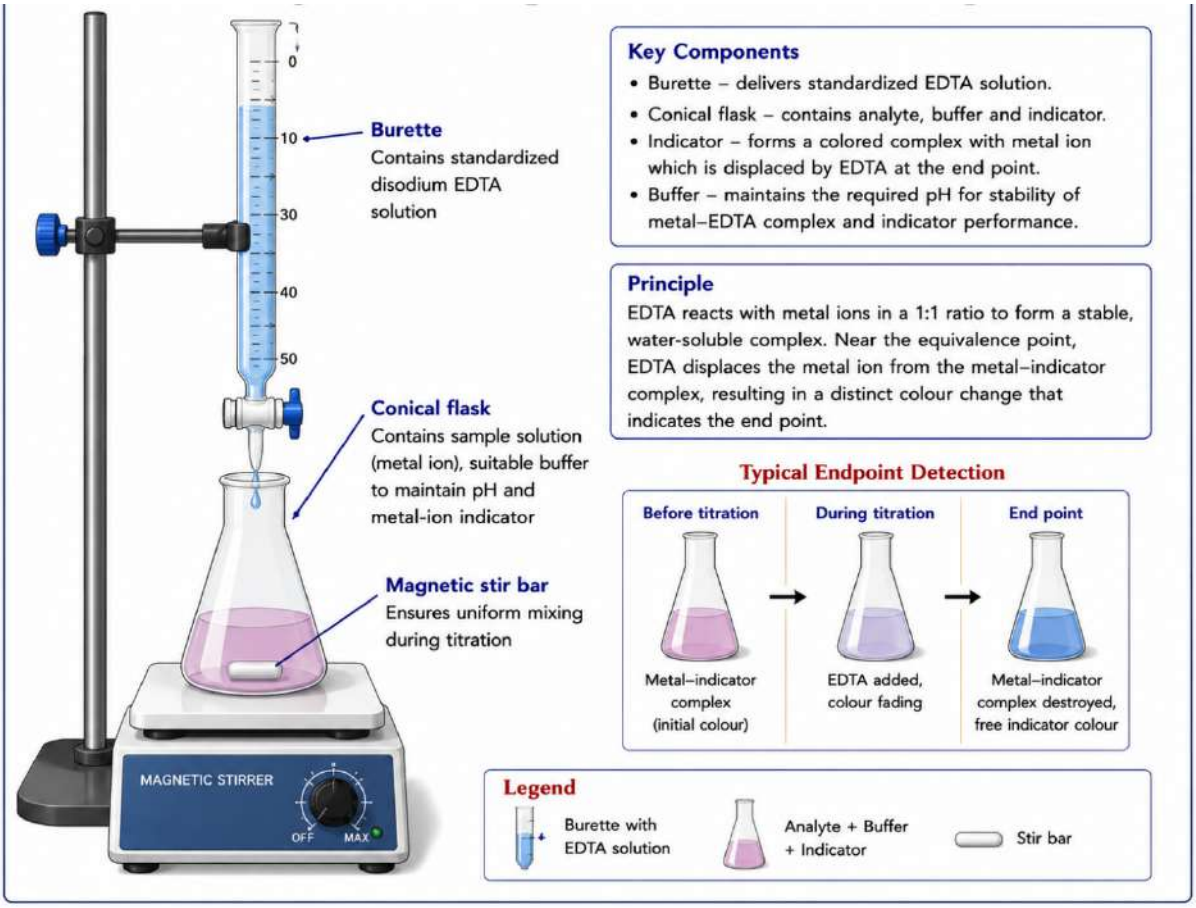

Figure 9.3. Complexometric Titration Setup

The standard procedure for complexometric titration consists of a burette containing the standardized disodium EDTA solution and a conical flask containing the sample of metal ions, buffer solution and metallochromic indicator. The solution is stirred throughout the titration and the end-point is determined by the sudden change of colour of the indicator from its metal complex to the EDTA complex. It is important to use the correct pH since the complex-stability and indicator colour are very dependent on the reaction medium.

9.6 Disodium EDTA

Properties

Disodium EDTA ($Na_2H_2Y{\cdot}2H_2O$) is widely used reagent in the complexometric titration which is actually dihydrate. It is the disodium salt of ethylenediaminetetraacetic acid, and is preferred to the free acid because the salt is much more convenient to dissolve in water. A solution often used in analytical chemistry that is prepared using EDTA is also referred to as an “EDTA solution.” The

reagent is a chelating ligand and it is capable of forming relatively stable complexes with many metal ions which are generally water soluble. One of the major advantages of the analysis is that it has a near 1:1 stoichiometry with the metal ion, irrespective of the charge (+2, +3, or others) on the metal ion, the chemical equation will change, depending on protonation and pH.

The stability of the metal–EDTA complexes is quite different for the various metals. There are a number of different complexes of the various ions of calcium, magnesium, zinc, copper, lead and iron. This variation provides some opportunities to analyze selectively; by controlling the pH and with the use of masking agents. When protonated EDTA species are involved in the reaction with a metal ion, hydrogen ions are liberated and control of the pH is critical. The higher acidity of the medium will increase the protonation of EDTA, thus decreasing its effective concentration as a metal-bounding species. To keep the pH at a desirable value during titration buffer solutions are then used.

The solutions of disodium EDTA are generally colorless and can be easily used in volumetric analysis. However, solutions of EDTA have to be standardized since the exact concentration cannot be taken for granted by direct weighing. The water used for making up the reagent must be of an appropriate quality and stored in a way that minimises the risk of contamination and/or changes in concentration. This is usually done in comparison to a primary or other well defined metal standard, using an appropriate indicator and buffer.

Disodium EDTA is highly complex and has a very predictable complex ratio, is water soluble and is very versatile, which make it an excellent analytical value. The properties, such as the pharmaceutical assays, hardness determinations, environmental analysis and determination of metal ions, are possible. However, it is not selective of itself, due to its wide reactivity. Therefore, pH control, appropriate indicators and masking/ separation techniques must be used if interfering metal ions are present to obtain an accurate analysis.

Preparation

Disodium EDTA solution is prepared by accurately weighing a suitable amount of disodium EDTA, dissolving it in purified or deionized water, quantitative transfer to 1000ml volumetric flask and diluting. The amount of mass required will be dependent on the desired molarity needed as well as the actual form of the reagent (here the dihydrate or another form of the hydrate). The molecular mass of the reagent used for the specific reagent should therefore be used in the preparation calculation. After making up the solution the bottle must be shaken after adding the water to get an even concentration throughout the volumetric flask.

Prior to preparing the reagent, it should be checked for appropriateness and stored correctly. The disodium EDTA should be analytical reagent grade and impurities could interfere with the concentration and metal ions could be added to the EDTA solution. The water to be used in preparing

the solutions should be sufficiently free of metals. Glassware is to be carefully cleaned; if necessary, rinsed with purified water prior to use. Theoretically, contamination from laboratory glassware or water may cause high sensitive determinations due to the tendency of EDTA to complex trace metal ions.

First step in the preparation is accurate weighing on an analytical balance. Water is added into a beaker part of it to dissolve completely the weighed reagent. Unless otherwise specified by the type of reagent, the mixture may need to be gently heated, if the dissolution isn't complete. The solution is then quantitatively transferred to a volumetric flask. The flask is washed several times with the original container and the washings added to the flask to minimise loss of reagent. Water is added until the liquid is almost to the calibration mark and then it is carefully adjusted to the calibration mark at the specified temperature. The flask is capped and inverted a number of times until it is thoroughly mixed.

Theoretical concentration can be calculated from the mass and molecular weight but it is better to standardise the solution before using it in the analysis. This is because of the preparation error, reagent purity, the hydration state and weighing error which can all lead to a deviation between the actual concentration and the theoretical concentration. Next assays are performed with a standardised EDTA solution. Its concentration is usually given in terms of molarity or as an equivalent factor of analyte. Therefore, the only way for successful complexometric analysis is to prepare and standardize the appropriate solution.

Standardization

Standardisation of Disodium EDTA: To get the exact concentration of the prepared solution a standard solution of metal of known composition and purity is used. All EDTA solutions must be standardized because they are not standard primary-standard solutions. The metal ion for the standardization procedure should be quantitative with EDTA in a controlled environment, and should have a suitable endpoint with an appropriate metallochromic indicator. Common Standards are calcium or other suitable metal standard depending on the application under analysis.

A known quantity of the chosen metal standard is dissolved and a suitable buffer is used to adjust the pH in a typical standardization. A metallochromic indicator is then added and a particular colour is formed corresponding to the metal–indicator complex. Then a standard EDTA solution is added from a burette, the solution is stirred continuously. As the EDTA chelates the metal ion, the metal ion is slowly replaced by the EDTA until the indicator is replaced. The colour will gradually fade to the colour of the free indicator at the endpoint. The quantity of EDTA consumed is noted and the molarity calculated using the quantity of metal and the ratio between metal and EDTA used. Most metal–EDTA reactions are of 1:1 stoichiometry so the calculation is often simple.

The standardization should be carried out in duplicate. The use of concordant titres is to get a reliable mean value and a significant difference between titres possibly points to a procedural or endpoint error. The following factors are important: pH, buffer composition, indicator concentration, temperature and cleanliness of glassware. The solution to be used is to be prepared as the standard and the burette must be rinsed with the EDTA solution, so that there is no dilution of the solution.

The standardization factor can then be used in pharmaceutical assays to determine the amount of analyte in the sample. For example, if 1 mL of EDTA corresponds to a known mass of magnesium sulphate or calcium gluco-nate then the titre can be used directly to find the amount of magnesium sulphate or calcium gluconate in the sample. Standardized disodium edetate solutions are recommended for the determination of various metals by the International Pharmacopoeia, and appropriate buffer/indicator combinations are recommended for various analytes. Standardization is thus the process which transforms an already prepared reagent into a reagent that is a quantitatively characterised titrant and is crucial for accurate assay results.

9.7 Estimation of Magnesium Sulphate

The complexation between Mg^{2+} and EDTA is stable and it can be quantitatively estimated by complexometric titration using the standardized solution of disodium EDTA. Although the species that are reacting depends on the pH, the fundamental reaction is represented as $Mg^{2+} + Y^{4-} \rightarrow MgY^{2-}$. The assay is typically performed at a buffered pH slightly higher than 10 that favor the formation of the magnesium–EDTA complex and that will provide a good endpoint with a suitable metallochromic indicator. Eriochrome Black T or Mordant Black 11 is used generally in association with the magnesium complexometric determination. Initially, there is a small quantity of coloured magnesium–indicator complex. The indicator is released as EDTA is added, and chelates the magnesium more strongly than the indicator. The endpoint is indicated by the colour change.

An accurately weighed amount of magnesium sulphate sample is dissolved in water for an assay. If required, the solution is acidified or treated in other ways to ensure complete dissolution as required by the analytical specification. Adjusting the pH to the desired value is achieved by adding a suitable ammonium chloride–ammonia buffer. The metallochromic indicator is then added (in a controlled quantity). This solution is then titrated to the endpoint colour with a standard solution of disodium EDTA. The exact colour shift will depend on the indicator and the pH medium, the end-point is usually noted as a change from violet/red-violet to blue with Mordant Black 11 in an appropriate pH 10 medium.

The change in the amount of magnesium ion consumed is proportional to the volume of EDTA consumed, because the ratio of magnesium ion to EDTA is 1:1. The molar relationship and specific chemical formula of magnesium sulphate specified in the assay are then used to calculate the mass of

magnesium sulphate. If it is a hydrate, the molecular mass should be equal to the declared hydration number. The analyst should not, therefore, use a conversion factor in the general case without knowing what substance is being analyzed.

Common sources of errors are incorrect sample weight, incomplete dissolution, incorrect pH of buffer solution, too much indicator, insufficient recognition of endpoint and contamination by other metal ions that react with EDTA. The buffer is particularly required as EDTA complexation takes place with pH. When the pH is too low, the effective concentration of the metal binding species of EDTA will be decreased and the endpoint will not be as distinct. On the other hand, high alkalinity may change the chemical form of the magnesium or other sample component. So it is necessary to standardise EDTA and repeat the titrations. The method introduces a basic approach to the controlled coordination chemistry analysis of the magnesium-containing pharmaceutical substances with a simple and accurate assay.

9.8 Estimation of Calcium Gluconate

The calcium content in calcium gluconate can be complexometrically titrated with the standardised disodium EDTA. The calcium ion-EDTA complex is stable as 1:1 complex, which is represented as $Ca^{2+} + Y^{4-} \rightarrow CaY^{2-}$. The assay is thus based on the amount of EDTA needed to bind quantitatively the calcium liberated from calcium gluconate. The analytical medium should be carefully adjusted since the reaction between calcium and EDTA as well as the indicator response is very sensitive to pH level. Depending on the analytical method used, an alkaline medium as well as metallocromic indicator which is sensitive to calcium, e.g., murexide, may be used. It is important to use an appropriate indicator since the endpoint must be able to clearly separate the calcium–indicator complex from free indicator.

The correct weight of calcium gluconate is dissolved in an appropriate volume of water with an acidification/treatment added, if required, to aid dissolution. Solution is adjusted to desired pH using reagent/buffer supplied. Then a small amount of one of the calcium indicators is added to this. The sample is stirred continuously while standardized disodium EDTA solution is put into the sample from a burette. Calcium ions initially bind to the indicator forming a colour complex of the calcium–indicator complex. As EDTA is added, it will eventually tie up the calcium so that it will release the calcium from the indicator more strongly. At equivalence point, the indicator will be in almost its free state, giving the typical endpoint colour.

The 1:1 ratio is the stoichiometric ratio between EDTA and calcium ion. If the calcium gluconate is fully dissociated, this will be equivalent to one mole of calcium and the number of moles of EDTA used will be proportional to the number of moles of calcium gluconate used in the sample. It should be calculated according to the form of calcium gluconate mentioned in the appropriate monograph.

The concentration of the titrant, the indicator, the pH range or the sample size or the equivalence factor as defined in the pharmacopoeial standard may be used as indicated and is not to be replaced by a general method if an assay is followed.

Other metal ions, improper pH, insufficient dissolution, incorrect indicator concentration, and endpoint overshooting can all have an impact on the accuracy. Suppression of magnesium or interfering metals may be necessary for the determination of calcium. Selective conditions are thus important. For calcium gluconate, complexometric estimation of calcium is an example that the calcium in the formulation is converted to a measurable volumetric response, using the pharmaceutical titration method of EDTA. The procedure is a convenient way to perform routine quality control analysis as long as the sample preparation, standardization, pH, indicator and endpoint are carefully controlled.

Chapter Summary

The reactions of coordination complex formation volumetric reactions are known as complexometric titrations. The most important complexometric titrant is EDTA which forms stable complexes with most metal ions (which are usually water soluble) reacts with most metal ions in 1:1 ratio. The effectiveness of EDTA is very pH dependent because the protonation state of the EDTA determines the concentration of the species that can bind metal ions. Many complexometric titrations, therefore, require the use of buffer solutions. The endpoint is detected visually, using metallochromic indicators which form coloured complexes with the metal. EDTA displaces the metal from the coloured complex when it forms a more stable complex with the metal.

The complexometric titration can be classified into 4 types, namely direct, back, displacement and indirect titration. The simplest method is direct titration method where the metal ion is directly titrated with EDTA solution of known standard. If a direct reaction or endpoint detection is not applicable, back titration may be utilized, or displacement titrations are for the release of a second metal ion from a pre-formed metal–EDTA complex. There are indirect procedures for species determination in instances where it is not possible to make a direct determination by EDTA. Selectivity can be improved by using precipitation, oxidation-state control and other techniques, and by using pH control and masking.

Masking reagents prevent the interference of other metal ions in the titration, while a demasking reagent releases ions from masking to be determined. It is a combination which enables the determination of several metal ions in complex samples in turn. In practice, disodium EDTA is generally used as the titrant as it is more soluble in water than the free acid and its complexometric behavior is predictable. The actual concentration needs to be determined by standardisation prior to use in quantitative assays.

The chapter also demonstrates the pharmaceutical applications in estimation of Magnesium Sulphate & Calcium gluconate. Conveniently, magnesium can be titrated using an alkaline buffer solution in the presence of an indicator such as Eriochrome Black T while calcium can be conveniently titrated in appropriate alkaline buffer solution using an indicator such as murexide, which is calcium sensitive. In the two cases the analytical result will be affected by the 1:1 ratio of EDTA to metal ion. The sample preparation, pH control, selection of the indicator, standardization and endpoint recognition is important to get reliable results.

Key Points

1. Complexometric titrations are based on formation of coordination complexes between metal ions and ligands.
2. EDTA is the most widely used complexometric titrant.
3. EDTA generally forms metal complexes in a 1:1 stoichiometric ratio.
4. EDTA complex formation is strongly influenced by pH.
5. Buffer solutions maintain the appropriate pH during titration.
6. Metallochromic indicators detect endpoints through colour changes associated with metal–indicator equilibria.
7. The metal–EDTA complex should be more stable than the corresponding metal–indicator complex.
8. Eriochrome Black T is widely used for magnesium and calcium systems around pH 10.
9. Murexide is commonly associated with calcium determination under alkaline conditions.
10. Xylenol orange is useful for several multivalent metal ions under appropriate conditions.
11. Complexometric titrations may be direct, back, displacement, or indirect.
12. Masking reagents prevent selected interfering ions from reacting with EDTA.
13. Demasking reagents release previously masked metal ions for subsequent determination.
14. Potassium cyanide can mask several heavy and transition-metal ions, although its toxicity requires strict safety control.
15. Triethanolamine and fluoride can be used for selective masking of particular metal ions.
16. Disodium EDTA should generally be standardized before quantitative analytical use.

17. Magnesium sulphate can be estimated through EDTA titration using an appropriate buffer and metallochromic indicator.
18. Calcium gluconate can be assayed through complexometric determination of its calcium content.
19. Accurate complexometric analysis requires control of pH, indicator concentration, titrant standardization, and endpoint detection.
20. Complexometric titration is widely applicable to pharmaceutical, environmental, industrial, and water-quality analysis.

Review Questions

Short-Answer Questions

1. Define complexometric titration.
2. What is meant by a coordination complex?
3. Why is EDTA widely used as a complexometric titrant?
4. Explain the significance of 1:1 metal–EDTA stoichiometry.
5. Why is pH control important in complexometric titration?
6. Define a metallochromic indicator.
7. What characteristics should an ideal metal-ion indicator possess?
8. Give three examples of metal-ion indicators.
9. What is masking in complexometric analysis?
10. Define a masking reagent and give two examples.
11. What is demasking?
12. Give two examples of demasking reagents or procedures.
13. Differentiate between direct and back complexometric titration.
14. What is displacement titration?
15. Why is disodium EDTA preferred over free EDTA in volumetric analysis?
16. Why must EDTA solution be standardized?
17. Explain the principle of magnesium sulphate estimation by EDTA.

18. Which indicator is commonly associated with magnesium determination at pH 10?
19. Explain the principle of calcium gluconate estimation by EDTA.
20. What factors can cause errors in complexometric titration?

Long-Answer Questions

1. Explain the principle and applications of complexometric titrations.
2. Discuss the classification of complexometric titrations with suitable examples.
3. Explain the principle, characteristics, and applications of metal-ion indicators.
4. Describe masking and demasking techniques and explain their importance in selective metal-ion analysis.
5. Discuss the chemical properties and analytical applications of disodium EDTA.
6. Explain the preparation and standardization of a disodium EDTA solution.
7. Describe the estimation of magnesium sulphate using standardized disodium EDTA.
8. Explain the assay of calcium gluconate by complexometric titration.
9. Discuss the role of pH and buffer solutions in EDTA titrations.
10. Compare direct, back, displacement, and indirect complexometric titrations.
11. Explain the formation and stability of metal–EDTA complexes.
12. Discuss the major sources of error in complexometric titrations and methods for minimizing them.

Multiple-Choice Questions

1. Complexometric titrations are primarily based on:

A. Oxidation reactions

B. Formation of coordination complexes

C. Acid-base neutralization

D. Gas evolution

Answer: B

2. The most widely used complexometric titrant is:

A. HCl

B. NaOH

C. EDTA

D. $KMnO_4$

Answer: C

3. EDTA generally reacts with metal ions in which stoichiometric ratio?

A. 1:1

B. 1:2

C. 2:1

D. 3:1

Answer: A

4. The main purpose of a metallochromic indicator is to:

A. Increase solubility

B. Detect the endpoint

C. Reduce pH

D. Precipitate the analyte

Answer: B

5. Eriochrome Black T is commonly used for the determination of:

A. Sodium only

B. Magnesium and calcium

C. Chloride only

D. Sulphate only

Answer: B

6. A reagent used to prevent an interfering metal ion from reacting with EDTA is called a:

A. Titrant

B. Demasking reagent

C. Masking reagent

D. Reducing agent

Answer: C

7. A reagent used to release a previously masked metal ion is called a:

A. Masking reagent

B. Demasking reagent

C. Indicator

D. Buffer

Answer: B

8. Which reagent is commonly associated with masking several heavy-metal ions?

A. Potassium cyanide

B. Sodium chloride

C. Sulphuric acid

D. Potassium nitrate

Answer: A

9. The pH of the solution is important in EDTA titration because:

A. EDTA complex formation depends on protonation state

B. EDTA becomes radioactive at low pH

C. Indicators never respond to pH

D. Metal ions do not react in solution

Answer: A

10. Murexide is particularly useful for complexometric determination of:

A. Calcium

B. Chloride

C. Sulphate

D. Sodium

Answer: A

11. Disodium EDTA is preferred to free EDTA mainly because it is:

A. More volatile

B. More water-soluble

C. Strongly coloured

D. Insoluble in water

Answer: B

12. Standardization of EDTA is performed to determine its:

A. Colour

B. Actual concentration

C. Melting point

D. Density only

Answer: B

13. In a direct EDTA titration, the analyte is:

A. Directly titrated with standardized EDTA

B. First precipitated and weighed

C. Converted into a gas

D. Oxidized with permanganate

Answer: A

14. A back titration is particularly useful when:

A. Direct titration or endpoint detection is unsuitable

B. No metal ion is present

C. EDTA cannot form complexes

D. The sample is completely insoluble

Answer: A

15. Magnesium sulphate can be determined by measuring its:

A. Chloride content

B. Magnesium content through EDTA complexation

C. Sulphur oxidation state only

D. Water content only

Answer: B

16. Calcium gluconate complexometric analysis is based primarily on determination of:

A. Gluconate oxidation

B. Calcium ions

C. Sodium ions

D. Chloride ions

Answer: B

17. The endpoint of a metallochromic indicator titration results from:

A. EDTA displacing metal from the indicator

B. Formation of a gas

C. Complete evaporation

D. Combustion of EDTA

Answer: A

18. Which factor is especially important for obtaining a sharp EDTA endpoint?

A. Controlled pH

B. High turbidity

C. Excessive indicator

D. Random heating

Answer: A

19. EDTA is described as a chelating ligand because it:

A. Forms multiple bonds with a metal ion through several donor atoms

B. Forms only hydrogen bonds

C. Always precipitates metals

D. Contains no donor atoms

Answer: A

20. The principal analytical advantage of EDTA is its ability to:

A. Form stable complexes with many metal ions

B. React only with sodium

C. Produce gases with all metals

D. Avoid all pH effects

Answer: A

Chapter 10

Redox Titrations

Learning Objectives

After completing this chapter, students will be able to:

1. **Explain** the fundamental concepts of oxidation, reduction, oxidation number, oxidizing agents, reducing agents, and electron-transfer reactions involved in redox titrations.
2. **Classify and differentiate** major redox titration methods, including permanganometry, cerimetry, iodimetry, iodometry, and potassium iodate titrations, based on their principles, titrants, indicators, and applications.
3. **Describe and perform** redox titration procedures used in pharmaceutical analysis and calculate the quantity or concentration of analytes from titration data.
4. **Select appropriate redox methods, indicators, and reaction conditions** for pharmaceutical assays while identifying important sources of analytical error and methods for improving accuracy.

10.1 Introduction

The redox titrations are volumetric analytical technique that is based on the oxidation-reduction reactions that will involve electron transfer between the chemical species. One substance is oxidized (loses electrons) and another is reduced (gains electrons). It is because the number of electrons in the transfer can be related to the amount of substance that reacts, thereby providing a powerful technique for a chemical quantitative analysis. A redox titration is a titration in which a solution which contains a known concentration of oxidizing or reducing agent is slowly added to a sample containing the substance to be determined. The titration is repeated until the stoicheiometric amount is reached and the volume of titrant used is used to calculate the concentration of the analyte. A number of medicinal substances, excipients, inorganic ions, oxidizing agents, reducing agents and antioxidants have chemically useful oxidation–reduction properties so redox titrations are very important in pharmaceutical analysis. They can be applied, e.g., for determination of hydrogen peroxide, iron salts, ascorbic acid, iodine containing substances, and some pharmaceutical oxidants and reductants. Redox titrations involve transfer of electrons and hence require taking into account oxidation state, electrode potential, reaction stoichiometry and reaction kinetics while acid–base titrations are based on proton transfer. It can be detected by the colour of titrant, using a redox indicator or an indicator system containing iodine and starch. For his oxidation or reduction potential, stability, rate of reaction, selectivity and for the analyte matrix, the right titrant is chosen. The most important redox titrations are: titrations with potassium permanganate as oxidising titrant (permanganometry); titrations with

cerium(IV) as oxidising agent (cerimetry); direct titration with iodine (iodimetry); indirect determination by the generated iodine (iodometry); titration with potassium iodate and iodine generating reactions (iodate). Because they can be used to determine results without the use of complicated instruments, these procedures have been used as reliable procedures in analytical chemistry and pharmaceutical chemistry. Control of acidity, reaction time, reagent concentration, temperature and the detection of endpoint are the important factors to be considered for successful redox titration. Thus, the knowledge of the electron transfer chemistry is crucial for choosing and using the appropriate method.

10.2 Concepts of Oxidation and Reduction

Always in a redox reaction, there is both oxidation and reduction. Oxidation is traditionally considered to be the addition of oxygen or the removal of hydrogen, but it can also be described as the loss of electrons or the increase in oxidation state. When the oxidation number decreases it is known as reduction. Electrons can never be produced or used in a chemical reaction, so that oxidation and reduction always go together. The substance that loses electrons is said to be the reducing agent because it reduces another substance, while the substance that gains electrons is said to be the oxidizing agent because it oxidizes another substance. For example, in an oxidation-reduction reaction, Zn is oxidized to Zn^{2+} in the reaction Zn + Cu2+ → Zn2+ + Cu and Cu2+ is reduced to Cu in the reaction. The oxidation half-reaction is $Zn \rightarrow Zn^{2+} + 2e^-$ while the reduction half-reaction is $Cu^{2+} + 2e^- \rightarrow Cu$. The half-reactions can then be added together to obtain the overall balanced redox equation. Another convenient method of identification of oxidation and reduction is by oxidation numbers. When the oxidation number of an element is increased, the process is called oxidation and when the oxidation number of an element is decreased, the process is called reduction. Balancing Redox reactions is particularly important in Analytical Chemistry where the number of electrons transferred in the reaction is used in calculations during titration. Half-reaction methods work well for more complex reactions, such as those that contain permanganate, dichromate, cerium(IV), iodine, and iodate. The nature and concentration of the reaction medium may greatly affect the products and the stoichiometry. For instance, the behavior of permanganate in strong acidic, neutral and alkaline solutions is different, where Mn^{2+} is the main reduction product in strongly acidic solution. Hence the concentration of the acid should be appropriate for permanganometric analysis. Similarly, iodine participates in a reversible reaction, $I_2 + 2e^- \rightleftharpoons 2I^-$ and can thus be used in direct and indirect titrations. The analysis point between oxidation/reduction is based on whether or not a given electron transfer reaction occurs – the concepts go beyond the basics in practice. However, the redox titration will not work if the reaction does not proceed rapidly enough, if it is not a predictable reaction, or if it does not occur to completion. So, all redox titration processes will be based on knowledge of electron transfer, oxidation states, half-reactions and reaction conditions.

10.3 Oxidizing and Reducing Agents

The oxidizing agents and reducing agents are the reactants that are used in redox titrations and are involved in the transfer of electrons. An oxidising agent is a substance that can accept electrons from another species, and will be reduced in the reaction; it is also called an oxidant. The one which loses an electron and is oxidized is called reducing agent or reductant. One of these substances is generally employed as a standard titrant; the other is the analyte or it can undergo a quantitative reaction with the analyte. The best redox titrant would have the following properties: it should react fast and quantitatively with the analyte, the concentration of the titrant should be known and stable with known uncertainty, the reaction stoichiometry should be known, and the endpoint should be easily detected. Among oxidising agents in analytical chemistry, potassium permanganate ($KMnO_4$), potassium dichromate ($K_2Cr_2O_7$), cerium(IV) salts, iodine and potassium iodate are commonly used. In acidic solution, potassium permanganate is a strong oxidizer that can be used particularly to test reducing agents like hydrogen peroxide, oxalate and iron(II) ions. Another powerful oxidant is cerium(IV) which is commonly used in cerimetry as the reduction to Ce(III) is a clean one-electron process. Iodine is a relatively mild oxidizing agent and can be used to reduce analytes like sulfites, arsenites and ascorbic acid. The commonly used reducing agents are sodium thiosulfate, iron(II), oxalate and some organic reductants. The reaction of interest in the iodometric analysis, quantitatively, is the reaction between the iodine and sodium thiosulfate as follows: $I_2 + 2S_2O_3^{2-} \rightarrow 2I^- + S_4O_6^{2-}$ Depending on the nature of the sample, the standard reduction potential, reaction kinetics, chemical stability, selectivity and the composition of the sample, the selection of the oxidizing or reducing agent will be different. Too high an oxidation potential will cause the reagent to react with something else besides the analyte, thus creating positive analytical errors. On the other hand, a weak reagent can not react quantitatively. Some redox titrants are also liable to decomposition when stored, so stability is also important. For instance, a solution of potassium permanganate must be carefully prepared and standardized, while a sodium thiosulfate solution may change slightly over time and, thus, must be standardized prior to use. Accordingly, the working of a redox method will be affected by the stability of the oxidizing agent or reducing agent, reaction conditions and the detection of endpoint and their compatibility with the sample matrix.

10.4 Classification of Redox Titrations

There are basically two types of redox titrations: those involving the titrant, and those involving the type of electron-transfer reaction. The main analytical and pharmaceutical techniques which are employed are Permanganometry, cerimetry, iodimetry, iodometry and potassium iodate titrations. The oxidizing titrant in permanganometry is potassium permanganate, which is usually in a strongly acidic solution. In many determinations the reagent can be used as an indicator, the permanganate ion is reduced to almost colourless Mn^{2+}. Cerimetry is the method of analysis based on the use of

cerium(IV) which is commonly used as an oxidizing agent in acidic medium. The reaction involves one electron reduction to produce Ce^{3+} which may be determined by a suitable redox indicator or potentiometrically. Iodimetry is a direct titration where the reducing substance is determined by the standard iodine solution used as titrant. The endpoint used for the usual test for starch is the blue complex it forms with iodine. The other method is indirect – Iodometry. Excess iodide reacts with the analyte or oxidizing species to free iodine which is then titrated with the standard sodium thiosulfate. This is the main difference between iodimetry and iodometry: In iodimetry, the iodine solution is directly titrated, in iodometry, the iodine is released to be titrated with an oxidising substance. The use of potassium iodate titrations takes advantage of the reaction of iodate with iodide in an acid solution to produce iodine. Potassium iodate is prepared in a high state of purity, it is relatively stable and it is beneficial in some analytical methods and as a source of iodine in titrations. Table 10.1 shows the principle titrants, type of reaction, endpoint systems and typical analytical applications for the major methods. This selection of the redox method is based on the oxidation state and chemical behavior of the analyte, the rate of the reaction, medium needed, interfering substances and detection of the endpoint. In pharmaceutical analysis, many drug active components can be quantitatively oxidized or reduced under controlled conditions and for this reason these are used. The method should be such that the redox reaction is sufficiently selective and the products of the redox reaction should be constant during the titration. This is particularly important for some redox systems which have different pathways depending on the pH, and the concentration of acid is important. The temperature may also influence reaction rates, as can be demonstrated by the permanganate titrations with oxalate. So it's not only the classification of the reagents, but the classification of the basic difference in the measurement of the electron transfer reactions is classified as redox titrations.

Table 10.1. Comparison of Redox Titration Methods

Method	**Principal titrant/reagent**	**General type**	**Endpoint detection**	**Representative applications**
Permanganometry	Potassium permanganate	Direct oxidation titration	Self-indicating or potentiometric	Fe^{2+}, oxalate, H_2O_2
Cerimetry	Cerium(IV)	Direct oxidation titration	Redox indicator/potentiometric	Fe^{2+}, reducing pharmaceutical substances
Iodimetry	Iodine	Direct oxidation titration	Starch	Ascorbic acid and other reducing agents

Iodometry	Sodium thiosulfate after iodine liberation	Indirect reduction titration	Starch	Oxidizing agents, copper, chlorine
Potassium iodate titration	Potassium iodate/iodine system	Direct or indirect iodine-generating method	Starch	Reducing substances and halogen-related assays

10.4.1 Permanganometry

Permanganometry is a redox titration in which the oxidising agent used is a strong oxidising agent, potassium permanganate ($KmnO_4$). One of the more commonly used redox titration methods due to the high oxidation potential of the permanganate in acidic solution and its striking purple colour, making it suitable as an indicator for many titrations. In a strong acid media the half-reaction for reduction of permanganate would be $MnO_4^- + 8H^+ + 5e^- \rightarrow Mn^{2+} + 4H_2O$. Hence in these conditions one mole of permanganate will gain five electrons. The analyte should thus be able to oxidize in a quantitatively measurable manner. Typical applications are the determination of iron(II), oxalate, hydrogen peroxide and other reducing substances. The medium in which the reaction takes place is very important because at different pH levels, permanganate can be reduced in a variety of different ways. The quantitative analysis has a predictable stoichiometry in strongly acid solutions where Mn^{2+} is favoured by the formation. Sulfuric acid is the acid which is generally preferred as it does not readily undergo undesirable redox reactions under the normal conditions. However, hydrochloric acid is not recommended for use in some procedures as it can be oxidized under strong oxidizing conditions. Another possible interference is due to the oxidizing activity of nitric acid. Permanganometric titration is a basic method of titrating an analyte, which involves adding analyte to an appropriate acid and titrating with a standard solution of $KMnO_4$ in acidic manner with continuous stirring. This is a very light pink colour which will not fade after mixing which is caused by a small amount of excess permanganate, and completes the end-point. In some reactions (especially with oxalate) the reaction is slow at the beginning, and autocatalytic when Mn^{2+} is formed. The permanganate solution should be standardized prior to the accurate quantitative analysis as $KmnO_4$ is not a primary standard. Standardisation may be effected by sodium oxalate, or some other suitable standard. The merits of permanganometry are as follows: (1) Provides a simple visual endpoint (2) Has a powerful oxidation ability (3) Has wide analytical application. Some limitations are very strict pH level requirements, a tendency for the reagent solution to decompose or become contaminated, and interference from other substances which may be oxidized. Permanganometry, however, is also a

valuable method in pharmaceutical and general analytical chemistry, but with the above mentioned limitations.

10.4.2 Cerimetry

A redox titration method that involves the oxidising property of cerium(IV) (typically provided as a solution of cerium(IV) salt in an acidic solution) is termed cerimetry. The basic reduction reaction is: Ce^{4+} + e- = Ce^{3+} and one mol of Ce^{4+} requires one mol of e- (electron) in the reduction reaction. This is a simple electron transfer which provides an easy analytical basis that is quantitative. Ce(IV) is a powerful oxidising agent and will oxidise a wide variety of reducing agents including iron(II), many pharmaceuticals, etc. Cerium(IV) is unlike permanganate and so it does not give a suitable intensity endpoint, and so a suitable redox indicator or instrumental method is usually required. If it is not possible to use ferroin and other indicators, use of a potentiometric endpoint indicator is possible, depending on the analytical system. The oxidation potential and the stability of Ce^{4+} depends on the medium so the cerimetry is usually conducted in acid medium. A suitable environment is provided by sulphuric acid. Note that no interfering reducing or oxidizing substances are present since cerium(IV) reacts with many chemically active substances. Great thing about cerimetry is the fact that Ce^{4+} can be prepared in relatively stable acid solution and has a simple reaction stoichiometry due to its one electron chemistry. The method can then be used for substances which can be cleanly oxidized without the creation of complex reaction mixtures. One of the classical applications is the determination of iron(II) in which Fe(II) is oxidized to Fe(III) and Ce(IV) to Ce(III). The reaction can be represented as $Fe^{2+} + Ce^{4+} \rightarrow Fe^{3+} + Ce^{3+}$. The volume and concentration of the cerium(IV) titrant can be used in the calculation of the amount of iron(II) because the ratio is 1:1. In situations where permanganate is not used, Cerimetry can be beneficial as it can adjust the endpoint with a proper indicator or potentiometric detection. But it is imperative that the acidity is carefully controlled and that there are no interfering reducing agents present. The analytical reagent should be standardized prior to use and the conditions should be the same as used in the titration. The choice of a redox reagent should not just be the one that is a strong oxidant, but the other conditions such as electron transfer chemistry, stability, rate of reaction and end point detection are appropriate to the analyte under investigation.

10.4.3 Iodimetry

Iodimetry is a direct redox titration which involves a standardized oxidizing titrant, iodine (I_2), used to determine reducing substances. Iodine gains an electron, following the half reaction $I_2 + 2e^- \rightleftharpoons 2I^-$. Iodine is sparingly soluble in water, and in aqueous solution, it is normally prepared by the reaction of iodine and excess iodide ions, which results in the formation of more soluble triiodide ions, I_3^-. The analytical behaviour of iodine is, therefore, related to a balance between the species of iodine, iodide and triiodide. Differentiation of pharmaceuticals like some antioxidants or reduction of reducing

organic compounds is particularly useful for iodimetry. A typical example of this is ascorbic acid which is quantitatively reduced under appropriate conditions. The reducing substance (analyte) is titrated with iodine solution from a burette and the titre is measured when all the reducing substance has been reacted. An indicator is typically used close to the end point. Molecular iodine is very intensely blue, and forms an intensely blue complex with starch, but iodine itself does not produce the characteristic colour. Throughout most of the titration the reducing analyte consumes iodine and the concentration of iodine will not build up to the level needed to form a permanent blue colour. If there is a little excess of iodine in the solution, it will continue to release a blue colour in the presence of starch at the equivalence point. In general, starch is not used at the beginning where a large amount of iodine is present as the iodine–starch complex can become relatively stable and may cause the endpoint to be less convenient to detect. Iodine solutions can be subject to changes in concentration during storage, such as volatilisation, photolysis and chemical reactions, and must be carefully standardised. The titration should be carried out in a dark place and under conditions that minimize the loss of iodine. Iodimetry is the most suitable method for the case of a very fast and quantitative reaction between the analyte and iodine with minimum side reaction. The method is applicable to the substances that can be easily oxidized, but are not easily determined by the more powerful oxidants. The mild oxidation potential of iodine can be beneficial in selective analysis for the pharmaceutical area. However, if the substance can react with iodine, but it is not the analyte, then this can create an interference. The pH also should be appropriate; some analytes could be subject to competing reactions or instability at extremes of pH. The reaction between two molecules of iodine using a very sensitive endpoint of starch makes iodimetry an important method for determining reducing substances in general.

10.4.4 Iodometry

Indirect redox reaction: The oxidising agent is added to excess iodide, releasing iodine which is then titrated with the standardised sodium thiosulphate. This is a procedure is quite different from iodimetry, in which the titrant itself is the iodine. Typically, the analyte in iodometry is an oxidizing agent. The oxidising analyte causes the iodide ions to be oxidised to iodine, through a suitable oxidation reaction. The free iodine is then reduced back to iodide with sodium thiosulfate, $I_2 + 2S_2O_3^{2-} \rightarrow 2I^- + S_4O_6^{2-}$ The volume of thiosulfate used is in direct proportion to the amount of oxidizing analyte, so it can indirectly measure the concentration of the analyte. Iodometry is broadly utilized to oxidizing materials and is particularly beneficial where the material to be determined cannot be conveniently titrated directly. The iodine made in the reaction is kept in excess with iodide ions, and partially turned into the more soluble triiodide form, which can be titrated. In the vicinity of an endpoint, a starch indicator is sometimes used because the iodine will make a complex with starch that is blue. Here, when the titration is made, the sodium thiosulfate is added up till all the iodine has been consumed. In most cases, this will be done at a fairly low concentration of starch (near the

endpoint), which will provide a more pronounced colour change. The endpoint is when the blue colour is gone. There is a possibility of a change in the concentration of sodium thiosulfate solutions during storage, therefore it is important to standardise them. Care must be taken to make sure that the solution is not subject to microbial degradation or other source of instability. The test is sensitive to experimental conditions in an iodometric reaction. The amount of iodide added, reaction time, acidity, and temperature, plus exposure to light and temperature, may influence liberation and recovery of iodine. For some analytes, the liberation of iodine may be incomplete if the pH is too high and undesirable reactions with thiosulfate and/or iodide may occur if the pH is too low. Iodometry is also useful in the determination of oxidizing agents like copper (II), oxidants related to chlorine, modified procedures used for the determination of dissolved oxygen and liquid pharmaceutical and industrial oxidants. The greatest merit is that many oxidants can be converted to an equivalent amount of iodine and then the quantitative determination can be readily performed by the known titration method with thiosulfate. Therefore, iodometry is an indirect method of analysis which is so versatile because it involves the liberation of iodine and its quantitative reduction in presence of thiosulphate.

10.4.5 Potassium Iodate Titrations

The potassium iodate (KIO_3) titrations are redox titrations, in which the strong and predictable oxidizing properties of the iodate in acidic solution is used, followed by the formation of iodine in the presence of the iodide. In acidic condition, iodate will react with iodide through a balanced reaction like $IO_3^- + 5I^- + 6H^+ \rightarrow 3I_2 + 3H_2O$. The iodine generated could then be reacted with the material to be analyzed (analyte) in a reduction reaction, or it could be titrated using sodium thiosulfate. The main advantages of potassium iodate in volumetric analysis is that it can be prepared to a high degree of purity and it is relatively stable so that the solutions of accurately known concentration can be prepared by using it in an appropriate analytical procedure. The reaction of iodate to iodine is a helpful connection between the chemistry of iodate and the well-known iodine–thiosulfate system. One way is to allow the precise amount of potassium iodate to react with an excess of potassium iodide in an acid solution to release a precise amount of iodine. The standardized solution of sodium thiosulfate can then be used to titrate the iodine. Or, the iodine produced could react directly with a reducing material in the sample. Starch is usually employed to help determine the endpoint of the iodine-based methods because it forms a very blue complex with iodine. The blue colour will be lost if the iodine has been used up. The acidity or pH of the analytical reaction is very important since it affects the reactions between iodate and iodide. The acidity may be too low to produce adequate iodine and if conditions aren't ideal, there may be risks of side reactions. The determination or standardization of reagents or reducing substances containing iodine is a method which has been used historically in potassium iodate systems. If an oxidising solution of known strength of iodine is required the method is of particular value. Potassium iodate is more stable than iodine solutions that might volatilize and be influenced by the environment and therefore is more convenient to use than an

iodine source that can be accurately measured. But all this still requires handling with care and control of the iodine, careful timing, controlled acidity, and proper “end point” detection. An indirect redox chemistry technique that can be very helpful for the reliability of the analysis is the use of potassium iodate, which is a stable primary-standard-type reagent that can be converted to a precisely known amount of reactive iodine. This method is also useful in volumetric analysis and shows the versatility of use of iodine redox system in the classical volumetric analysis.

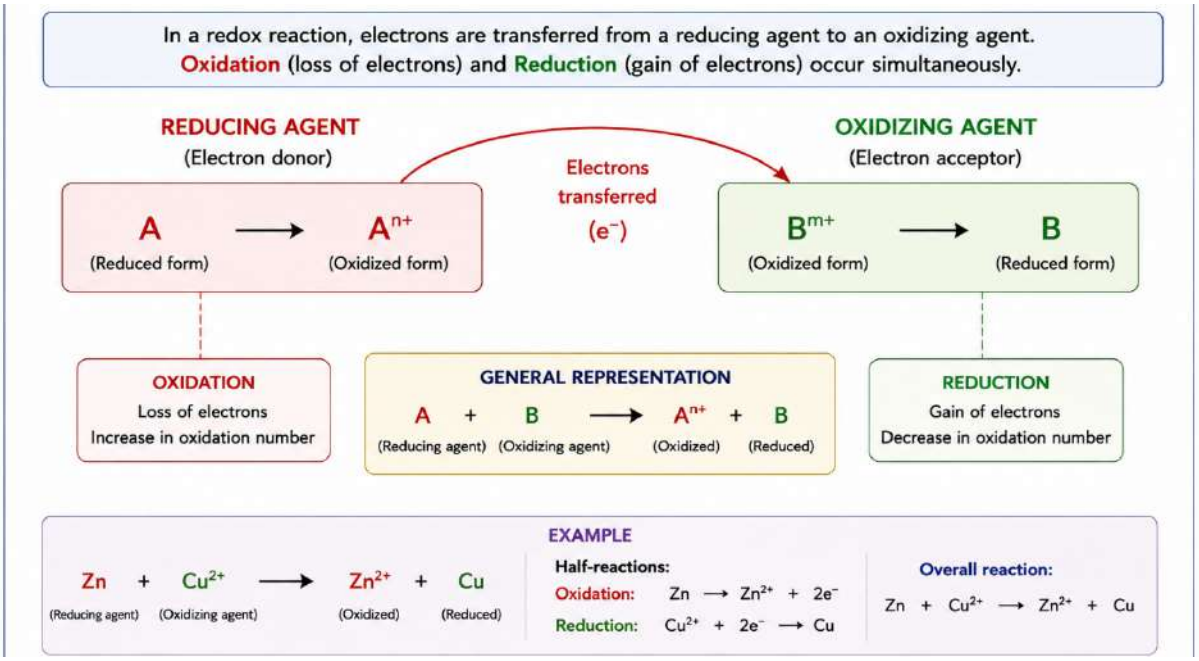

Figure 10.1. Oxidation–Reduction Process

One oxidation and one reduction occur at the same time between two reacting species in the oxidation–reduction process. The oxidation/reduction relationship is clearly illustrated in Figure 10.1, in which oxidation equals a decrease in the number of electrons and reduction equals an increase in the number of electrons. Redox reaction involves a change in oxidation number of the reducing agent as well as the oxidizing agent. For Example: Fe^{2+} will lose one electron to the oxidising agent to form Fe^{3+} and the oxidising agent will gain one electron to form its reduced form. The two half-reactions should be "balanced", that is the same number of electrons should be released on one side as should be consumed on the other side. Stoichiometry calculations for the concentration of an analyte during redox titration can be done by this electron balance.

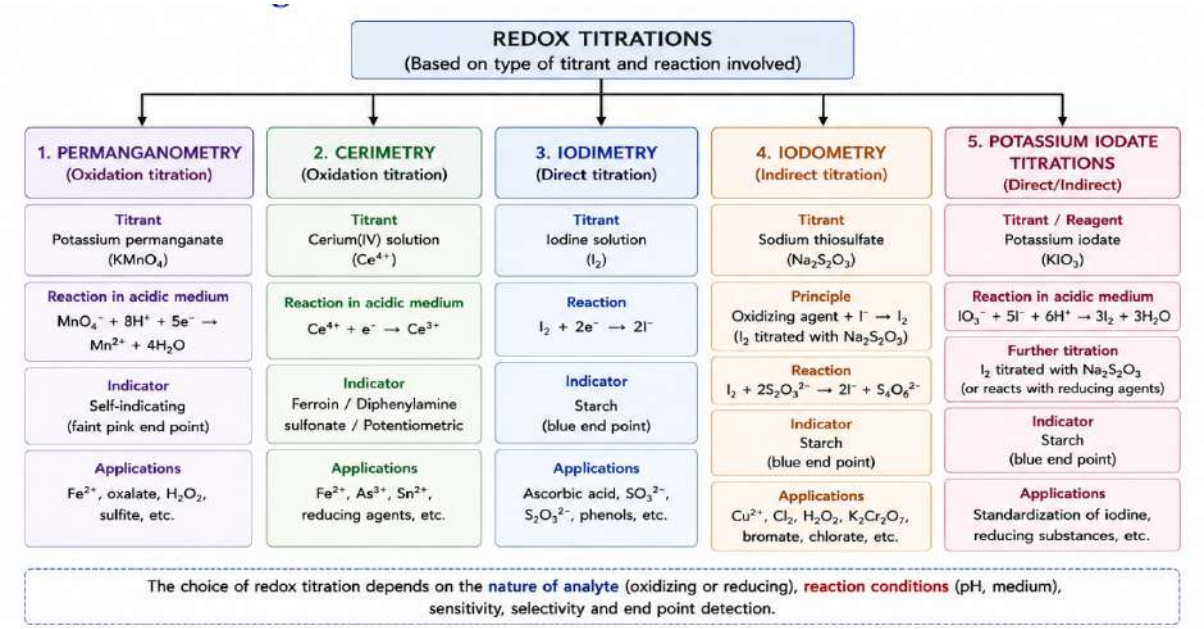

Figure 10.2. Classification of Redox Titrations

The figure 10.2 presents list of all major redox titration techniques based on type of titration and type of analytical reaction. In Permanganometry, KMnO4 is used as an oxidizing titrant and in Cerimary, Ce4+ is used as an oxidizing titrant and in Iodimetry, the iodine is used directly as an oxidizing agent against reducing agent and in Iodometry, it is used indirectly through liberation of iodine in the presence of acidic conditions and the same iodine is titrated using sodium thiosulfate and in Potassium Iodate-procedure, it is used for the liberation of iodine from iodide in the presence of an oxidizing agent of KIO4 under acidic conditions. This classification helps students to identify the direct oxidation titration and indirect oxidation titration by iodine and understand why different titrants are used for different analytes

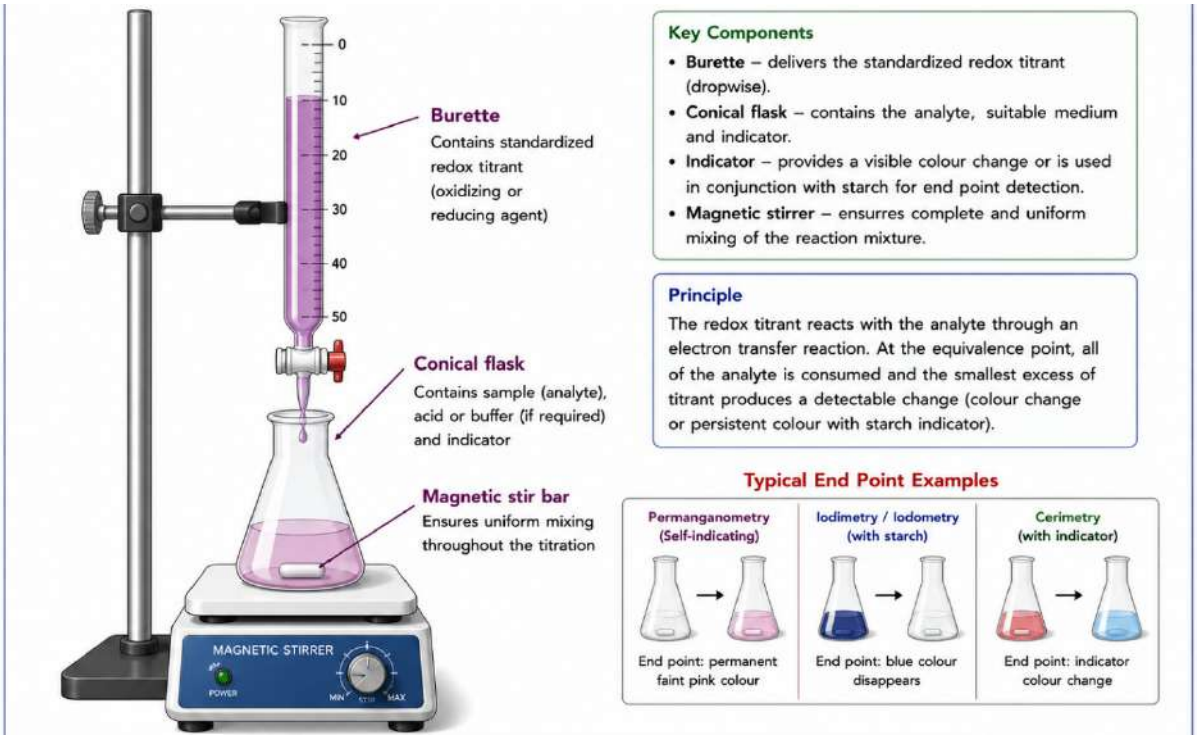

Figure 10.3. Typical Redox Titration Setup

The basic set up for a redox titration is a burette containing the oxidising or reducing titrant, a conical flask containing the analyte and the appropriate reaction medium, and an indicator system (if required). Figure 10.3 shows the basic setup and titrant being added to the flask while the flask is continually stirred. The persistent colour of permanganate (redox indicator), or the starch–iodine colour system can be used to determine the endpoint. The proper apparatus (the burette) and operation of the burette (proper volume measurement, mixing, and controlled reaction conditions) are all critical factors in the ability to obtain reproducible analytical results.

10.5 Applications of Redox Titrations in Pharmaceutical Analysis

Oxidation/reduction reactions take place for many of the active pharmaceutical ingredients, antioxidants, preservatives, inorganic salts and excipients and they can be volumetrically measured, making redox titrations commonly used in the pharmaceutical field. Substances which can be oxidized by permanganate can be determined using permanganometry such as hydrogen peroxide and some materials containing iron. In addition to oxygen, other methods of oxidation are used for the reduction of pharmaceuticals, such as cerimetry which is particularly suitable for certain substances that oxidize in a well-defined manner, including the determination of iron(II). The pharmaceuticals which need a moderate and selective oxidising agent, like iodine, are more easily reduced by iodimetry. The disadvantage of iodometry is that the substances being oxidized is first oxidized to iodine by the analyte, then the iodine is reacted with sodium thiosulfate to find the amount of iodine. Analytical methods should be simple, selective, reproducible, and accurate, and fit for routine use in

pharmaceutical quality control. When suitably manipulated, redox titrations can meet these requirements. They are also useful for the standardisation of pharmaceutical reagents and for testing the oxidising/reducing capacity. The ascorbic acid can be determined by iodine based titration because it is easily oxidised to dehydroascorbic acid and reduces iodine back to iodide. Under appropriate acidic conditions, hydrogen peroxide can be titrated with permanganate. Depending upon the formulation and analytical requirement, iron(II) salts can be determined using permanganometry or cerimetry. Oxidizing agents and compounds which react indirectly to yield iodine can be used as a basis for iodometric procedures. Pharmaceutical matrix should always be considered as the excipients or degradation products may also exhibit redox reactions which may result in analytical interferences. Therefore, sample preparation may involve the following steps: dissolution, dilution, adjustment of pH, extraction, and/or selective chemical treatment. Another factor to consider is the stability of the titrant. Concentrations of permanganate solution, iodine solution and thiosulfate solution may change during storage, and so it is necessary to standardise these solutions. A few of the iodine based procedures are also temperature and light sensitive. In the official pharmaceutical analysis the conditions of the monograph in regard to sample size, concentration of titrant, solvent, acid/buffer, indicator, end point etc. and calculation factor must be followed. It is not universal but for certain substances redox titration is still of great importance as here the chemical change can be matched with a quantitative measurement. Together with its relatively low cost, developed reaction chemistry and potentially great precision, it is a valuable addition to the traditionally used pharmaceutical quality-control analysis.

Chapter Summary

Oxidising and reducing titrations are known as redox titrations. Oxidation is the gain of an oxidation number and the loss of an oxidation number is reduction. During the simultaneous oxidation and reduction a quantitative relationship may be established between the amount of analyte and the volume of the redox titrant used for the simultaneous process. Oxidizing agent is reduced (gains electrons) and reducing agent is oxidized (loses electrons). It is essential to understand these roles correctly in order to be able to understand redox titration reactions. The important methods of redox titration are Permanganometry, Cerimetry, Iodimetry, Iodometry and Potassium Iodate titration. Potassium permanganate is a strong oxidizing titrant, which is used in permanganometry, a method in which the solution is usually done in an acidic medium, and is often self-indicating due to its deep purple colour. Cerimetry is based on Cerium(IV) that is reduced to Cerium(III) in a one electron reaction. Iodometry is an indirect titration in which an oxidizing substance releases iodine from iodide and then the released iodine is titrated with sodium thiosulfate while in iodimetry the reducing substance is titrated with iodine. Potassium iodate procedures involve the use of a reaction of iodate with iodide in acidic conditions to produce a known amount of iodine. Endpoint detection can be by self-indication, redox indicators, starch or instrumental detection. This will depend on the chemical

nature of the analyte, the stoichiometry of the reaction, the rate of the reaction, the redox potential of the reagents, the stability of the reagents, and the possible interference. Redox Titrations have wider applications particularly in pharmaceutical analysis for the estimation of oxidising and reducing agents like antioxidants, iron salts, hydrogen peroxide and iodine and its compounds. To obtain accurate results, the following must be done: Use standardized titrants, ensure the conditions of the reaction are under control, use the correct indicator, ensure that the sample is prepared properly, and make the correct stoichiometric calculations. Redox titrations are significant even though instrumental analytical methods have been developed, because they are inexpensive, very widely available in the laboratory, and can provide a highly accurate quantitative result if the chemical conditions are met.

Key Points

1. Redox titrations are based on **electron-transfer reactions**.
2. **Oxidation** involves loss of electrons or an increase in oxidation number.
3. **Reduction** involves gain of electrons or a decrease in oxidation number.
4. An **oxidizing agent accepts electrons** and is reduced.
5. A **reducing agent donates electrons** and is oxidized.
6. Redox reactions can be balanced using oxidation-number or half-reaction methods.
7. **Permanganometry** uses potassium permanganate as an oxidizing titrant.
8. $KMnO_4$ can act as a **self-indicator** because of its intense purple colour.
9. **Cerimetry** uses Ce^{4+} as an oxidizing agent.
10. Ce^{4+} is reduced to Ce^{3+} through a one-electron process.
11. **Iodimetry** is a direct titration using iodine to determine reducing substances.
12. **Iodometry** is an indirect titration involving liberation of iodine followed by thiosulfate titration.
13. Starch is commonly used as an indicator in iodine-based titrations.
14. Potassium iodate can generate iodine quantitatively in the presence of iodide under acidic conditions.
15. Redox titrations require carefully controlled reaction conditions.
16. Acid concentration can significantly affect redox reaction stoichiometry.
17. Many redox titrants require **standardization before use**.

18. Pharmaceutical applications include analysis of ascorbic acid, hydrogen peroxide, iron salts, and other oxidizing or reducing substances.
19. Interfering oxidizable or reducible substances can affect analytical accuracy.
20. Correct stoichiometry, endpoint detection, and titrant concentration are essential for reliable results.

Review Questions

Short-Answer Questions

1. Define a redox titration.
2. What is oxidation?
3. What is reduction?
4. Define an oxidizing agent.
5. Define a reducing agent.
6. What happens to an oxidizing agent during a redox reaction?
7. What happens to a reducing agent during a redox reaction?
8. Explain the importance of oxidation number in redox reactions.
9. What is permanganometry?
10. Why can potassium permanganate act as a self-indicator?
11. Why is an acidic medium used in permanganometric titrations?
12. What is cerimetry?
13. What is the oxidation state change of cerium during cerimetry?
14. Define iodimetry.
15. Define iodometry.
16. State one major difference between iodimetry and iodometry.
17. What is the function of starch in iodine titrations?
18. Why is sodium thiosulfate used in iodometry?
19. Explain the principle of potassium iodate titrations.

20. List four applications of redox titrations in pharmaceutical analysis.

Long-Answer Questions

1. Explain the fundamental principles of oxidation and reduction with suitable examples.
2. Discuss oxidizing and reducing agents and describe the characteristics of an ideal redox titrant.
3. Explain the principle, procedure, advantages, and limitations of permanganometry.
4. Describe cerimetry and explain its applications in pharmaceutical analysis.
5. Explain the principle and analytical applications of iodimetry.
6. Describe iodometry and differentiate it from iodimetry.
7. Explain the role of potassium iodate in redox titrations.
8. Compare permanganometry, cerimetry, iodimetry, and iodometry.
9. Discuss the factors affecting the accuracy of redox titrations.
10. Explain the applications of redox titrations in pharmaceutical quality control.
11. Describe the role of indicators in redox titrations and give suitable examples.
12. Explain how redox titration methods can be selected according to the chemical properties of a pharmaceutical analyte.

Multiple-Choice Questions (MCQs)

1. Oxidation involves:

A. Gain of electrons

B. Loss of electrons

C. Gain of protons only

D. Loss of neutrons

Answer: B

2. Reduction involves:

A. Loss of electrons

B. Gain of electrons

C. Loss of oxygen only

D. Increase in oxidation number

Answer: B

3. An oxidizing agent is:

A. Oxidized during the reaction

B. Reduced during the reaction

C. Always a metal

D. Always an acid

Answer: B

4. A reducing agent:

A. Accepts electrons

B. Donates electrons

C. Cannot undergo oxidation

D. Always produces oxygen

Answer: B

5. Permanganometric titrations commonly use:

A. Sodium thiosulfate

B. Potassium permanganate

C. Sodium chloride

D. EDTA

Answer: B

6. In strongly acidic solution, permanganate is reduced primarily to:

A. MnO_2

B. MnO_4^{2-}

C. Mn^{2+}

D. Mn^{3+}

Answer: C

7. Potassium permanganate can act as:

A. A masking agent

B. A self-indicator

C. A buffer

D. A precipitating indicator only

Answer: B

8. Cerimetry uses:

A. Ce^{4+}

B. Fe^{2+}

C. I^-

D. Mn^{2+}

Answer: A

9. In cerimetry, Ce^{4+} is reduced to:

A. Ce^{2+}

B. Ce^{3+}

C. Ce^{5+}

D. Ce^{6+}

Answer: B

10. Iodimetry is generally used for determination of:

A. Reducing substances

B. Insoluble precipitates

C. Strong acids only

D. Alkali metals only

Answer: A

11. Iodometry is generally used for determination of:

A. Oxidizing substances

B. Neutral salts only

C. Weak acids only

D. Complexing agents

Answer: A

12. The standard titrant commonly used after iodine liberation in iodometry is:

A. $KMnO_4$

B. EDTA

C. Sodium thiosulfate

D. Cerium(IV)

Answer: C

13. The characteristic indicator used in iodine titrations is:

A. Methyl orange

B. Phenolphthalein

C. Starch

D. Eriochrome Black T

Answer: C

14. Iodine reacts with starch to produce a:

A. Red colour

B. Blue colour

C. Green colour

D. Yellow precipitate

Answer: B

15. In iodometry, the analyte generally causes:

A. Liberation of iodine from iodide

B. Precipitation of iodine

C. Formation of EDTA

D. Reduction of starch

Answer: A

16. Potassium iodate reacts with iodide in acidic medium to produce:

A. Oxygen only

B. Iodine

C. Chlorine

D. Hydrogen peroxide

Answer: B

17. Which of the following is important for accurate redox titration?

A. Correct stoichiometry

B. Random pH

C. Excessive indicator

D. Unstandardized titrant

Answer: A

18. Ascorbic acid can be determined by:

A. Iodimetry

B. Gravimetry only

C. Complexometric titration only

D. Precipitation titration only

Answer: A

19. Hydrogen peroxide can be determined using:

A. Permanganometry

B. Complexometry only

C. Argentometry only

D. Acidimetry only

Answer: A

20. The principal chemical basis of redox titration is:

A. Electron transfer

B. Precipitation only

C. Proton transfer only

D. Complex formation only

Answer: A

UNIT IV

GASTROINTESTINAL AGENTS, ANTIMICROBIALS AND RADIOPHARMACEUTICALS

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CHAPTER 11

GASTROINTESTINAL AGENTS

Learning Objectives

After completing this chapter, students will be able to:

1. Define and classify gastrointestinal agents, including acidifiers, antacids, laxatives, and other agents that modify gastrointestinal function.
2. Explain the mechanism of action, pharmaceutical properties, preparation, identification, assay, uses, and storage requirements of important inorganic gastrointestinal agents.
3. Differentiate between commonly used gastrointestinal agents based on their chemical composition, therapeutic purpose, mechanism, and analytical characteristics.
4. Describe the sites and mechanisms of action of gastrointestinal agents and apply appropriate pharmaceutical analysis principles to their quality-control evaluation.

11.1 Introduction to Gastrointestinal Agents

Gastrointestinal agents include compounds which prevent, diagnose or treat gastrointestinal tract diseases, particularly those in which gastrointestinal fluid and electrolyte balance is disturbed, bowel movement is impaired or constipation occurs or stomach acid is excessive. The gastrointestinal tract has several important physiological roles such as digestion, absorption of nutrient, secretion of gastric and intestinal fluids and elimination of waste products. The following symptoms may occur when there is an imbalance in these processes: heartburn, acid indigestion, nausea, abdominal discomfort, constipation, and changes in bowel elimination pattern. These drugs when used in the gastrointestinal tract may have several effects, including decreasing the acidity in the stomach, modifying the pH of the gastrointestinal tract, trapping water in the bowel, stimulating bowel activity, or altering the consistency of stool. In the pharmaceutical inorganic chemistry, special attention is paid to inorganic materials used as bowel stimulators, as antacids and as acidifiers. Acidifiers are substances that can cause acidification; they can be used therapeutically to lower the acidity of the stomach, or to acidify a number of pharmaceutical products. These may be either sodium acid phosphate or dilute

hydrochloric acid. Antacids, however, are alkaline agents which neutralize excess gastric hydrochloric acid and alleviate gastrointestinal discomfort symptoms. These include for instance sodium bicarbonate and aluminium hydroxide. Bowel stimulants act to stimulate bowel movements, or increase the water content of the intestinal lumen by increasing the osmotic content, and thus the water and the urge to defecate. These are the agents which contain magnesium hydroxide and/or phosphates. The gastrointestinal agent chosen is based on the chemical agent, therapeutic effect, onset and duration of action and patient factors and potential adverse effects. The importance of pharmaceutical analysis is that the pharmaceuticals should meet some standards of identity, purity, strength and stability. A large number of gastrointestinal preparations used in medicine are given internally and hence the purity and suitable concentration is a must for safe use. An overall classification of the important gastrointestinal agents (discussed in this chapter) according to their principal therapeutic action and some typical pharmaceutical agents.

Table 11.1. Classification and Uses of Gastrointestinal Agents

Class	Representative agents	Principal action	Major use
Acidifiers	Sodium acid phosphate, dilute hydrochloric acid	Increase acidity	Gastric/systemic acidification where clinically indicated
Antacids	Sodium bicarbonate, aluminium hydroxide gel	Neutralize gastric acid	Relief of acid indigestion and heartburn
Bowel-movement-promoting agents	Magnesium hydroxide, sodium orthophosphate, sodium potassium tartrate, magnesium trisilicate	Increase intestinal water content and/or alter stool characteristics	Constipation and bowel evacuation
Adsorbent/protective inorganic agents	Magnesium trisilicate and related preparations	Neutralization/protective effects	Acid-related gastrointestinal symptoms

11.2 Acidifiers

Acidifiers: substances used in a pharmaceutical way that increase the acidity of a biological system or pharmaceutical product. In gastrointestinal therapy acidifiers may be used if acidity in the stomach is

insufficient; however, this type of therapy is not routinely applied for gastric disorders, but rather therapy aimed at the underlying cause is used. The topic of acidifiers, from the pharmaceutical inorganic chemistry's point of view, is significant as they are an example of the controlled use of acidic materials and acid salts in medical formulations. Examples are sodium acid phosphate and dilute hydrochloric acid. Sodium acid phosphate, a chemically called sodium dihydrogen phosphate, is an acidic salt that may be a source of acidification and phosphate supplementation, where suitable, in clinical situations. The acid reaction is due to the ability of the dihydrogen phosphate ion to engage in acid–base equilibria. Hydrochloric acid dilute is a hydrochloric acid solution and is a strong acid that dissociates completely in water. It may be used as an acidifying agent in pharmaceutical formulations when used in an appropriate manner. When using an acidifier, it is important to maintain a proper concentration as levels that are too high may lead to tissue irritation, mucosal damage, metabolic imbalance or other problems. Therefore, pharmaceutical quality acidifiers should be tested for their identity, assay, purity and controlled storage. Acidifiers are also of analytical value as their concentration can be measured by acid–base titration with standard alkali solution. Sodium acid phosphate can be determined by appropriate acid–base titrimetric methods and concentration of hydrochloric acid can be determined by titration with a standard solution of a strong alkali, like sodium hydroxide solution. The analytical procedure will vary as per applicable Pharmacopoeial specification and formulation. Acidifiers are not to be mistaken with acidifying foods or with normal food or feed. Their application is based on well-defined pharmacological or pharmaceutical goals, and is adequate to the patient and dosage form. Concentration, pH, buffer systems and other ions have a significant effect on the chemical behaviour of the acidifiers. Packaging is also important as concentrated or acidic preparations could react with unsuitable containers. In general, acidifiers are a group of inorganic compounds, both used for therapeutic purposes in the gastrointestinal tract and in medicine, that require controlled manipulation of acidity.

Definition and Uses of Acidifiers

Acidifiers are substances which can increase the acidity or the concentration of the hydrogen ions in a system, that are used in the therapeutic or pharmaceutical use when a controlled acid environment is needed. Their effects are related to chemical nature of the substance, its concentration, its dissociation behaviour, its buffering capacity and its route of administration. Acidifiers have been used in gastrointestinal applications where acidity is lacking, as hydrochloric acid is a normal part of gastric secretions and plays a significant role in protein digestion, the activation of pepsin and maintenance of the acidic gastric environment. Some common substances used in pharmaceutical inorganic chemistry are Sodium acid phosphate and dilute HCL. Sodium acid phosphate is an acid phosphate salt which can undergo an acid base reaction and hydrochloric acid will donate hydrogen ions directly. Acidifiers might also be used in other medical applications other than gastrointestinal therapy. For instance, a controlled acidification could be needed in the formulation, preparation or analysis. Acidifiers need to

be given as part of a therapy and need not be used indiscriminately. Over administration of acid can lead to the irritation of the gastrointestinal mucosa or alter the body's acid–base balance, especially with the use of excessive amounts of acid or when there is impaired renal or metabolic function. So only use acidifiers for the correct indications and concentrations. In principle, acid-base titration is used as an analytical protocol for acidifiers. A standard volume of the substance is titrated using a standardised alkali and the pH or the use of an appropriate indicator is used to detect the endpoint. A stoichiometric relationship between the acid (or acidic salt) and the titrant is then used to determine the analytical result. Impurities may also be a problem for the assay and may require acidity testing and/or purity and identity testing. Depends on the substance or material. Strong acid preparations should be stored in containers that will not be affected by the acid, and should be protected from inappropriate environmental exposure. Sodium acid phosphate should be stored in a suitable container which should be enclosed tightly and in specific conditions to avoid any contamination and moisture changes. Therefore, acidifiers are pharmaceutically relevant compounds with an acidity which can be controlled to a large extent, and hence has a therapeutic value.

Sodium Acid Phosphate

Synonyms

Sodium acid phosphate is also known as sodium dihydrogen phosphate, monosodium phosphate or monobasic sodium phosphate. It can be anhydrous or hydrated salt, depending on the pharmaceutical purity. The name should then refer to the particular chemical form employed in the preparation of a pharmaceutical product or for an analytical method. Sodium acid phosphate differs from disodium hydrogen phosphate in respect of its acid–base properties and acidity.

Category

Sodium acid phosphate is an inorganic acidifying agent and gastrointestinal acidifying agent, which is an acid salt. It is also a powerful medicine that has phosphate as a main component. Its classification is based on the presence of the dihydrogen phosphate ion, H_2PO_4- which can engage in acid–base equilibria and plays a role in the acidic reaction of the salt in water. It can also be found in formulations which need phosphate ions.

Chemical Formula

The formula of anhydrous sodium acid phosphate is NaH2PO4 and its approximate molecular mass is 119.98 g/mol. Molecular mass of hydrated forms is different as there are additional water molecules attached. It is essential in formulating or analysis to know the hydration state.

Preparation

Sodium acid phosphate can be prepared by partial neutralisation of phosphoric acid with the appropriate sodium base (or carbonate) to produce sodium acid phosphate under conditions that favour the formation of the monosodium salt. You can write a simplified reaction for sodium hydroxide and phosphoric acid as follows: $H_3PO_4 + NaOH \rightarrow NaH_2PO_4 + H_2O$. Industrial and pharmaceutical preparation involves reaction control and purification, crystallization, drying, and appropriate quality testing. The actual production method varies depending upon the desired grade and degree of hydration.

Properties

Sodium acid phosphate is generally available as a crystalline powder or crystals. Is soluble in water and makes an acidic solution when dissolved. It's acid–base behaviour is determined by the phosphate equilibria (dihydrogen phosphate dissociation). Sometimes can precipitate with some metal ions or buffer reaction with a number of aqueous pharmaceutical systems.

Identification

The following tests are useful to help identify: physical examination, solubility, reaction to sodium ions, specific tests for phosphate. Sodium can be identified with a suitable flame test and/or a suitable pharmacopoeial test and phosphate can be detected by suitable qualitative reactions that give characteristic precipitates under certain conditions. Official identification procedures should be used in the event of the presence of a Pharmacopoeial standard.

Assay

It may be by titration with an alkaline titrant (standardized) under specified conditions, using the sodium acid phosphate method. The volume of titrant used, and its concentration, can be used to calculate the amount of sodium acid phosphate, which is equal to the amount of titrant used. The final product and the calculation varies according to the official analytical method and the degree of hydration.

Uses

Sodium acid phosphate can be used as a pharmaceutical ingredient, acidifying agent, source of phosphate and buffer in suitable formulations. Electrolyte management and bowel preparations may also be useful in phosphate containing preparations if the particular formulation and dosage is suitable.

Storage

Sodium acid phosphate should be kept in the storage recommended for the particular pharmaceutical grade in a well closed container, away from contamination and excess moisture. Chemical purity is preserved and physical changes resulting from environmental exposure are avoided by proper storage.

Dilute Hydrochloric Acid

Category

Dilute hydrochloric acid is an inorganic acidifying agent that is a solution of hydrochloric acid in purified water at a specified concentration. Hydrochloric acid is a strong acid, and dissociates to a large extent in aqueous solution. Concentration of the pharmaceutical dilute hydrochloric acid is an important factor which influences its pharmaceutical activity and analytical activity; hence it must be prepared and standardized as per the relevant specification.

Preparation

Hydrochloric acid used for diluting should be prepared by carefully diluting with purified water an appropriate concentrated hydrochloric acid preparation. The exothermic nature of concentrated acid dilating with water means that the acid needs to be poured slowly into the water, and not the water poured into the concentrated acid. Appropriate precautions should be taken and verified preparation procedures followed. In pharmaceutical preparations the final concentration needs to be determined correctly.

Properties

Hydrochloric acid is clear, colourless, has an acidic smell and is a mixture of water and hydrochloric acid. It has a high acidity level and will neutralize bases, carbonates, bicarbonates and many metal compounds. Very soluble in water. The chief factors of its chemical activity are its hydrogen ion concentration and the chloride content.

Identification

Hydrochloric acid is detected by its high acidity and by chemical tests which reveal the presence of the chloride ion. It shows typical reactions with proper silver salts and under proper conditions it forms the salt of silver chloride. Offlicial pharmacopoeial identification procedures should be used when possible.

Assay

Dilute hydrochloric acid can be titrated against a standard alkali such as sodium hydroxide and an acid–base indicator can be used to determine the concentration of the acid. The molecular equation that represents this reaction is $HCl + NaOH \rightarrow NaCl + H_2O$. The volume and molarity of NaOH used at the endpoint is used to determine the amount of hydrochloric acid present.

Uses

In suitable pharmaceutical formulations, hydrochloric acid may be utilised as an acidifying agent, and it has been used traditionally to treat gastrointestinal disorders due to gastrointestinal acidity defects. It can also be used in the pharmaceutical production and analysis processes with controlled acidification.

Storage

Hydrochloric acid should be stored in a tightly closed container of chemical-resistant material and not in contact with inappropriate materials or excessive environmental exposure. Pots used for acidic solutions should be resistant to the acid and care should be taken in handling the solution.

11.3 Antacids

Antacids are basic compounds that act as buffers or alkaline substances of HCl in stomach that increase the pH of the stomach. Their primary uses are the treatment of the symptoms associated with stomach acidity such as occasional heartburn, acid indigestion and dyspepsia. Their main action is through an acid-base reaction between the antacid and the hydrochloric acid in the stomach. The neutralizing properties, reaction rate, solubility and physiological action in the gastrointestinal tract of the various antacids are different. The reaction of sodium bicarbonate with hydrochloric acid yields sodium chloride, water and CO_2 as products: $NaHCO_3 + HCl = NaCl + H_2O + CO_2$. Aluminium hydroxide is a slow reacting compound and forms aluminium chloride and water; $Al(OH)_3 + 3HCl \rightarrow AlCl_3 + 3H_2O$. Gastric acid can also be neutralized by magnesium containing antacids. There are several differences in the different types of antacids, one of which is whether the antacid is absorbed into the bloodstream or not. Soluble substances, e.g., sodium bicarbonate, can have a high systemic absorption rate and, if ingested in excess, can produce either metabolic alkalosis or sodium loading. The major actions of unabsorbed antacids such as aluminium hydroxide are in the gastrointestinal tract. There are also other salts with opposing effects on bowel function, such as aluminium salts, which tend to have a constipating effect and magnesium salts which tend to have a laxative effect. Thus, the various combinations of antacids, such as aluminium and magnesium, are used to counteract these effects. An ideal antacid should neutralize the acid, be rapidly effective, have an appropriate duration of action, be poorly absorbed systemically and have few side effects. They should also not result in excessive gas production, electrolyte imbalances, acid rebound or disruption of the absorption of other medications. The identity, assay of the active ingredient, impurity testing and determination of the acid-neutralizing capacity (if required) are all part of the pharmaceutical quality control of antacids. Particle size, sedimentation, viscosity and redispersibility can also influence product performance, so physical properties of suspensions and gels are also important. Antacids are still useful drugs as they offer a relatively quick symptomatic effect but for the treatment of recurrent

or persistent acid-related symptoms, the correct clinical evaluation must be done, not continuing to take antacids without supervision.

Definition of Antacids

Antacids lower the number of free hydrogen ions available to cause acid-related symptoms and are weakly basic and neutralize the hydrochloric acid in the stomach or raise the intragastric pH. Mainly taken orally and act primarily in the stomach. Sodium bicarbonate, aluminium hydroxide, magnesium hydroxide, magnesium trisilicate and mixtures of aluminium salts and magnesium salts are all examples of common inorganic antacids. There are several types of chemical neutralisation reactions, depending on the chemical used. Physical change: When hydroxides react with hydrochloric acid, chlorides and water are formed. A chemical change takes place when the bicarbonates react with hydrochloric acid to form the chlorides, water and carbon dioxide. Carbonates also give off carbon dioxide. The solubility and activity of antacids varies. Highly soluble antacids will react faster with the gastric acid than the relatively insoluble (hydroxides, silicates) ones. The half-life is also influenced by the time it takes to pass from the stomach, and the time spent in the stomach. Antacid treatment is only symptomatic and may not be effective in treating the underlying cause of excessive acid production. Recurrent symptoms, therefore, might need to be assessed for gastroesophageal reflux or peptic ulcer disease, medication related irritation, or other causes. Antacids can also interact with other drugs in two ways: The first is that they alter the pH of the gastrointestinal tract, which affects how other drugs are absorbed. The second is that they bind some drugs making them unavailable to the body. Thus, the proper spacing between antacids and interacting drug may be needed. In the case of persons in whom sodium content is clinically significant, sodium containing antacids should be given special attention. If taken in excess aluminium in preparations can cause constipation and magnesium in preparations can cause diarrhoea or loose motions. Acid neutralizing and clinical needs should thus be taken into account. Analytically antacids are analyzed by identification and assay procedures to get the concentration and purity of the active principle. Another important factor to consider with the acid neutralising capacity of an antacid, since its effectiveness is related to the ability to neutralise the acid in the stomach. Thus, the antacids are chemically heterogeneous family of gastrointestinal drugs, but have the common property of their ability to neutralize or buffer the gastric acidity.

Mechanism of Action of Antacids

So the main mode of action of antacids is to chemically neutralize the hydrochloric acid in the stomach and thereby raise the pH of the stomach and decrease the concentration of hydrogen ions. The general reaction may be written as Base + HCl → Salt + Water, but that is not the case for bicarbonate- and carbonate-based antacids which produce carbon dioxide as well. The reaction between sodium bicarbonate and hydrochloric acid to form sodium chloride, water and carbon dioxide

is an example of a reaction giving carbon dioxide gas. Both aluminium hydroxide and magnesium hydroxide give their chlorides and water when reacted with hydrochloric acid. The rise in stomach pH may result in the reduction of acidity of stomach fluids, and may reduce irritation of the mucosa of the stomach and oesophagus. Also the enzyme, pepsin, which is optimum at very low pH, decreases as a function of pH. Therefore, antacids can also reduce direct acid activity and/or acid related proteolytic activity. Solubility, particle size, formulation and gastric conditions are the major factors which determine the action speed. Generally soluble antacids have a short action, while less soluble compounds will have a longer local effect. An antacid medicine can be made in the form of a suspension, chewable tablet, powder or liquid medicine. Suspensions are suspensions of dispersed particles that have a large surface area, and may require adequate shaking for uniformity of dose. The mechanism can be summed up graphically in Figure 11.2 in which representative basic antacid substances are reacted with hydrochloric acid in the stomach to give off less acidic products and raise the stomach's pH. The clinical effect is not to be taken as complete neutralization of gastric acid, as this can have a negative effect on the digestive physiology. Some antacids also have other physiological actions in addition to their acid neutralising action. Magnesium salts activate the intestine whereas aluminium salts slow down the motility of the intestine and thus cause constipation. Sodium bicarbonate can result in systemic sodium loading and CO2. Consequently, combination products might be developed so that a gastrointestinal balance of desirable and undesirable effects is achieved that is acceptable. Antacids may also affect how other drugs are absorbed by the body or may complex with the drugs. These interactions are important in the counselling of patients with pharmacists. The overall mechanism of action of antacids is simple acid-base action, but the therapeutic effects and side effects of antacids are dependent on the chemical characteristic of the particular antacid and its interaction with the gastrointestinal environment.

Ideal Properties of Antacids

An ideal antacid should have a combination of chemical, pharmacological and pharmaceutical properties, which enable it to neutralise the gastric acid without causing any serious systemic or gastrointestinal side effects. Firstly it should be able to neutralise a large amount of hydrochloric acid using a small amount of it, which equates to a high acid neutralising capacity. It should also be relatively rapidly acting, and relieve symptoms promptly. Concurrently, the length of action should be of sufficient duration to ensure relief, but not so long that superfluous dosing is necessary. Ideally, an antacid will be absorbed minimally from the gastrointestinal tract, to ensure that its effect is limited to the gastrointestinal tract and systemic acid–base and electrolyte disturbances are avoided. Should not be correlated with appreciable acid rebound, excessive alkalinization or metabolic alkalosis. Also, the antacid should be chemically stable, palatable, compatible with other formulation ingredients, and be able to be manufactured into a consistent pharmaceutical dosage form. It shouldn't cause excess gas, bloating, upset stomach or diarrhea. It is also preferable if it will not cause constipation. Sodium

bicarbonate is rapidly acting, may lead to CO2 production and increases sodium ion in systemic circulation therefore not recommended in all patients. Aluminium hydroxide is a good neutralising agent with low systemic absorption and may cause constipation. Magnesium hydroxide is effective, and can be laxative at higher doses. This is why it is common to find different ingredients in antacid mixtures. An ideal antacid is one that will not interfere also with the action or absorption of other drugs. However, many antacids can have an impact on the pH of the gastrointestinal tract, or interact with certain drugs and may also need to adjust the timing of drug administration. Pharmaceutically, it is necessary to have an accurate drug assay, and the physical properties of dosage forms should be suitable, especially for liquid suspensions. The product should be sufficiently disperse after shaking and give a uniform dose. It should also conform to appropriate requirements for purity, microbial quality (if applicable) and stability. Thus, it is not just the strongest base that is the best antacid. That is, the substance or combination must have an appropriate combination of acid neutralising capacity, speed, duration, safety, tolerability, formulation and have a low drug interaction.

Combination of Antacids

Combination of antiacids are designed to achieve the best therapeutic effect and consist of two or more antiacids combined that have complementary chemical and physiological properties. None of the antacids has all the desired properties of an ideal agent. For instance, aluminium hydroxide is effective in neutralizing the gastric acid but can also cause constipation while magnesium hydroxide can act as a laxative. Thus, using a source of aluminium with a source of magnesium may provide a counterbalancing effect on their bowel impact. Combination products can also be a combination of antacids with varying onset and duration of effect to offer a quick onset of effect with sustained activity. The choice of components is based on their acid neutralizing ability, compatibility, stability, safety profile and effect on gastrointestinal motility. Sodium bicarbonate could result in rapid acid neutralization, but also gives off the gas carbon dioxide when reacting with hydrochloric acid and it contains sodium ions that may be clinically significant in sensitive individuals. Therefore, it is not always advisable to use for extended time periods or for too long. Aluminium hydroxide and Magnesium hydroxide often are used together, because they neutralize acids but do not cause as much bowel effect as the individual components. Other excipients can also be used in pharmaceutical formulations to improve the stability of the suspension, the flavour or the viscosity or palatability. The action ingredients should not undergo any changes in chemical nature in storage and should also maintain their intended neutralising effect through the shelf-life of the product. Combination antacids must be analyzed individually for each active ingredient or an appropriate validated method for the combination product must be used for the analysis. The acid-neutralizing capacity may also be measured, if necessary, on the sample(s). The formulation should be sufficiently stirred to ensure that the correct ratios of active ingredients are present in each dose. The sedimentation, caking, viscosity and redispersibility are important quality attributes of liquid preparations. Combination antacids can

also help to minimize the potential for side effects when taking large amounts of one drug, but cannot prevent interactions between drugs. The absorption or dissolution of other medicines may be changed if the pH of the stomach changes; some anti-acids containing metal salts can chelate drugs, reducing the absorption of the drug. This may then be the dosage interval needed. One of the formulation principles is to use combination therapy, that is, using more than one agent to overcome the weaknesses and capitalise upon the strength of each. However, the number of combinations should not be limited to simply combining the number of active ingredients, but should be based on scientific evidence provided by established pharmaceutical and clinical studies.

Sodium Bicarbonate

Synonyms

In non-pharmaceutical applications, sodium bicarbonate is called bicarbonate of soda or sodium hydrogen carbonate, or baking soda. Pharmaceutical grade sodium bicarbonate is manufactured and rigorously quality tested.

Category

Sodium bicarbonate is a component of the systemic antacids class of medications, also known as alkaline inorganic salts. It rapidly neutralizes the hydrochloric acid in the stomach and is relatively soluble as a result of which it can be absorbed to a greater extent into the blood stream than poorly soluble antacids.

Chemical Formula

Chemical formula is $NaHCO_3$, its relative molecular mass is approximately 84.01g/mol.

Preparation

Sodium bicarbonate is industrially produced by sodium chloride, ammonia, carbon dioxide and water, and then is precipitated and purified. There is a controlled purification and quality testing with the production of pharmaceuticals, which can be compared to a simplified chemical representation of bicarbonate formation, as is done in the Solvay process.

Properties

Sodium bicarbonate is a white crystalline powder, freely soluble in water and which yields a slightly alkaline solution. Under conditions of heating it decomposes into sodium carbonate, carbon dioxide and water, $2NaHCO_3 \rightarrow Na_2CO_3 + CO_2 + H_2O$. It reacts very rapidly with acids giving off CO_2.

Identification

Reactions found to identify: Reactions of sodium ions, reactions of bicarbonate ions. When it is mixed with an appropriate acid, it effervesces—it bubbles with carbon dioxide gas. An appropriate method as specified in the Pharmacopoeia may be used to identify sodium.

Assay

Acid–base titration of sodium bicarbonate can be used in its assay. Neutralisation reaction is $NaHCO_3$ (sodium hydrogen carbonate) + HCl (hydrochloric acid) → NaCl (sodium chloride) + H_2O (water) + CO_2 (carbon dioxide). The quantity of sodium bicarbonate used is dependent upon the quantity of standard acid used.

Uses

Sodium bicarbonate is an antacid as well as an alkalinising agent (provided clinical conditions are appropriate). It can also be applied in the pharmaceutical industry as a buffering agent and/or pH control substance for pharmaceutical formulations.

Storage

Must be stored in a tightly closed container, out of excess moisture and contamination. The materials should be exposed to the environment as little as possible in order to prevent physical and/or chemical changes,

Aluminium Hydroxide Gel

Category

Aluminium hydroxide gel is an inorganic antacid, made of aluminium hydroxide in gelatinous or colloidal form and water. It has a low solubility, and predominantly functions in the lower digestive tract.

Preparation

Aluminium hydroxide gel can be obtained by controlled precipitation from a soluble aluminium salt by using an appropriate alkali, washing and purification. A simplified reaction is: $Al^{3+} + 3OH^- \rightarrow Al(OH)_3\downarrow$. For pharmaceuticals, the particle characteristics must be controlled and the soluble impurities have to be eliminated.

Properties

Aluminium hydroxide gel is a white viscous or gelatinous preparation. Readily absorbs water but is slightly soluble, and reacts with acids. The overall equation for the reaction with hydrochloric acid is $Al(OH)_3 + 3\ HCl \rightarrow AlCl_3 + 3\ H_2O$ It has a moderate degree of solubility and therefore, has a local gastrointestinal activity.

Identification

Specific reactions of aluminium and hydroxide ions. Aluminium ions give characteristic precipitates on reaction with suitable reagents and the official procedure for the Pharmacopoeia may include a conversion to an appropriate chemical form, followed by a confirmatory reaction.

Assay

The assay typically includes the measurement of the level of aluminium or the acid-neutralizing capacity from an appropriate and validated method. The method may be used as complexometric or Titrimetric method as per the official specification of method used.

Uses

Aluminium hydroxide gel is an antacid that is prescribed to treat the symptoms of acid indigestion and heartburn. It may also be available in combination with magnesium salts as an antacid.

Storage

The preparation has to be stored in the stated conditions in a suitable, closed container. Liquid or gel should not be administered in too cold or too hot environments; the liquid or gel should be shaken as directed before it is administered.

11.4 Agents Promoting Bowel Movements

Constipation remedies are the substances which help to promote bowel movements. In the pharmaceutical inorganic chemistry, several such substances work primarily by osmosis, absorbing or binding water in the intestinal lumen that results in an increase in the amount of stool and promotes defecation. The agents are inorganic or inorganic associated, for example, magnesium hydroxide, sodium orthophosphate preparations, and sodium potassium tartrate. Magnesium hydroxide is a base that is poorly absorbed and will neutralize gastric acid and when sufficient amounts are present in the intestine it will have an osmotic laxative effect. Phosphate salts can increase the osmotic load of the intestinal lumen and both this and increased bowel evacuation can result in softer stools. Saline cathartics have also been used for bowel movements in the past, such as sodium potassium tartrate. Furthermore, magnesium trisilicate is a principal antacid, and depending on the formulation and dose has effects on the digestive content and on the stool. The agents promoting defecation include those which increase the water content of the stool, promote motility or otherwise facilitate the movement of stool. Generally, inorganic salts are fast acting (as compared to bulk forming agents). But overuse can lead to dehydration and electrolyte imbalance, especially when using phosphate and magnesium containing products. Therefore, these should be appropriately administered and adjusted to the patient's age, renal function, hydration status and clinical condition. Pharmaceutical formulations can be provided as powder, solution, suspension or any other dosage form. The number of active salts per

unit volume is very important as it can make a significant difference in the osmotic activity, and therefore has to be determined with accuracy in the composition. The quality control includes identity testing, assay, purity test, and pH, water content or physical test (if applicable). Some bowel preparations may cause large electrolyte disturbances if used (those containing phosphate) and some may be retained in renal failure (those containing magnesium). These drugs should therefore not be considered completely harmless because they may occur in readily available gastrointestinal medicines. The relevance of pharmaceutical chemistry is related to correlation between ionic composition, solubility and osmotic activity, acid-base behavior and gastrointestinal physiological response. Thus, formulation and dosage play an important role for successful bowel emptying, but without any undesirable systemic effects.

Magnesium Hydroxide

Category

Magnesium hydroxide is an inorganic antacid and osmotic laxative. Has therapeutic action in a dose and formulation-dependent manner. Small doses can have antacid action and larger doses can act as a laxative via an osmotic effect.

Formula

Its chemical formula is $Mg(OH)_2$ and the relative molecular mass is about 58.32g/mol.

Preparation

The following precipitation processes can be used to obtain magnesium hydroxide from a soluble magnesium salt: using an appropriate alkali. The simplified reaction is $Mg^{2+} + 2OH^- \rightarrow Mg(OH)_2\downarrow$. The obtained precipitate is washed and treated to obtain the desired pharmaceutical grade.

Assay

The assay can be done by acid–base titration with a standard acid. When magnesium hydroxide reacts with hydrochloric acid they form magnesium chloride and water, with the equation being $Mg(OH)_2 + 2HCl \rightarrow MgCl_2 + 2H_2O$. The amount of acid will be in direct proportion to the amount of magnesium hydroxide.

Uses

Magnesium hydroxide is an antiacid and laxative drug. It has low water solubility and therefore does not absorb systemically and is able to reach the intestine where it can stimulate bowel movements due to its osmotic activity.

Sodium Orthophosphate

Category

The sodium salts of orthophosphoric acid are called sodium orthophosphate. It may be acid, neutral or alkaline, depending on the salt that is used. In pharmaceutical preparations for the gastrointestinal tract phosphate salts may be employed as saline laxatives or bowel-cleansers.

Formula

The formula will vary depending upon the particular sodium phosphate. Typically used as NaH_2PO_4 (Sodium dihydrogen phosphate) and Na_2HPO_4 (disodium hydrogen phosphate). Salts are a part of commercial preparations in fixed amounts.

Preparation

Sodium phosphate salts can be prepared by a controlled neutralization of phosphoric acid with sodium hydroxide or sodium carbonate, concentrating, crystallization, purification and drying.

Assay

Assay procedures are related to the type of phosphate salt and can be acid–base titration, gravimetric phosphate determination or official methods. The method of preparation shall be the same as the chemical form and Pharmacopoeial specification.

Uses

Appropriate sodium phosphate preparations may be used as saline laxatives and bowel-cleansing agents. They have an osmotic effect which leads to increased water absorption in the intestinal lumen and aids in bowel elimination. Use should be related to the dose and clinical precautions due to the electrolyte abnormalities it can generate as the result of a phosphate load.

Sodium Potassium Tartrate

Category

Sodium potassium tartrate is an inorganic–organic salt preparation, that was formerly considered a saline cathartic. Rochelle salt is also referred to as this.

Formula

For the more common tetrahydrate form it has the chemical formula $KNaC_4H_4O_6{\cdot}4H_2O$.

Preparation

It is prepared by neutralising with a suitable sodium and potassium base/carbonate and crystallising and concentrating. The crystals formed are then purified and dried in a controlled environment.

Assay

The assay may be either a titrimetric or gravimetric procedure as outlined in the Official Method. Stoichiometric composition of both sodium and potassium parts and the tartrate part should be taken into account for the analysis.

Uses

Sodium potassium tartrate has been used as a saline cathartic, which stimulates bowel movements. It is osmotically active, so that the water content in the intestine is more. Today, it is used less than by some of the newer bowel preparations.

Magnesium Trisilicate

Category

Magnesium trisilicate is a primary class of the inorganic antacid, and has been historically employed in preparations that are used to relieve symptoms of gastric acidity.

Formula

Magnesium trisilicate is not a discrete molecule, but is represented in the variable hydrated form by an approximate formula $2MgO{\cdot}3SiO_2{\cdot}xH_2O$.

Preparation

May be formed by precipitation from suitable magnesium, silicate source material, under controlled conditions and washed, dried and controlled in particle size. Composition may vary depending on the manufacturing process and the hydration.

Assay

May be assayed by determining the magnesium and/or acid-neutralising capacity, as per the official method, which is a complex hydrated silicate. Titrimetric or gravimetric methods are used for analytical procedures.

Uses

The main use of magnesium trisilicate is as an antacid. It is gradually neutralized by the gastric acid and can provide a sustained neutralizing effect (not as high soluble alkaline substances). May be used with other drugs to treat the stomach.

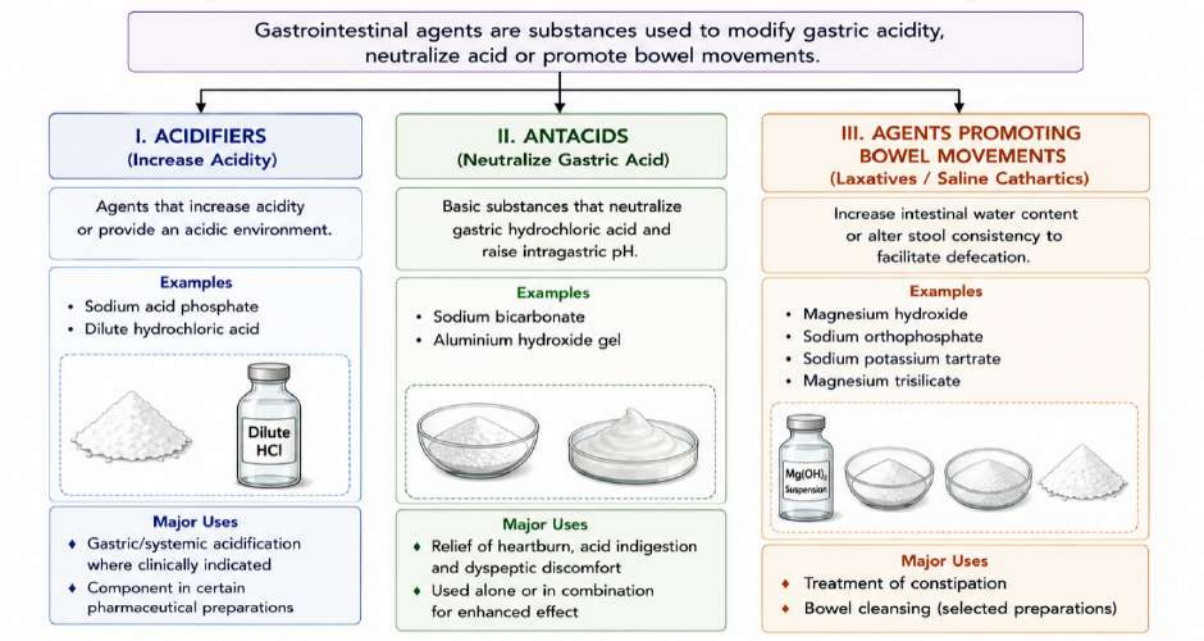


Figure 11.1. Classification of Gastrointestinal Agents

The large numbers of gastrointestinal agents are categorized according to their main chemical and therapeutic actions in Figure 11.1 and described in this chapter. Acidifiers contribute to making the stomach extremely acidic, antacids neutralize gastric acid and bowel stimulants encourage defecation primarily by osmotic and/or gastrointestinal effects. Classification shows that a chemical activity which appears to be opposite can be of pharmaceutical importance for different physiological condition, such as acidification for the treatment of acidosis and neutralization for the treatment of alkalosis. Sodium acid phosphate and dilute hydrochloric acid are representative substances used as acidifiers and sodium bicarbonate and aluminium hydroxide are representative antacids. Agents that can stimulate bowel movements include magnesium hydroxide and salts that contain phosphate.

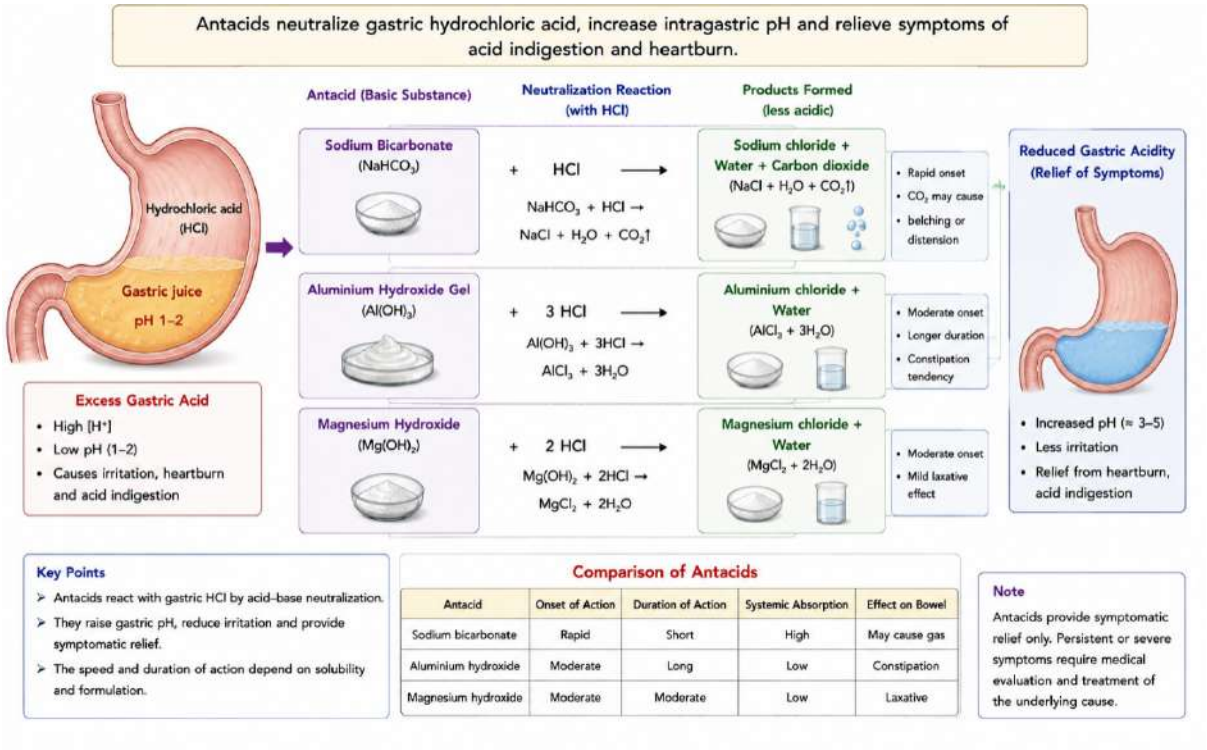


Figure 11.2. Mechanism of Action of Antacids

The antiacids used that were selected neutralise the hydrochloric acid present in the stomach as seen in figure 11.2. These hydroxide-containing agents will react with the hydrogen ions to produce water, the bicarbonate will react to yield water and carbon dioxide as well. This will reduce the hydrogen ion concentration and increase the pH of gastric fluids and so reduce their acidity. This figure also reveals that the rate and extent of the reaction of the antacids is related to their solubility and formulation. Aluminium hydroxide and magnesium hydroxide are poorly soluble, and have a gastrointestinal effect, whereas sodium bicarbonate is more soluble and could have a systemic effect if taken in excess.

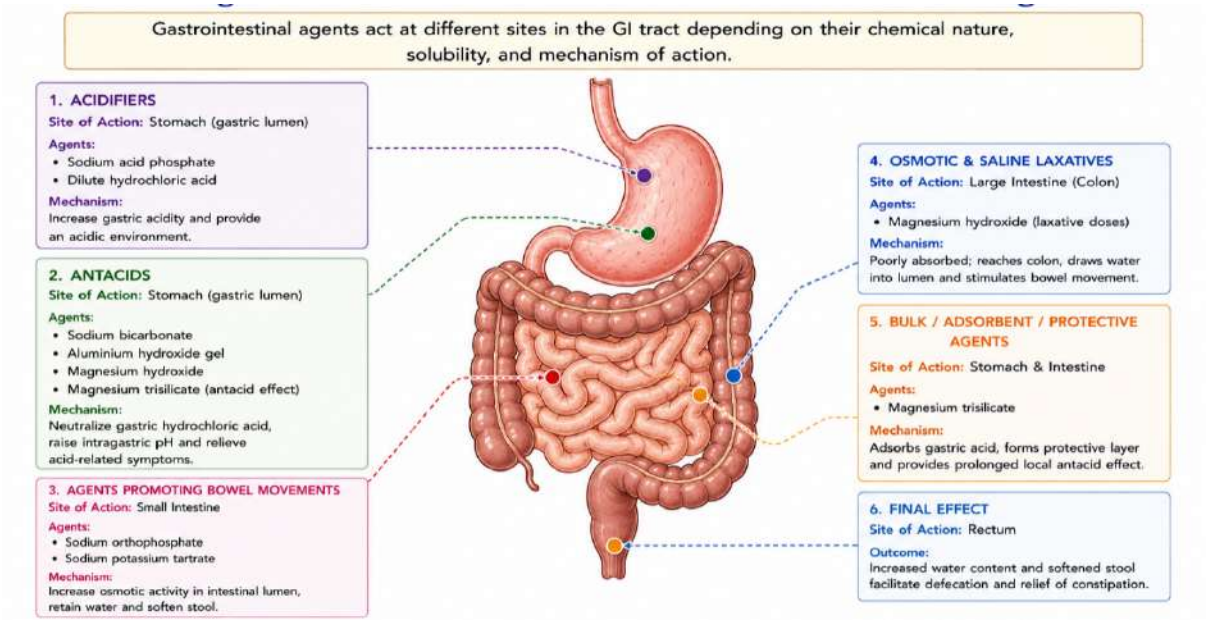


Figure 11.3. Gastrointestinal Sites of Action of GI Agents

The major gastrointestinal sites of action of the agents mentioned in this chapter are shown in Figure 11.3. Acidifiers can exert their effects primarily by altering the acid/saline contents, particularly the upper gastrointestinal tract, while antacids neutralise gastric acid in the stomach. Further down the gut can be the effects of the magnesium hydroxide and the bowel agents containing saline that increase the water content and help bowels to move. The figure illustrates that the relationship between the site of action and the solubility, absorption, chemical reactivity and amount of drug remaining in the gastrointestinal lumen is a correlation. This knowledge is useful in the understanding of the differing therapeutic effects of various inorganic agents, all introduced in the gastrointestinal tract.

Chapter Summary

There are many different medications available to help with gastrointestinal symptoms, including those that change the acidity of the stomach, relieve acid symptoms, and stimulate bowel action. Specific instances of this in the inorganic medicinal chemistry field are acidifiers such as sodium acid phosphate, as well as weak hydrochloric acid; antacids such as sodium bicarbonate and aluminium hydroxide; bowel stimulants such as magnesium hydroxide, sodium phosphate preparations, sodium potassium tartrate and other magnesium salts. When used for pharmaceutical or therapeutic purposes only, acidifiers are used to increase acidity. Sodium acid phosphate is an acid salt of phosphate and dilute hydrochloric acid supplies hydrogen ions as such. The reverse effect of antacids is chemical, in which they neutralize the hydrochloric acid of the stomach. Sodium bicarbonate is more rapidly reacting with hydrochloric acid and forms carbon dioxide and sodium ions, and aluminium hydroxide is more insoluble and is more effective in the gastrointestinal lumen. Magnesium hydroxide has an osmotic laxative effect as well as antacid effect. Combination antacids are made up of a range of

ingredients, some with benefits and some with drawbacks, such as a combination of aluminium (anti diarrheic) and magnesium salts (laxative). Bowel stimulants act by increasing the osmotic effect of the contents of the intestine and by retaining them, but excessive amounts of these can lead to electrolyte imbalance or dehydration. Pharmaceutical analysis of these substances includes identity, assay, purity and physical and stability testing. A titration of an acid–base reaction is particularly important for substances that undergo acid–base reactions. Proper storage is also important as moisture, contamination, temperatures and compatibility of containers may affect product quality. The chemical activity – solubility, acid base properties, ionic composition and reactivity – has a high influence upon the gastrointestinal activity. Thus, the knowledge of pharmaceutical inorganic chemistry is critical to have an appreciation of their therapeutic action and their analysis. These are the principles behind the safe preparation, and quality control and proper pharmaceutical use of gastrointestinal agents.

Key Points

1. Gastrointestinal agents modify gastric acidity, gastrointestinal contents, or bowel movement.
2. Acidifiers increase acidity and include sodium acid phosphate and dilute hydrochloric acid.
3. Antacids neutralize gastric hydrochloric acid.
4. Sodium bicarbonate is a rapidly acting alkaline antacid.
5. Aluminium hydroxide is a relatively insoluble antacid.
6. Magnesium hydroxide can act as both an antacid and laxative.
7. Bicarbonates release carbon dioxide when they react with gastric hydrochloric acid.
8. Aluminium-containing antacids may contribute to constipation.
9. Magnesium-containing preparations may promote bowel movement.
10. Combination antacids can balance the gastrointestinal effects of individual ingredients.
11. Sodium acid phosphate has the formula NaH_2PO_4.
12. Sodium bicarbonate has the formula $NaHCO_3$.
13. Aluminium hydroxide has the formula $Al(OH)_3$.
14. Magnesium hydroxide has the formula $Mg(OH)_2$.
15. Magnesium trisilicate is a hydrated magnesium silicate with variable composition.
16. Saline laxatives act largely through osmotic retention of water in the intestinal lumen.

17. Sodium phosphate preparations require careful use because of possible electrolyte disturbances.
18. Acid–base titration is an important analytical method for several gastrointestinal agents.
19. Proper identification, assay, purity, and storage are essential for pharmaceutical quality.
20. Chemical properties such as solubility, acid–base behaviour, and ionic composition determine gastrointestinal activity.

Review Questions

Short-Answer Questions

1. Define gastrointestinal agents.
2. Classify gastrointestinal agents discussed in this chapter.
3. Define acidifiers and give two examples.
4. What is sodium acid phosphate?
5. Give the chemical formula of sodium bicarbonate.
6. Define antacids.
7. Explain the general mechanism of action of antacids.
8. List four ideal properties of an antacid.
9. Why are aluminium and magnesium antacids frequently combined?
10. What is the chemical formula of aluminium hydroxide?
11. What are the two major pharmaceutical uses of magnesium hydroxide?
12. Define saline laxatives.
13. What is the principle of osmotic action of saline laxatives?
14. Give two examples of phosphate-containing bowel-movement-promoting agents.
15. What is magnesium trisilicate?
16. Explain the pharmaceutical importance of acid–base titration in the assay of gastrointestinal agents.
17. Why can sodium bicarbonate produce carbon dioxide in the stomach?
18. Why may magnesium-containing antacids promote bowel movement?

19. Why can aluminium-containing antacids cause constipation?
20. State the importance of proper storage of pharmaceutical inorganic substances.

Long-Answer Questions

1. Discuss the classification, pharmaceutical importance, and mechanism of action of gastrointestinal agents.
2. Explain acidifiers with reference to sodium acid phosphate and dilute hydrochloric acid.
3. Describe sodium acid phosphate under the headings of preparation, properties, identification, assay, uses, and storage.
4. Discuss dilute hydrochloric acid as a pharmaceutical acidifier.
5. Define antacids and explain their mechanism of action.
6. Discuss the ideal properties of antacids.
7. Explain the rationale for combining different antacids in pharmaceutical formulations.
8. Describe sodium bicarbonate in detail, including its preparation, properties, identification, assay, uses, and storage.
9. Discuss aluminium hydroxide gel as an antacid.
10. Explain magnesium hydroxide as an antacid and laxative.
11. Discuss sodium phosphate preparations as agents promoting bowel movements.
12. Describe sodium potassium tartrate and magnesium trisilicate.
13. Compare sodium bicarbonate, aluminium hydroxide, and magnesium hydroxide.
14. Explain the pharmaceutical and analytical significance of gastrointestinal inorganic compounds.
15. Discuss the mechanism and gastrointestinal sites of action of major gastrointestinal agents.

MCQs

1. Which of the following is an acidifier?

A. Aluminium hydroxide

B. Sodium bicarbonate

C. Sodium acid phosphate

D. Magnesium hydroxide

Answer: C

2. The chemical formula of sodium bicarbonate is:

A. Na_2CO_3

B. $NaHCO_3$

C. NaOH

D. NaH_2PO_4

Answer: B

3. Sodium bicarbonate is primarily classified as a:

A. Acidifier

B. Antacid

C. Cathartic only

D. Adsorbent antibiotic

Answer: B

4. Aluminium hydroxide has the formula:

A. $AlCl_3$

B. Al_2O_3

C. $Al(OH)_3$

D. AlH_3

Answer: C

5. Magnesium hydroxide is used as:

A. Only an acidifier

B. Antacid and laxative

C. Only an antiseptic

D. Only a preservative

Answer: B

6. The reaction of sodium bicarbonate with hydrochloric acid produces:

A. Oxygen

B. Nitrogen

C. Carbon dioxide

D. Hydrogen

Answer: C

7. Antacids primarily act by:

A. Increasing gastric acid secretion

B. Neutralizing gastric acid

C. Increasing intestinal acidity

D. Inhibiting all gastrointestinal enzymes

Answer: B

8. Which antacid is associated with constipation?

A. Aluminium hydroxide

B. Magnesium hydroxide

C. Sodium bicarbonate

D. Sodium chloride

Answer: A

9. Magnesium-containing antacids may produce:

A. Constipation only

B. Laxative effects

C. Increased gastric acid secretion

D. Severe dehydration in every patient

Answer: B

10. Sodium acid phosphate is chemically:

A. NaH_2PO_4

B. Na_2CO_3

C. $NaHCO_3$

D. Na_2SO_4

Answer: A

11. The principal chemical reaction involved in antacid action is:

A. Oxidation

B. Reduction

C. Acid–base neutralization

D. Complex formation only

Answer: C

12. Saline laxatives primarily act by:

A. Increasing intestinal osmotic activity

B. Destroying intestinal bacteria

C. Inhibiting gastric acid

D. Precipitating proteins

Answer: A

13. Magnesium trisilicate is primarily used as a:

A. Antacid

B. Acidifier

C. Oxidizing agent

D. Reducing agent

Answer: A

14. Sodium potassium tartrate is also known as:

A. Epsom salt

B. Rochelle salt

C. Glauber's salt

D. Baking soda

Answer: B

15. The formula of magnesium hydroxide is:

A. $MgCO_3$

B. $MgCl_2$

C. $Mg(OH)_2$

D. $MgSO_4$

Answer: C

16. Which substance is a strong acid?

A. Aluminium hydroxide

B. Sodium bicarbonate

C. Hydrochloric acid

D. Magnesium hydroxide

Answer: C

17. A common analytical method for assay of sodium bicarbonate is:

A. Acid–base titration

B. Complexometric precipitation only

C. Redox titration only

D. Flame photometry only

Answer: A

18. Aluminium hydroxide is relatively:

A. Highly volatile

B. Insoluble in water

C. Strongly acidic

D. Gaseous

Answer: B

19. Which component of sodium bicarbonate contributes to systemic sodium load?

A. Hydrogen

B. Sodium

C. Carbon

D. Oxygen

Answer: B

20. The main purpose of combining aluminium and magnesium antacids is to:

A. Increase toxicity

B. Balance their gastrointestinal effects

C. Eliminate acid-neutralizing activity

D. Prevent all drug interactions

Answer: B

CHAPTER 12:

ANTIMICROBIAL AGENTS

Learning Objectives

After completing this chapter, students will be able to:

1. Define antimicrobial agents and explain their major mechanisms of antimicrobial action, including oxidation, protein denaturation, membrane disruption, and interference with essential cellular processes.
2. Classify important pharmaceutical antimicrobial agents and describe the chemical properties, preparation, identification, assay, uses, and storage of representative inorganic antimicrobial substances.
3. Explain the pharmaceutical importance of potassium permanganate, boric acid, hydrogen peroxide, chlorinated lime, and iodine preparations, including their therapeutic and antiseptic applications.
4. Differentiate iodine-containing preparations such as iodine solution, strong iodine solution, and povidone-iodine on the basis of composition, release of active iodine, applications, and safety considerations.

12.1 Introduction to Antimicrobial Agents

Antimicrobial agents are chemicals that stop the growth of microorganisms or kill microorganisms including bacteria, fungi, viruses and, in some cases, protozoa. Microorganisms play an important role in the pharmaceutical science as they can contaminate medicines, can cause infection, can decrease the stability of the product, are hazardous to patients etc. Antimicrobials used in pharmaceuticals and health care products include antiseptics, disinfectants, preservatives and chemotherapeutic agents. Antiseptics are used to decrease the number of microbes in living tissue, disinfectants are used primarily with inanimate surfaces and objects. The difference will be important because an environmental disinfectant may be too irritating or toxic to apply to the skin or mucous membranes. Among inorganic chemicals, potassium permanganate, boric acid, hydrogen peroxide, chlorinated lime and iodine preparations are mentioned especially in the pharmaceutical inorganic chemistry field because they are antimicrobial substances which are closely related to their chemical properties. Potassium permanganate is a strong oxidant that reacts with vulnerable parts of microbes, destroying them. Hydrogen peroxide can also produce the reactive oxygen species and molecular oxygen, these are the mechanisms for which hydrogen peroxide can have an oxidative antimicrobial activity. The activity of iodine is linked to the free form of iodine and it's a broad-spectrum antiseptic that interacts with microbial proteins and with other cellular components. Povidone-iodine is a formulation of

povidone and iodine which acts as a iodine reservoir from which iodine is released slowly. Boric acid has relatively weak antimicrobial activity and historically use in topical formulations was restricted but this is not as extensive now as it depends on safety when used topically, which in turn depends on route, concentration and exposure. Chlorinated lime releases antimicrobial constituents, through the formation of a chlorine species. The effectiveness of an antimicrobial is related to its concentration, contact time, temperature, pH, organic matter, microbial species and formulation. Some microorganisms are more resistant than others; spores may be more resistant to inactivate. Consequently, the importance of taking into account antimicrobial effectiveness and toxicity when deciding on appropriate pharmaceutical uses. Quality control is also essential since the activity of an antimicrobial preparation depends upon the concentration and chemical stability. Proper identification, proper packaging, proper storage and the accuracy of the test are all crucial to maintaining product quality. Hence, the choice of antimicrobials depends on the intended use, spectrum of activity, formulation, safety profile and conditions of contact.

12.2 Mechanism of Antimicrobial Action

Antimicrobial agents have a negative impact on microorganisms either by interrupting the life functions of the microbe or by destroying the microbe itself. The exact mechanism will vary according to the chemical properties of the agent and the microorganism. The oxidizing agents like potassium permanganate and hydrogen peroxide injure microorganisms by oxidizing their intracellular components such as proteins, lipids, enzymes and other sensitive molecules. Additionally, materials that release chlorine also release a reactive chlorine species that can oxidize or chlorinate important parts of the microorganisms. The effect of iodine is mainly through its action on the structure of proteins, such as those in microbes, and the inhibition of their biological activity. Others antimicrobial agents disrupt the microbial membranes by making them leaky and increasing their permeability. Others either inactivate proteins, destabilize enzyme activity, cause damage to nucleic acids or affect important metabolic pathways. The chemical activity of an antimicrobial substance will not only depend on the activity of the antimicrobial substance itself, but also be influenced by the accessibility of the target. Biofilms, resistant organic material or structures can require longer exposure or "special treatment" (such as heat, cold, or chemicals) to destroy the organisms. Table 12.1 gives an overview of the major ways by which antimicrobial drugs act and explains how the chemical characteristics of the drug leads to damage to the microorganism either at the structural or functional level. This is particularly important if the agent is used as a concentration, since inhibition and microbicidal activity are possible at two different concentrations. Contact time is also important as the effect of the antimicrobials will usually need sufficient contact time for the chemical reaction to take place. The temperature and/or pH can influence the microbiologic activity, either by chemical reactivity or by the stability of the molecule or the sensitivity of the microorganisms. There are also some oxidizing and halogen-releasing agents that are inhibited by

organic matter, as the active species can be scavenged by the organic matter before it can react with the organics. That's not to say the range of activity is also not very wide. Some agents work against a variety of bacteria, fungi and viruses, and others work against select bacteria, fungi and viruses. Most vegetative (active) bacteria are much more sensitive to many common antiseptics than microbial spores. The activity against microbes should not be considered as straight 'killing germs', but should also be understood as interactions between a substance and a microbial structure. Pharmaceutical scientists can select either appropriate concentrations, formulations, contact time and storage conditions. It also describes the reason for not using different antimicrobial agents interchangeably even if used for similar purposes.

12.3 Classification of Antimicrobial Agents

Based on their chemical properties, mechanism of action, spectrum of activity, intended site of action and ability to kill or inhibit microorganisms, antimicrobial agents can be classified into different types. An important classification from the pharmaceutical inorganic chemistry point of view is that of oxidizing agents, halogen-releasing agents, weak acids and iodine-containing preparations. Examples of oxidizing antimicrobial compounds are potassium permanganate and hydrogen peroxide. They are related to the oxidation of sensitive microbial cell components. Chlorinated lime is a member of the chlorine-releasing agents and is active as a result of the generation of antimicrobial activity in the aqueous environment. Iodine and its preparations are antiseptics that contain a halogen. The difference between iodine solution, strong iodine solution, and povidone-iodine is due to the differences in their formulas and the amount of free iodine they contain. Boric acid is a weak inorganic acid with antimicrobial activity and has been used in some pharmaceutical formulations in the past. Antimicrobial agents can also be grouped based upon their use as antiseptics, disinfectants, preservatives, and systemic antimicrobial drugs. The main activity of antiseptics is against living tissues, and disinfectants are used against non-living surfaces. Preservatives are added to pharmaceutical products to prevent microbial growth in storage and use. Systemic antimicrobial drugs work in the body, such as antibiotics for bacteria, anti-fungal drugs for fungi, anti-viral drugs for viruses and anti-parasitic for parasites. The present chapter is limited to mainly inorganic and iodine-containing agents as pharmaceuticals and not to the systemic antimicrobial chemotherapy. The selection of an antimicrobial substance depends on the microorganism, application site, spectrum of activity, concentration, contact time, tissue compatibility, stability and toxicity. For instance, a very strong oxidizing agent can kill microorganisms but not be used at a high concentration on sensitive tissues. Likewise, a chlorine-releasing disinfectant might be effective at decontaminating the environment but not at regular use on living tissues. Table 12.1 classifies the main antimicrobial agents that are discussed in this chapter by chemical class, representative examples, main antimicrobial mechanism and major pharmaceutical application. This classification shows that while the end result, microbial inhibition or destruction, may be the same, many different chemical

processes can be involved in the activity. Understanding of these chemical differences is critical to rational selection, preparation, analysis, storage and safe use of antimicrobial preparations..

Table 12.1. Classification of Antimicrobial Agents and Their Uses

Class	Representative agents	Principal antimicrobial action	Major applications
Oxidizing agents	Potassium permanganate	Oxidation of cellular constituents	Selected topical antiseptic applications
Peroxide/oxidizing agent	Hydrogen peroxide	Oxidative damage and oxygen generation	Antiseptic/cleansing applications
Chlorine-releasing agents	Chlorinated lime	Formation of active chlorine species	Disinfection and sanitation
Weak acid	Boric acid	Interference with microbial growth	Selected topical preparations
Halogen antiseptics	Iodine solution	Iodination/oxidation of microbial components	Skin antisepsis
Iodine complex	Povidone-iodine	Controlled release of free iodine	Skin and wound antisepsis

Potassium Permanganate

Synonyms

Potassium permanganate is also termed as permanganate of potash or potassium permanganate. It is one of the well-known inorganic oxidizing substances which is employed in pharmaceutical and chemical applications. The solid has a deep purple to dark violet colour and the aqueous solution is coloured purple to dark violet. Potassium Permanganate is a strong oxidant and should be used with caution and kept away from materials that are easily oxidized.

Category

Potassium permanganate is a powerful oxidising agent and has been used as a topical antiseptic/disinfectant in appropriate dilute solutions. The main antimicrobial activity is related to the oxidation of microorganisms' cell components. It is concentration-dependent for its therapeutic application, and can be irritating and harmful to tissues in high concentrations.

Formula

Potassium permanganate has a chemical formula of KMnO4, and a relative molecular mass of about 158.03 g/mol. It is composed of potassium, manganese and oxygen, in the +7 oxidation state.

Preparation

Potassium permanganate is commercially produced by oxidation reactions of manganese dioxide and potassium ion containing compounds. During the industrial production, the formation of potassium manganate and further oxidation/dispositionorisation to potassium permanganate can be possible. Products are purified and quality controlled to the standards applicable for pharmaceutical grade product.

Properties

Potassium permanganate is a dark purple or black crystalline compound, which has a metallic appearance. It is soluble in water and gives purple solutions of various colour which depend on the concentration of the solution. It is a powerful oxidising agent and will reduce to manganese dioxide or manganese ions under some circumstances. It may be explosive when coming into contact with organic materials and reducing agents. Thus, it is essential that its aqueous solutions be prepared precisely and kept correctly.

Identification

Characteristic physical properties, chemical properties, both are used for identification. Its aqueous solution is intensely purple and suitable reduction reactions may decolourize it and under suitable conditions, manganese dioxide may be formed. If an official identification test is available, a pharmacopoeial standard must be carried out.

Assay

Potassium permanganate can be assayed by redox titration, typically with a reducing agent, such as sodium oxalate, in a particular acid and temperature. The substance which is reduced in the reaction is in a stoichiometric ratio with the amount of potassium permanganate in the reaction.

Uses

KMnO4 is a very weak antiseptic and cleaners topical solution that has been used on certain skin diseases. It also can be used in the laboratories in chemical oxidation or analysis. Should be used clinically with appropriate dilution as higher concentration may cause tissue irritation or staining.

Storage

Elementary precautions should be taken when storing potassium permanganate to prevent it from coming into contact with combustibles, readily oxidizable materials, excessive heat, moisture and contamination. It is recommended to be treated as a strong oxidizing agent.

Boric Acid

Synonyms

Boric acid is also called orthoboric acid, boracic acid. A weak inorganic acid which also contains boron, used in some pharmaceutical preparations and as a topical treatment, but many of its historical uses have been restricted due to its ability to enter the systemic circulation and toxicity in inappropriate use.

Category

Boric acid is weak, inorganic acid and mild antimicrobial agent. It possesses limited antimicrobial activity as compared with various contemporary antiseptics and thus has limited pharmaceutical uses, which is formulation-dependent.

Formula

Boron trichloride's chemical formula is H3BO3 or B(OH)3. It has a relative molecular mass around 61.83 g/mol.

Preparation

Boric acid can be obtained by acidification of borate minerals or of borax, and then by crystallization and purification, using an appropriate mineral acid. For instance, sodium tetraborate is simplified to boric acid under acidic conditions.

Properties

Boric acid is normally white crystalline or colourless crystals. It is slightly acid and it is slightly soluble in cold water, but is more soluble in hot water. It can be used to form borates and it can be used with suitable polyhydric compounds to form complexes. Its solutions have been used in some topical preparations in the past.

Identification

Characteristic reactions of borate and boric acid can be used for identification. Polyhydric alcohol can form a complex with borice acid under appropriate conditions and borate can undergo characteristic colour reactions with appropriate reagents. Pharmaceutical grade material can be identified by a pharmacopoeia.

Assay

Boric acid can be titrated, usually by making it more acidic by adding an appropriate polyol, usually glycerol to it. The species thus formed can then be standardized titrated under controlled conditions.

Uses

Boric acid was used in some antiseptic and medicinal ointments since time immemorial. The use of modern is limited in numerous applications due to requirements of concentration, route, duration and systemic absorption. It should not be considered as a general antiseptic.

Storage

The boric acid should be stored in a tightly-closed container and stored away from contamination and excessive moisture and under the conditions recommended for the pharmaceutical grade.

Hydrogen Peroxide

Category

Hydrogen peroxide is an antimicrobial agent that acts as an oxidizing agent, and is applied as an antiseptic, cleansing and disinfecting agent in properly prepared and diluted solutions. It's related to the antioxidant activity and ROS production.

Formula

The chemical formula for hydrogen peroxide is H2O2, and its relative molecular mass is about 34.01g mol-1.

Preparation

The industrial process to make hydrogen peroxide primarily the anthraquinone process. Pharmaceutical preparations are made from concentrated hydrogen peroxide solutions which are first diluted and stabilized by means of the appropriate purified water and approved stabilizing systems.

Properties

Hydrogen peroxide is a clear liquid, which is pale yellow when pure. It is thermodynamically unstable and it can be decomposed to water and oxygen $2H_2O_2 \rightarrow 2H_2O + O_2$. Decomposition can be speeded up with the presence of light, heat, alkaline conditions and some metal ions. If a piece of tissue is put into a sample of hydrogen peroxide, it is likely to foam or effervesce.

Identification

Oxidative reactions that are characteristic of the molecule and the release of oxygen could be included in the identification process. Peroxide activity may be demonstrated with suitable reagents, by carrying out a qualitative test. If applicable, official identification procedures should be followed.

Assay

The determination of hydrogen peroxide can be carried out by a redox titration with potassium permanganate using an acid medium. The number of moles of standardized potassium permanganate used is proportional to the number of moles of hydrogen peroxide used.

Uses

When formulated properly, hydrogen peroxide has been used locally as an antiseptic and washer. For non-pharmaceutical uses it is used as an oxidizing and disinfecting agent. Only used when necessary and appropriate for concentration and intended use.

Storage

Hydrogen peroxide must be stored in a proper container which is tightly closed, away from light, heat, contamination and catalytic impurities. Use of an appropriate stabilized pharmaceutical preparation should be used instead of an improperly diluted concentrated pharmaceutical preparation.

Chlorinated Lime

Category

A more widely used name for the product is chlorinated lime, which was formerly known as bleaching powder, and is an antimicrobial (AM) and disinfecting agent that releases chlorine. It contains chlorine, and will convert to chlorine species when combined with water.

Formula

Chlorinated lime is a variable composition compound and is usually written as either Ca(OCl)Cl or $Ca(OCl)_2$ depending on the convention or composition. Pharmaceutical property of this which is important is available chlorine.

Preparation

Chlorinated lime is a reaction product of dry hydrated calcium hydroxide and chlorine gas in reaction conditions which are controlled by the reaction. The product of the reaction is calcium hypochlorite, calcium chloride and others compounds containing chlorine. Then the product is standardized according to the quantity of chlorine that is available.

Properties

Chlorinated lime is typically pale or whitish in colour, and has a chlorine smell. It dissociates into active chlorine species when it comes in contact with water and it possesses a high oxidising and antimicrobial capacity. Acids can liberate chlorine gas if exposed to them and incompatible chemicals should not be used.

Identification

Characteristics of chlorine reaction used for identification, release of active chlorine when subjected to proper conditions. Iodometric methods can be used to demonstrate freely available chlorine.

Assay

The quality parameter is main (available) chlorine, which is normally determined by iodometric titration. This active chlorine will release the iodine out of potassium iodide solutions and the liberated iodine will be titrated with the known solution of sodium thiosulfate.

Uses

Main use of chlorinated lime is as a disinfectant and sanitizer especially in water treatment and disinfection. Due to irritant and corrosive effects it is not used for living tissues.

Storage

Should be stored in a closed dry container away from moisture, heat, acids, organic matter and other incompatible substances. Loss of available chlorine can be hastened by moisture.

Iodine and Its Preparations

Iodine is a member of the group of halogens, with broad antimicrobial activity, and has been used extensively in topical antiseptic products. The antimicrobial activity is associated mainly with molecular iodine, which easily binds to the proteins, enzymes, membranes and other components of microorganisms. There is no uniformity in the free iodine content of pharmaceutical preparations of iodine. Older iodine solutions are a mixture of iodine in a solvent, usually with the addition of iodide which helps to dissolve the iodine to provide triiodide. Weaker solutions of iodine have less iodine and less iodide than strong iodine solution. Povidone-iodine is an iodine complex with povidone and is a reservoir from which free iodine can be released over a period of time. The importance of these differences is related to the antimicrobial activity, stability, tolerability in tissues, and retention of active iodine. The iodine preparations are normally applied topically as an antiseptic and for other topical applications. These are effective if they are focussed, left in contact with the skin for a certain amount of time and moulded properly and formulated in the correct manner – and if organic matter is involved. The use of povidone-iodine is especially beneficial due to complexation, which results in a lower concentration of free iodine and yet maintains a release rate. The association of the complexes or systems containing iodine and the biologically active antimicrobial active molecular iodine which is released is presented schematically in Fig. 12.3, depending upon the amount of iodine. Iodine preparations should be kept in a suitable place because iodine could be volatile and affected by light, temperature and container characteristics. They can also stain the skin and clothes, and cause skin irritation or allergic reactions in sensitive people. Hence formulation is essential in order to make the

application suitable. Never substitute one preparation of iodine for another because the concentration, vehicle and/or purpose is different. For example, a povidone-iodine will provide a slower release of iodine than a regular iodine solution. In the pharmaceutical analysis of iodine preparations, the iodine–thiosulfate reaction titrimetric procedure can be used. Hence it is very important to understand the chemistry of iodine, for quality control and also in order to explain the antimicrobial activity of these valuable preparations.

Iodine Solution

Topical antiseptic solution that contains iodine in an appropriate solvent system. Elemental iodine is poorly soluble in water, so iodide is sometimes added, in order to facilitate its dissolution by the formation of soluble polyhalide species such as the triiodide ion. The active antimicrobial agent is in the main, molecular iodine that is released in the formulation. Iodine can very quickly react with the proteins of microorganisms and other cell constituents, causing the loss of microbial function. Antisepsis and preparation of the skin before procedure has been carried out with traditional iodine solutions. They have adequate contact and concentration. Iodine solutions will produce unique brown discolorations and may discolor skin and fabric. Iodine may be volatile and can be sensitive to light so they should be kept in appropriate and tightly closed containers. During production and product testing, it is important to monitor the concentration of iodine. Iodine can be estimated by a titration reaction between iodine and standard sodium thiosulfate which is called iodometric titration. The reaction can be represented as $I_2 + 2S_2O_3^{2-} \rightarrow 2I^- + S_4O_6^{2-}$. Starch is widely used as an indicator in the vicinity of endpoint since it forms a blue complex with iodine. When using the preparation, follow the instructions in the pharmaceutical specification as overuse and misuse may lead to systemic iodine toxicity or irritation at the site. Iodine solution, therefore, is an example of influence of formulation chemistry on solubility, stability, release and antimicrobial activity of an inorganic active substance.

Strong Iodine Solution

Strong Iodine Solution includes a relative high concentration of iodine and iodide in an aqueous solution. In the presence of iodide, iodine is more soluble as both triiodide and other species are formed and the primary antimicrobial species is molecular iodine. Historically, strong iodine preparations have been used for topical antisepsis and for other pharmaceutical uses, but the use of such preparations is subject to issues of concentration and tissue tolerance. It is important that the formulation is prepared properly because excess iodine concentration can lead to greater irritation and absorption into the body. The strong iodine solution may change during storage due to the fact that iodine is sensitive to light, temperature, evaporation and container properties, like other iodine containing preparations. Properly stored in a closed container in a light-protective environment it is recommended. The concentration and type of the preparation can be determined by iodometric assay. This is a kind of assay where a fixed quantity of sodium thiosulfate will react with iodine to form

iodide and the volume of titrant used will be a measure of the amount of iodine reduced. Strong iodine solution is not related to the povidone-iodine because they have different formulations and iodine releasing properties. Povidone-iodine is a polymeric formulation which contains free iodine, while a standard iodine solution contains free iodine and iodide in the vehicle. The selection of preparation depends on the intended application, the composition of the preparation and the standards to be met for the clinical or pharmaceutical application.

Povidone-Iodine

Povidone-iodine is a combination of povidone (a water soluble polymer) with iodine, and used as an antiseptic for the skin. The complex is utilised as a repository of molecular iodine from which it is gradually released. The major antimicrobial activity is ascribed to the molecular iodine reacting with the proteins, enzymes, membranes and other cell components of the microorganisms. Controlled release of free iodine allows for more antimicrobial activity and lower amount of unbound iodine than some traditional iodine solutions. Povidone-iodine preparations are available in a variety of strengths and formulations, such as solutions, scrubs and topical solutions. Depending on the formulation and indications, an exact use will be indicated. The activity of povidone-iodine depends on concentration, contact time, organic material and formulation environment. Packaging and storage are important as iodine may be influenced by environmental factors. The storage of povidone-iodine should be based on the manufacturer's and applicable pharmaceutical specifications and is typically by storage in a closed container which is shielded from unintended environmental exposure. The validated iodometric methods can be used to determine the available iodine in pharmaceutical analysis. The ratio of bound iodine to free molecular iodine is a crucial property of the chemistry of povidone-iodine. If free iodine is consumed, or utilized by microorganisms, then more free iodine will be released from the complex. This represents a dynamic system as opposed to fixed levels of free iodine. But povidone-iodine is not the best choice for everyone or for every application and over-use or prolonged exposure can lead to increased iodine exposure. So it must be used in accordance with the appropriate pharmaceutical and clinical recommendations.

Uses and Applications

Antimicrobials can be used in the pharmaceutical industry, in clinical use, in the home, in public health, and in the laboratory; the latter is heavily dependent upon the specific antimicrobial agent used in the practice and the concentration of the agent. For some dermatological and cleansing applications, topically applied suitably dilute solutions of potassium permanganate can be used. It has had limited use in selected topical pharmaceutical preparations in the past, and boric acid is only safe when used at specific concentrations and routes of exposure. Hydrogen peroxide may be used in properly formulated antiseptic or cleansing solutions, as an oxidizing agent. Most important disinfectant and water-treatment substance because it yields active chlorine is chlorinated lime. Very

chemically active and not really appropriate for many direct tissue applications. Some important iodine preparations for use on the skin as antiseptics are iodine solution and povidone-iodine. Considering the controlled source of molecular iodine in the polymeric complex, the use of povidone-iodine has been extended. For use as an antimicrobial, the intended target (living tissue, wound surface, medical equipment, pharmaceutical product or environmental surface) should always be considered. Don't automatically assume that a disinfectant that can be used on a floor or water supply is suitable for use on the skin. Similarly, an antiseptic can't be included in an oral pharmaceutical product. These are: antimicrobial activity, concentration, contact time, compatibility with tissues, presence of organic matter, stability and toxicity. Microorganisms are resistant and tolerant organisms too. Antiseptics may be more effective against vegetative bacteria than against bacterial spores, and vegetative bacteria may survive under conditions where other microbes species are rapidly destroyed. Consequently, quality control is an important aspect of the manufacture of anti-microbials. If the concentration of oxidizing or halogen-releasing ingredients in the product is reduced during the storage period, the antimicrobial effectiveness can also be reduced. Therefore proper packaging, temperature control, prevention of light and contamination are important. The antimicrobial activity of the pharmaceuticals is thus a controlled chemical action, rather than mere ‘antiseptic/ disinfectant' presence.

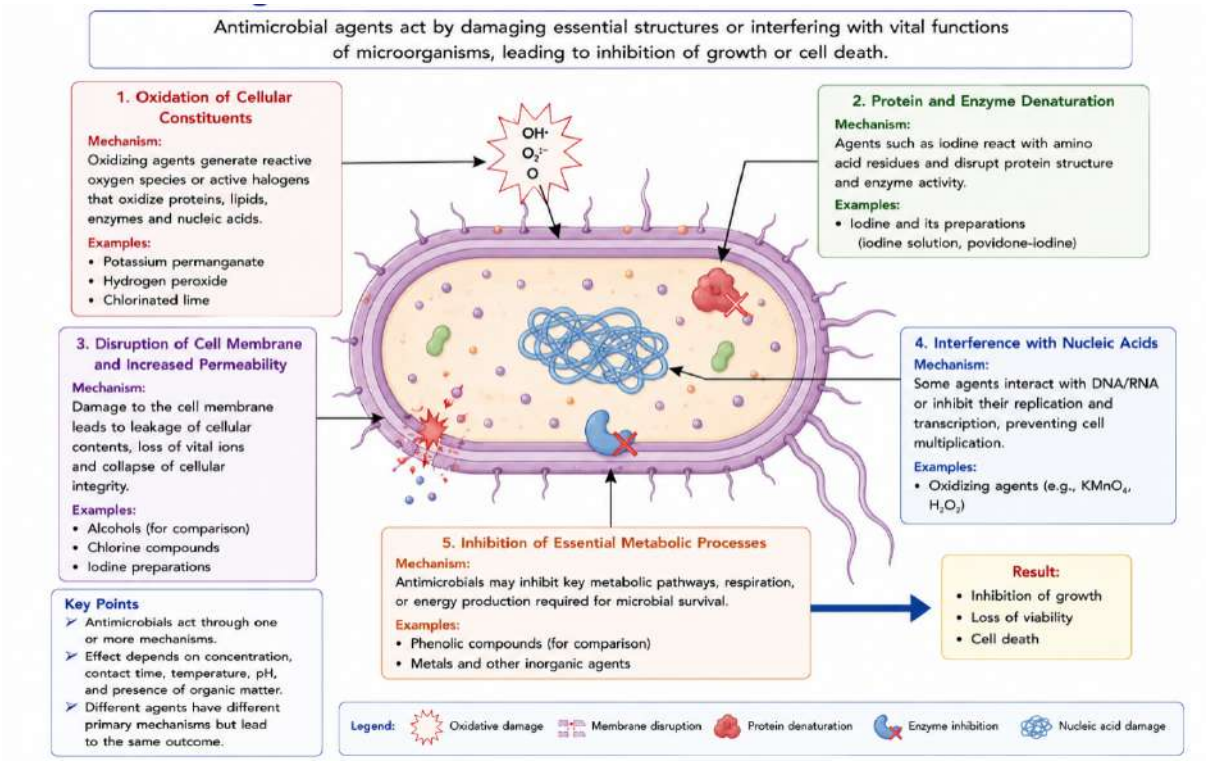


Figure 12.1. Mechanism of Antimicrobial Action

The major pathways in which antimicrobial agents can cause damage to microorganisms should be shown in Figure 12.1. There are four main ways of connecting to the main microbial cell: oxidation of

cellular components, protein and enzyme denaturation, disruption of membranes and interference with normal cell function. Potassium permanganate and hydrogen peroxide have been demonstrated to have oxidative effects and iodine have been linked to protein and enzyme alteration. Chlorine releasing agents may be associated with cell oxidation or chlorination of cell constituents. These lead to the leakage of cell membranes, the inactivation of enzymes, the disruption of metabolism, damage to cells and the inhibition of microbial growth or death. The figure should help emphasize the fact that different antimicrobial chemicals have similar overall effects, but act in different chemical ways.

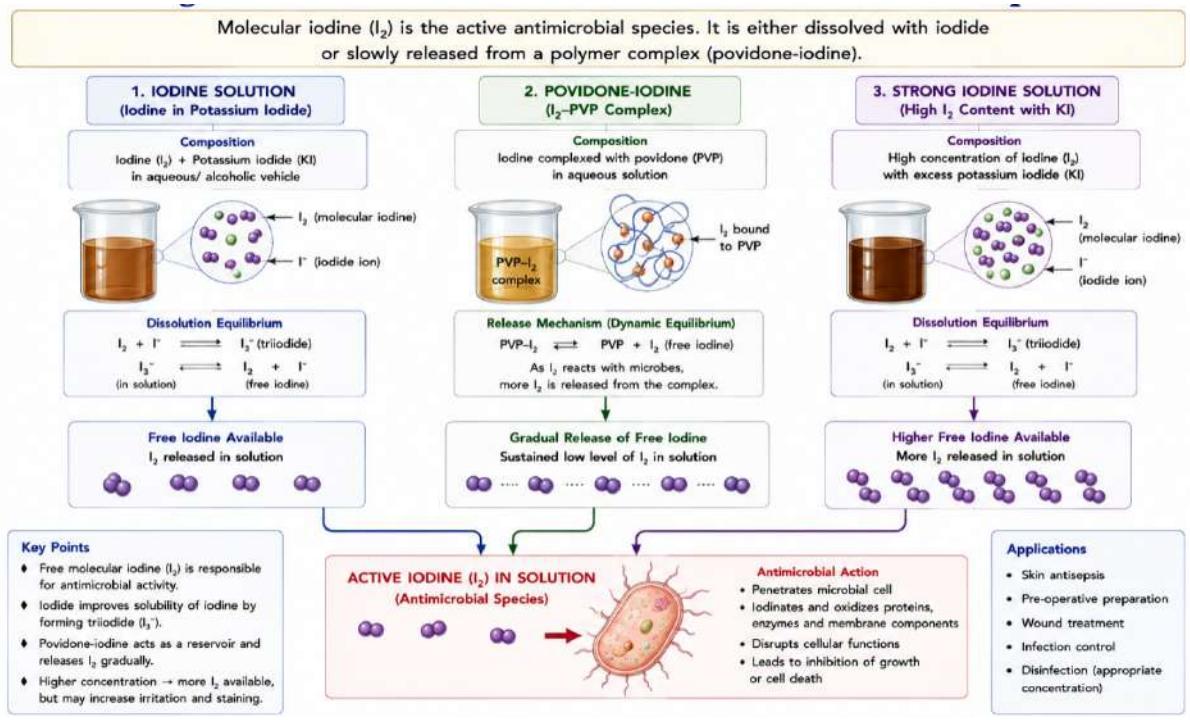


Figure 12.2. Classification of Antimicrobial Agents

The classification of antimicrobial agents is shown in a schematic manner in Figure 12.2 which is divided into the broad group of antimicrobial substances and the groups based on the mechanism of action: oxidizing agents, chlorine-releasing agents, weak acids, iodine-containing preparations and other pharmaceutical groups in which antimicrobial activity is achieved. Potassium permanganate, hydrogen peroxide are under oxidizing agents, chlorinated lime are under chlorine-releasing agents, boric acid are under weak acids and iodine solution, strong iodine solution, povidone-iodine are under iodine preparations. A second level can differentiate antiseptics, disinfectants and other uses. Useful classification since the chemical class is often predictive of the main mechanism, suitable concentration, stability requirements and final use in a pharmaceutical application..

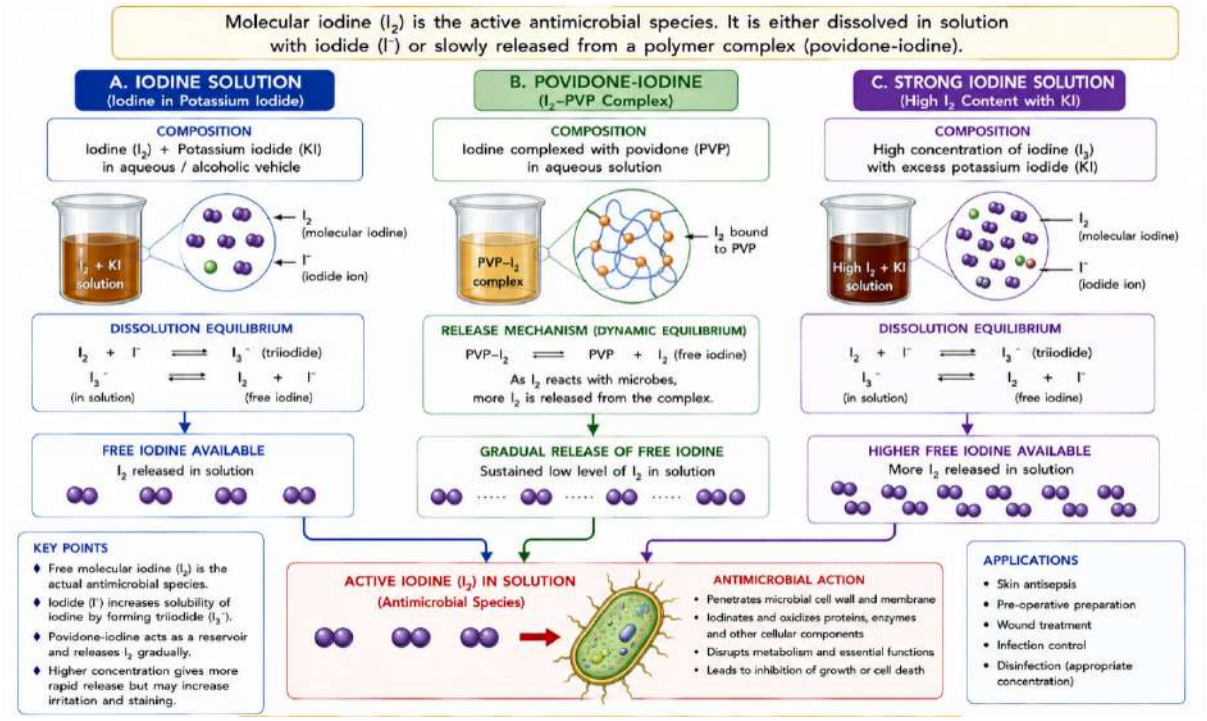


Figure 12.3. Release of Active Iodine from Iodine Preparations

The chemical reactions of the different forms of iodine are displayed in Figure 12.3. Elemental iodine is not very soluble in water, but in the presence of iodide, iodine-containing species are formed, such as triiodide. In povidone-iodine, the iodine remains attached to the polymer, povidone, and is slowly released as molecular iodine. The main antimicrobial species is free molecular iodine. May interact with microbial proteins, enzymes, membranes and other cellular components and inhibit or destroy microorganisms. Thus, it is desirable that these steps should be separated in the figure: storage/complexation of iodine, formation of molecular iodine, contact of molecular iodine with microbial components and antimicrobial effect of iodine. This is the basis for the different stabilities and antimicrobial properties of iodine preparations..

Chapter Summary

The antimicrobial agents are the ones that prevent or kill microorganisms and are used in medicine preparations, in practice, disinfection and in public health. Potassium permanganate, boric acid, hydrogen peroxide, chlorinated lime and iodine preparations are the major inorganic antimicrobial agents covered in this chapter. The antimicrobial activity depends on the various mechanism of action. The principle mechanism of action of potassium permanganate and hydrogen peroxide is to oxidize vulnerable components of microbial cells. The chlorinated lime gives off active chlorine species which oxidize and alter the microbial component. Boric acid is a relatively weak antimicrobial agent, and was used in some topical formulations previously. The antimicrobial activity of iodine is broad, and is mainly related to its interaction with microbial proteins and other cellular components.

Iodine solution is iodine in the form of iodide and is therefore soluble in water, strong iodine solution is also iodine in the form of iodide and the amount of water in it is high, povidone-iodine is a polymeric complex of iodine, which releases molecular iodine. Microbial species, formulation, organic matter, pH, temperature, contact time and concentration are all factors which influence the effectiveness of all antimicrobial agents. Antiseptics and disinfectants are not interchangeable as their site of use, level of toxicity etc. varies. Pharmaceutical quality control is extremely significant since in the event of the loss of the active oxidizing (active releasing) radicals of the halogens, the antimicrobial activity is lost. Redox titration is a method of assaying frequently used. The amount of potassium permanganate, hydrogen peroxide, chlorinated lime and iodine preparations can be determined by appropriate reducing agent titration, permanganate titration, iodometric determination of available chlorine and iodometric assay with sodium thiosulfate respectively. The use of an appropriate storage system is also essential. The material to be oxidized should be kept a safe distance from incompatible material, hydrogen peroxide from light, chlorinated lime from moisture and acids, and iodine from excess light and evaporation. Therefore, it is essential to have a good knowledge of the chemistry, mechanism, therapeutic properties and analytical characterisation of the antimicrobial agents for their safe and effective use.

Key Points

1. Antimicrobial agents inhibit or destroy microorganisms.
2. **Antiseptics** are primarily intended for living tissues, whereas disinfectants are mainly used on inanimate surfaces.
3. Potassium permanganate is a strong oxidizing antimicrobial agent.
4. The formula of potassium permanganate is $KMnO_4$.
5. Boric acid has the formula H_3BO_3 and possesses relatively mild antimicrobial activity.
6. Hydrogen peroxide has the formula H_2O_2.
7. Hydrogen peroxide produces antimicrobial effects through oxidative mechanisms.
8. Chlorinated lime is a chlorine-releasing disinfectant.
9. Available chlorine is an important quality parameter of chlorinated lime.
10. Iodine is an important broad-spectrum topical antiseptic.
11. Iodide improves the aqueous solubility of iodine through formation of iodine-containing species.
12. Povidone-iodine is a complex of iodine with povidone.

13. Molecular iodine is the principal active antimicrobial species released from iodine preparations.
14. Antimicrobial activity depends on concentration and contact time.
15. Organic matter may reduce the activity of certain oxidizing and chlorine-releasing agents.
16. Bacterial spores are generally more resistant to many antiseptic agents than vegetative cells.
17. Potassium permanganate can be assayed by redox titration.
18. Hydrogen peroxide can be assayed using standardized potassium permanganate.
19. Chlorinated lime can be assayed by determining available chlorine using iodometric titration.
20. Iodine preparations can be assayed by iodometric titration using sodium thiosulfate.
21. Proper storage is essential to prevent loss of antimicrobial activity.
22. Antimicrobial agents should be selected according to their chemical properties, intended application, concentration, safety, and stability.

Review Questions

Short-Answer Questions

1. Define antimicrobial agents.
2. Differentiate between antiseptics and disinfectants.
3. List four major mechanisms of antimicrobial action.
4. What is the chemical formula of potassium permanganate?
5. Why is potassium permanganate considered an oxidizing agent?
6. State the category and two uses of potassium permanganate.
7. What is the formula of boric acid?
8. Why is boric acid considered a weak acid?
9. Give the chemical formula of hydrogen peroxide.
10. Explain the decomposition of hydrogen peroxide.
11. What is chlorinated lime?
12. What is meant by available chlorine?

13. Why is chlorinated lime mainly used as a disinfectant?
14. What is the role of iodide in iodine solutions?
15. Define povidone-iodine.
16. What is the principal antimicrobial species released from iodine preparations?
17. Explain the difference between iodine solution and povidone-iodine.
18. State two factors affecting antimicrobial activity.
19. What is iodometric titration?
20. Why should antimicrobial preparations be stored under controlled conditions?

Long-Answer Questions

1. Define antimicrobial agents and discuss their pharmaceutical importance.
2. Explain the major mechanisms of antimicrobial action with suitable examples.
3. Classify antimicrobial agents according to their chemical nature and pharmaceutical application.
4. Describe potassium permanganate under the headings of synonyms, category, formula, preparation, properties, identification, assay, uses, and storage.
5. Discuss boric acid as a pharmaceutical antimicrobial agent.
6. Explain the pharmaceutical properties and antimicrobial action of hydrogen peroxide.
7. Describe chlorinated lime, including its preparation, properties, identification, assay, uses, and storage.
8. Discuss iodine and its pharmaceutical preparations.
9. Compare iodine solution, strong iodine solution, and povidone-iodine.
10. Explain the mechanism of antimicrobial action of iodine.
11. Describe the importance of available chlorine in chlorinated lime.
12. Discuss the analytical methods used for the assay of important antimicrobial agents.
13. Explain the factors affecting the effectiveness of antimicrobial agents.
14. Discuss the pharmaceutical applications and limitations of inorganic antimicrobial agents.
15. Explain the release of active iodine from iodine-containing preparations.

MCQs

1. Potassium permanganate is primarily a:

A. Reducing agent

B. Oxidizing agent

C. Buffer

D. Chelating agent

Answer: B

2. The formula of potassium permanganate is:

A. $KMnO_4$

B. K_2MnO_4

C. $KClO_3$

D. $KMnO_2$

Answer: A

3. Potassium permanganate is characterized by its:

A. White colour

B. Green colour

C. Purple colour

D. Yellow colour

Answer: C

4. Boric acid has the formula:

A. H_2BO_3

B. H_3BO_3

C. HBO_2

D. B_2O_3

Answer: B

5. Hydrogen peroxide has the formula:

A. H_2O

B. H_2O_2

C. HO_2

D. H_3O

Answer: B

6. Hydrogen peroxide decomposes to produce:

A. Hydrogen and nitrogen

B. Water and oxygen

C. Chlorine and water

D. Carbon dioxide and water

Answer: B

7. Chlorinated lime is primarily used as a:

A. Systemic antibiotic

B. Disinfectant

C. Antacid

D. Laxative

Answer: B

8. The principal quality parameter of chlorinated lime is:

A. Available chlorine

B. Available sodium

C. Available iodine

D. Available oxygen only

Answer: A

9. Povidone-iodine contains iodine complexed with:

A. Sodium chloride

B. Povidone

C. Borax

D. Calcium carbonate

Answer: B

10. The principal antimicrobial species released from iodine preparations is:

A. Sodium iodide

B. Molecular iodine

C. Potassium iodide

D. Iodate ion only

Answer: B

11. Iodide is added to traditional iodine solutions primarily to:

A. Reduce iodine solubility

B. Increase iodine solubility

C. Neutralize iodine

D. Remove antimicrobial activity

Answer: B

12. Potassium permanganate can commonly be assayed by:

A. Redox titration

B. Precipitation titration only

C. Complexometric titration only

D. Gravimetry only

Answer: A

13. Hydrogen peroxide may be assayed using:

A. Potassium permanganate

B. Sodium chloride

C. Boric acid

D. Calcium carbonate

Answer: A

14. Chlorinated lime can be assayed by determining:

A. Available chlorine

B. Available iodine

C. Available boron

D. Available potassium only

Answer: A

15. Iodine is commonly determined by:

A. Iodometric titration

B. Acidimetric titration only

C. Gravimetric precipitation only

D. Complexometric titration only

Answer: A

16. Sodium thiosulfate is commonly used in the titration of:

A. Iodine

B. Boric acid

C. Sodium bicarbonate

D. Aluminium hydroxide

Answer: A

17. Which factor can reduce the effectiveness of some chlorine-releasing agents?

A. Organic matter

B. Pure water only

C. Low microbial load

D. Proper storage

Answer: A

18. Povidone-iodine acts as a reservoir for:

A. Molecular iodine

B. Molecular chlorine

C. Hydrogen peroxide

D. Potassium permanganate

Answer: A

19. Antimicrobial action of oxidizing agents mainly involves:

A. Oxidation of cellular components

B. Increasing microbial nutrition

C. Increasing ATP production

D. Stimulating microbial growth

Answer: A

20. Which of the following is an iodine-containing antiseptic preparation?

A. Povidone-iodine

B. Sodium bicarbonate

C. Magnesium hydroxide

D. Potassium chloride

Answer: A

CHAPTER 13

RADIOPHARMACEUTICALS

Learning Objectives

After completing this chapter, students will be able to:

1. Define radiopharmaceuticals and explain the basic principles of radioactivity, radioactive decay, and different types of ionizing radiation.
2. Describe the pharmaceutical and medical applications of important radioisotopes, particularly iodine-131, technetium-99m, cobalt-60, and phosphorus-32.
3. Explain the principles of safe handling, storage, transportation, and disposal of radiopharmaceuticals to minimize radiation exposure and contamination.
4. Discuss the importance of radiation-safety regulations and quality assurance in the preparation, use, and control of radiopharmaceuticals.

13.1 Introduction to Radiopharmaceuticals

Radiopharmaceuticals are drugs containing a radionuclide which are used in the diagnosis, treatment or investigation of disease. What is special is that they must meet the requirements for a conventional pharmaceutical product (identity, purity, sterility, stability and suitable formulation) as well as the radiation related standards (radionuclide identity, activity, contamination, shielding, handling and disposal). The vast majority of radiopharmaceuticals consist of a carrier molecule, biological substance or a pharmaceutical agent that determines the location of the agent within the body, with a radioactive element attached to it. Depending on the radionuclide and pharmaceutical carrier, the preparation can be directed towards a particular organ or tissue, metabolic pathway or disease process. Diagnostic radio pharmaceuticals are used to release radiation that can be detected from the outside of the body, allowing the visualization and/or evaluation of the function of the tissues. The therapeutic radiopharmaceuticals are used to treat diseased tissues, such as malignant tissues, and to deliver radiation to the tissue with the goal of damaging the cells in the target tissue. Conventional drugs are given at doses that are relatively large in terms of therapeutic and diagnostic effects and very small in terms of pharmacological effects, but not the same for radiopharmaceuticals. Some important characteristics are physical half-life, type and energy of emitted radiation, biological half-life, chemical form and biodistribution. The physical properties of technetium-99m and the ability to chemically bind it to a large number of drugs to form a myriad of diagnostic radiopharmaceutical agents make it particularly significant in diagnostic nuclear medicine. Iodine-131 is both diagnostic and therapeutic, and is used primarily in the treatment of thyroid diseases. Cobalt-60 is an important gamma emitting radionuclide used mainly in radiation therapy and radiation applications;

Phosphorus-32 is an important beta emitting radionuclide, which is used in therapeutic application. The pharmaceutical and the radiation property are important; in particular the patient's safety and the efficacy of the therapy, the quality of the pharmaceutical properties is also crucial for the quality of the radiation property. According to WHO, special medicines that contain radioisotopes are called radiopharmaceuticals, and the production, use and storage of radioisotopes and radiopharmaceuticals are regulated by the requirement for pharmaceuticals and radioactive materials as outlined by competent authorities. A number of radionuclides have relatively short half lives and so the production and quality control of radiopharmaceuticals must be undertaken within a relatively short time window. Thus, radiopharmacy is a process of coordination of the procedures concerning preparation, measurement of activity, quality control, administration, radiation protection and disposal of wastes.

13.2 Basics of Radioactivity

The spontaneous process of changes that takes place in the unstable atomic nuclei that emit ionizing radiation from their nucleus and form more stable nuclei is called radioactivity. If the nucleus is unstable, it is called a radionuclide, and the process of change, radioactive decay. The decay constant (rate of decay) is a characteristic of each radionuclide, and the physical half-life. The half-life is defined as the length of time it takes for 50% of radioactive nuclei in a sample to decay. Radioactivity is usually expressed in the unit of Becquerels (Bq), 1 Bq per second. The curie might also be found in older literature. Radioactive decay is not a chemical reaction as it involves the nucleus of an atom and affects the chemical bonds. The time of decay emits alpha particles, beta particles, gamma rays or a combination of these, depending on which radionuclide it is. The radiation have different masses, electrical charge, energy, penetration and biological effect. The physical half-life of the radionuclide considered must also be taken into account in the medical applications, because the shortest possible radiation exposure is desirable in order to have a long enough imaging time, the medically appropriate radionuclide. Range of tissues and particle energy may be one of the properties necessary for various kinds of therapeutic radionuclides. The radioactivity decreases exponentially with time, $A = A_0e^{-\lambda t}$, where A is the radioactivity at time t, A_0 is the radioactivity at time t = 0 and λ is the decay constant. One of the factors to take into account in Practice is the decay of radiopharmaceuticals. Loss of a radionuclide from the body can occur by physiological elimination/metabolism and radioactive decay. The overall exposure to which the patient is exposed is the combination. The understanding of radioactivity is very crucial for the calculation of administered activity, for the calculation of the expiry times, in order to plan the transport and for the estimation of residual activity and management of the radioactive waste. For the quality control, further the radiochemical purity and the radionuclidic purity of the radiopharmaceutical, the chemical purity, the sterility of the radiopharmaceutical and the appropriate activity must be considered. Current international guidelines stress the need for special

attention in the quality control of radiopharmaceuticals, due to their short testing windows, their different radiation types and their special constraints associated with handling radiation.

Radioactive Decay

Radioactive decay is the spontaneous process of the unstable nucleus transforming into another nucleus or nuclide, and emitting radiation. The daughter product may be stable or it may be radioactive and decay more. The modes which are important in pharmaceutical and medical field are alpha decay, beta decay and gamma emission. Alpha decay: Nucleus emits an alpha particle (consists of 2 protons and 2 neutrons) and consequently the mass number and atomic number of the nucleus decrease. In beta-minus decay, a neutron transforms to a proton, and an electron and an antineutrino are ejected from the nucleus: The mass number remains the same but the atomic number increases by one. Beta-plus decay is the conversion of a proton to a neutron, a positron and a neutrino are emitted. The other method for the capture of the inner electron is characterized as electron capture (or proton capture) where a proton in the nucleus is changed to a neutron. If too much energy is emitted, as electromagnetic radiation, the nucleus does not change and this is known as gamma emission. The rate of decay of a radioactive substance is 1st order in the radioactive substance and is exponential with time. The physical half-life may be unique for the radionuclide and will not depend on the chemical form of the radionuclide. Only possible under the condition of the physiological behaviour and the pharmaceutical formulation, biological elimination. It is important to note that in radiopharmacy the radionuclide may remain physically radioactive even during the elimination of the radiopharmaceutical from the body. Effective half-life takes into consideration both physical and biological processes and can be shorter than the physical and/or biological half-life, especially if both processes are significant. The use of radioactivity is directly linked with the processes of preparation of radiopharmaceuticals and clinical use. There can be a significant difference between the activity in the product at manufacture and the activity at administration, particularly for short-lived radionuclides. Therefore, the activity calculations have to be accurate and measuring the dose has to be calibrated.This includes accuracy calibration and time calibration of activity calculations and dose measuring instruments. Storage and transportation, waste management and expiry specifications are also affected by decay. Pharmacists can use an understanding of radioactive decay to determine the activity of a radioactive substance at any time, and to safely dispose of radioactive substances.The information gained about radioactive decay allows nuclear medicine practitioners to calculate the activity at any point in time and safely dispose of radioactive material.

Types of Radiation

Besides alpha particles, beta particles and gamma rays, the different emissions of radionuclides can also be positrons, X-rays, or neutrons in nuclear medicine and radiation science. Called α particles, they are relatively heavy, have a high ionization potential, but low penetrating power and are

positively charged. Beta radiation has intermediate penetration and ionization properties, and consists of high energy electrons or positrons, a gamma ray is a high energy electromagnetic photon, is mass-less, has no electrical charge and has relatively great penetration and ionization properties. The usefulness of each type of radiation in medicine is determined by its physical properties. Radiation that passes through the body is especially useful to enhance diagnostic imaging in general, and gamma emitting radionuclides are particularly useful. Therapeutic applications such as Beta radiation use particles which will deposit energy in tissue over a relatively short distance, resulting in damage to the cells. The biological effects of radiation exposure could be linked to direct interaction with the DNA and other structures of cells or be attributed to the radiolysis of water and the formation of the reactive species. The amount of biological damage depends on the type of radiation, the energy of the radiation, the dose of radiation, the dose rate, the length of exposure and the sensitivity of the tissue to the radiation. The aim of radiation protection is therefore to minimise the exposure of unnecessary radiation resources and yet give the effect of the diagnosis or therapy. Figure 13.1 indicates the relative depth penetration of the three major emission types that are important for this chapter and the typical medical consequences of these emissions. Manufacturers of shielding materials also need to be aware of the type of radiation as well. The stopping power for alpha radiation is usually the case provided that relatively thin material is used, beta radiation will need proper low atomic number protection to minimise the amount of secondary radiation that is produced and for gamma radiation a large amount of dense material will be required. The design of shielding in practical radiopharmacy should be determined by the radionuclide, the energy of the emissions, the activity, workload, distance, and exposure time and not type of radiation.

Radionuclides emit different types of radiation during decay. The physical nature of each emission determines its penetration, ionizing ability and clinical use.

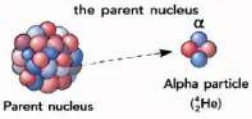
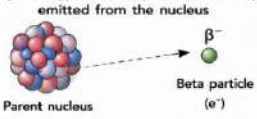
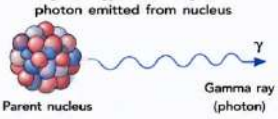
Property	1. ALPHA PARTICLES (α)	2. BETA PARTICLES (β)	3. GAMMA RAYS (γ)
Nature/ Diagram	Helium nucleus emitted from the parent nucleus 	High-energy electron (β^-) or positron (β^+) emitted from the nucleus 	High-energy electromagnetic photon emitted from nucleus 
Symbol	α	β^- , β^+	γ
Constituent	2 protons + 2 neutrons (He^{2+} nucleus)	Electron (β^-) or Positron (β^+)	Photon (electromagnetic wave)
Charge	+2	−1 (β^-) or +1 (β^+)	0
Mass (relative)	4	1/1836 (very small)	0
Speed (approx.)	0.05 – 0.1 c	0.3 – 0.99 c	c (3×10^8 m/s)
Ionizing Power	Very high	Moderate	Low (indirect ionization)
Penetrating Power (in tissue)	Very low (few cell diameters)	Moderate (mm to few cm)	Very high (can traverse whole body)
Penetration (Shielding)	Stopped by paper, skin or a few cm of air	Stopped by a few mm of plastic, aluminium or glass	Requires thick lead, concrete or dense materials
Typical Energy Range	4 – 9 MeV	0.1 – 3 MeV (up to several MeV)	10 keV – several MeV
Biological Effect	High ionization density; severe damage if inside body	Moderate ionization; tissue dose depends on energy and range	Lower ionization per unit path; profound whole-body exposure
Typical Sources	Po-210, Ra-226, Ac-225, etc.	P-32, I-131, Sr-90, Y-90, etc.	Tc-99m, Co-60, I-131, etc.
Medical Significance	• Not used for external imaging (cannot exit body)	• Useful for therapy (beta emitters)	• Excellent for diagnostic imaging

Figure 13.1. Types of Radioactive Emissions: Alpha Particles, Beta Particles, and Gamma Rays

Alpha Particles

alpha particles are positive particles in the nucleus and consist of two protons and two neutrons that make a helium-4 nucleus. These are more massive and more energetic than beta particles and gamma photons. They have a high linear energy transfer, a property which causes them to deposit a large amount of energy in a small distance and to produce a dense ionization along their path. Their power of penetrating matter, however, is very little. Alpha particles are stopped by a sheet of paper or the outermost dead layer of the skin, but can be dangerous if inhaled, ingested, injected or absorbed through a cut or broken skin. For targeted radionuclide therapy, their short range is beneficial, as the radionuclides can be delivered over short distances, with the potential to seriously damage the diseased tissues, but not the healthy ones. Targeted alpha therapy is a new technique that uses radionuclides that have alpha particles, which are attached to molecules that can target tumour-associated components selectively. Pharmaceutical students should already be familiar with the following main concepts: high ionization density, short tissue range and avoidance of internal contamination. Exposure due to external alpha particles is not as important as internal exposure as they do not penetrate very well. However, strict containment and contamination-control precautions are needed for alpha emitting radioactive materials. Not spilling, not generating aerosols, using appropriate protective equipment, monitoring surfaces and using radiation safety institutional procedures are all appropriate handling practices. Alpha radiation is therefore a good example of the relationship between radiation penetrating power and biological effects, which is not the same; a radiation type that is not very penetrating externally, but is very effective when deposited in tissue and close to living cells. It is mainly used in targeted radionuclide therapy for specific purposes rather than exposure to external radiation.

Beta Particles

Radioactive decay gives off high-energy electrons or positrons known as beta particles. In β-minus decay, a neutron is transformed into a proton, and an electron and an antineutrino are emitted. The decay of a proton into a neutron, a positron and a neutrino is called betaplus decay. The alpha particle penetrates less deeply than the beta particle which does penetrate, but less than gamma radiation. They do not penetrate as deeply as some of them, some up to a few millimetres, more. Useful if it is desired to use beta-emitting radionuclides for treatment; radiation can be given in a designated area of disease. Specific therapeutic uses in the past have included a beta emitting radionuclide called phosphorus-32. High energy beta radiation can also produce secondary X-rays (bremsstrahlung) when it collides with the high atomic number shielding material. Hence the shielding should be carefully selected, depending on the energy of the beta-particle and amount of radioactive material. Low atomic number materials like plastic or other appropriate material may be used as a initial shielding material for the beta emitters with secondary radiation taken into account. Radiation can be external and internal hazards, depending on the type of radiation that is involved, from a radiation-protection standpoint, beta radiation can pose a hazard. For very radio active beta radiation sources,

contamination of the skin and eyes may be all that is required and internal contamination may result in radiation doses to the sensitive organs. Thus, proper containment, monitoring, shielding and contamination control are all important. Biological effects of beta particles are mainly due to ionization and excitation of atoms and molecules in the tissue. These interactions can lead to damage to the DNA directly or through the generation of reactive species that can do indirect damage to DNA. The ability to deliver adequate radiation doses to the target tissue with minimal radiation exposure to surrounding normal tissue is critical to therapeutic treatment with beta emitters. The type of radionuclide, chemical carrier, radioactivity dose administered, distribution of radioactivity in the body, and the physical half-life are consequently quite significant.

Gamma Rays

A gamma ray is a very energetic electromagnetic photon which is emitted from an excited atomic nucleus. They do not have mass nor an electrical charge and therefore can penetrate biological materials and other materials better than an alpha and beta particle. In the body, one of the most useful properties of the gamma radiation emitted from the radiopharmaceutical is that the photons can penetrate the tissues and be detected by special imaging equipment, which is of benefit to diagnostic nuclear medicine. Technetium-99m is one of the more important gamma emitting radionuclides, and is widely used in diagnostic imaging. Radionuclides may also be radioactive with gamma radiation, such as the historically important cobalt-60, which are used in external beam therapy or irradiation systems. Exposure to external radiation may be appreciable from high activity sources due to the high penetrating power of gamma radiation. The selection of shielding is dependent on the type of photon energy and activity, and is provided by using dense materials such as lead, tungsten or by well-designed structural shielding. In the case of gamma emitting sources therefore the three fundamental reasons for radiation protection (time, distance and shielding) are of particular importance. Proximity to the source can be reduced, including by using adequate distance for the source where possible and using adequate shielding, to reduce occupational exposure. When gamma photons interact with matter there are three types of reactions: photoelectric absorption, Compton scattering, and at high energy, pair production. The level of importance of these interactions varies with the energy of the photons and the composition of the absorber. The photon's energy emitted from the energy source should be sufficient to be detected by the imaging system and to produce an energy output which does not result in an unnecessary radiation dose. So, the choice of the radionuclide, the dose (activity), the imaging protocol, and the route of administration are important considerations for using gamma-emitting radiopharmaceuticals. Gamma radiation can be used in diagnosis but as far as possible, excessive exposure should be avoided based on principles of radiation protection.

13.3 Applications of Radioisotopes in Pharmacy and Medicine

Applications involve the use of radioisotopes in which radiation can be detected for diagnosis or the use of radiation in the body to treat the disease itself. There are 2 ways to design a radiopharmaceutical: to follow a physiological process or to localize to an organ or target a molecular target. The general principles of selecting diagnostic and therapeutic radionuclides are to detect the radiation at a tolerable dosage to the patient, and to deliver damaging radiation to the disease tissue, respectively. Examples of major isotopes are phosphorus-32, technetium-99m, cobalt-60 and iodine-131. Iodine-131 has a relatively long physical half-life, emits beta particles and emits gamma photons, making it useful. Iodine-131 is an important therapeutic agent and some diagnostic agent for the thyroid since the thyroid is a natural concentrator of iodine. One of the most commonly used diagnostic radionuclides, technetium-99m has a short physical half-life and emits gamma radiation that is appropriate for nuclear imaging. Cobalt-60 has been used for a long time in external radiation therapy and irradiation and emits penetrating gamma radiation. Phosphorus-32 is a beta-emitter which can be administered to tissues or cells, and emits radiation to the tissues. The clinical usefulness of these radionuclides depend on the physical half-life, the nature of the radiation, the energy of this radiation, the chemical form and the biological half-life and the biodistribution. The major radionuclides discussed in this chapter are summarized in Table 13.1 and are related to typical diagnostic or therapeutic applications. A careful consideration of the benefit to the patient, the dose of radiation and the pharmaceutical risks should be taken into account in selecting the radiopharmaceutical. The need for quality includes radionuclidic identity of the isotope, purity, radiochemical purity, chemical purity, level of activity and stability of the product during its usage. WHO and IAEA stress the need for special requirements of testing and handling radiopharmaceuticals that require special quality control procedures.

Table 13.1. Important Radioisotopes and Their Applications

Radioisotope	**Major radiation**	**Principal characteristic**	**Representative application**
Iodine-131 (^{131}I)	Beta + gamma	Thyroid uptake; therapeutic beta emission	Thyroid diagnosis and therapy
Technetium-99m (^{99m}Tc)	Gamma	Short half-life; suitable gamma emission	Diagnostic nuclear imaging
Cobalt-60 (^{60}Co)	Gamma	High-energy penetrating photons	External radiation therapy/irradiation
Phosphorus-32 (^{32}P)	Beta	Therapeutic beta emission	Selected therapeutic applications

Sodium Iodide I-131

Characteristics

Radiopharmaceutical: Sodium iodide I-131, a radioactive iodine compound of sodium. Iodine-131 has a physical half-life of about 8 days, and releases both beta particles and gamma photons. Considerable attention must be paid to its biological activity as iodine is actively taken up by the thyroid tissue, and is involved in pathways in the synthesis of thyroid hormones. The iodine-131 is a thyroid selective, beta emitting isotope of iodine and is especially useful for therapeutic purposes relating to thyroid tissue. It can also be measured and imaged under the proper conditions by means of its gamma emissions. The pharmaceutical preparation can be formulated as oral dosage form and the type of formulation and activity will depend on the clinical indication and regulatory requirements.

Diagnostic Applications

Although historically iodine-131 has been used for thyroid uptake studies and imaging, it may be desirable for some diagnostic uses to use shorter-lived radionuclides or newer imaging techniques. The physiological uptake into the thyroid tissue makes it possible to assess thyroid function and distribution. The benefit or information obtained from diagnostic uses should be weighed against the radiation dose received by the patient from iodine-131. If the radiation burden is not the most important or the superior imaging capabilities are preferred, then other diagnostic radionuclides might be chosen due to the longer half-life and the presence of beta emission in the decay of iodine-131.

Therapeutic Applications

Iodine-131's current main use is for treatment of the thyroid gland. It selectively concentrates iodide and then releases beta radiation which provides cytotoxic energy to the thyroid tissue. It is employed in suitable patients who have hyperfunctioning thyroid tissue and in some differentiated thyroid cancers. Treatment should be tailored to the individual, patients should be informed and prepared for the treatment of radiation safety and follow up treatment should be offered. Following radiation protection measures are important after iodine-131 administration, as it is excreted, in part, via urine and other bodily mechanisms. The use of radiation therapy for therapy involves a trade-off between targeting the thyroid and being exposed to other tissues.

Technetium-99m

Characteristics

One of the most important radionuclides used in diagnostic nuclear medicine is technetium-99^{m}Tc. It has a half-life of approximately six hours and it decays to emit gamma radiation which is measurable with gamma cameras and imaging equipment. Has a short half-life, is useful for imaging in a short period of time in the clinical situation and has reduced long term radiation exposure when compared

to longer half-life radioisotopes. The technetium 99m can be used to make many different complexes for imaging a variety of organs and physiological processes. In nuclear medicine practice is readily available from a technetium-99m generator system.

Diagnostic Applications

Technetium-99m can be used in the imaging of a variety of organs and physiological systems, such as the skeleton, heart, kidneys, lungs and hepatobiliary system, depending on the pharmaceutical ligand. Physical radiation characteristics depend on the radionuclide, the biodistribution and localisation of the target depends on the chemical carrier. The use of technetium-99m in diagnostic nuclear medicine is very large, in part due to this versatility. Quality control is required as the presence of radiochemical impurities may lead to changes in the biodistribution pattern and affect image quality. The short half-life also necessitates effective preparation, quality testing, activity measurement and administration.

Cobalt-60

Characteristics

The radioactive isotope cobalt-60 will give off gamma radiation characteristic of the isotope, first to make excited nickel-60, then gamma radiation. Has a physical half life of about 5.27 years, and emits high-penetrating gamma rays. It has a relatively long half-life, which is beneficial for applications that require a stable radiation source for long periods of time. The penetrating nature of the gamma emissions from Cobalt-60 sources makes them extremely difficult to shield and control the source management. The use of Cobalt-60 has been modified by new technology in some clinical fields, but Cobalt-60 is still of historical and technical significance in radiation therapy and irradiation.

Therapeutic Applications

Cobalt-60 is commonly applied to external beam radiation by teletherapy system, where gamma radiation is focused on the tumour causing damage to the cells. The radiation affects the DNA directly and indirectly by generating reactive species which prevent proliferation of tumour cells. Cobalt-60 has had several applications beyond that of irradiation, such as those for direct patient use. The radioactive inventory of the source is extremely high for several years and source security, maintenance, monitoring and regulatory control is required. Although many centres have now switched to modern linear accelerators as sources of therapeutic gamma radiation, cobalt-60 is still a vital source of radiation for special applications.

Phosphorus-32

Characteristics

Phosphorus-32 is a radioactive isotope of phosphorus, with a physical half-life of about 14.3 days, that emits beta particles. Phosphorus-32 has a natural role in cell metabolism and nucleic-acid biosynthesis, so it can enter into a biological system following administration. It may be employed in medicine because the beta particles emitted have short range. Therefore, phosphorus-32 is not considered a common diagnostic agent and is used only as a therapeutic agent.

Therapeutic Applications

Phosphorus-32 has been incorporated into a few therapeutic uses such as certain haematologic disorders and localized therapies in which beta radiation can be of therapeutic benefit. Historical indications are for the treatment of some myeloproliferative disorders and certain diseases that require inhibition of abnormal cell growth. Although radiation with phosphorous-32 is not the only treatment for unhealthy cells, it must be used wisely and carefully and only with patients who are suitable for treatment. This activity needs then to be carefully selected so as to ensure and match the therapeutic effect with the radiation induced toxicity. It also has a longer half-life, which extends the time frame for radiation-safety concerns.

13.4 Safe Handling of Radiopharmaceuticals

Radiopharmaceuticals handling is based on the fundamental principles of radiation protection (justification, optimization and dose limitation for occupational and public exposure) and proper clinical control for patients. The practical principles of time, distance and shielding are very important. The principle of radiation workers is that unnecessary radiation exposure is to be avoided and as much as possible appropriate radiation protection is to be used, by means of shielding and/or distance. Only suitable trained and authorized personnel should handle the items in designated radiation controlled areas. Personal contamination should not occur as a result of the use of appropriate laboratory practice such as suitable protective clothing, gloves as indicated, controlled work surfaces and contamination monitoring. Radioactive materials may cause internal contamination when the spills or aerosols result in open radioactive materials, which are of special concern. Appropriate equipment, properly calibrated activity measuring devices, shielding devices, remote handling equipment and radiation survey meters must be present. Staff should be familiar with the characteristics of the radionuclides which are being used, such as half-life, type of radiation, energy, route of administration and biological elimination. Planning should be done before introducing radioactive materials into the working area to ensure that unnecessary exposures are avoided. Eating, drinking, cosmetics application etc. that can contribute to increase in the contamination hazard should not be allowed in controlled radioactive work areas. Spills should be responded to in accordance with institutional emergency response procedures and the area should be isolated and checked for contamination before restored to normal operations. Existing regulations require occupational specific advice for specific workers, e.g. pregnant workers. Patients who receive therapeutic radionuclides can

also receive their own radiation-safety instructions to limit their exposure to family and the public. WHO and IAEA have agreed that radiopharmaceuticals are produced and handled under special procedures because of the additional risks associated with their use, compared to that of traditional medicines.

13.5 Storage of Radiopharmaceuticals

Radiopharmaceuticals must be stored in separate controlled storage areas in containers and protection appropriate for the radionuclide, activity, energy of the radiation and physical form of the preparation. Arrangements of storage should exclude the possibility of unauthorized access, accidental exposure, cross-contamination or loss of radioactive material. All radioactive preparations should be labelled with information relating to the radioactive substance, the amount of radioactivity or radioactivity concentration, the date and time of the preparation, expiration information and other information required for institutional or regulatory purposes. When selecting shield, the type and energy of the radiation emitted should be considered. Lead or tungsten may be needed for shielding with gamma emitters while other shielding may be needed with beta-emitting preparations. The storage conditions must also meet pharmaceutical requirements, such as the temperature, light protection, sterility and container compatibility with the preparation. One of the factors determining the storage time is the decay of the radioactive activity versus time, depending on the physical half-life and clinical usefulness of the preparation. It may therefore be important to prepare, QC, release and administer short-lived radiopharmaceuticals quickly. Radioactive materials should be segregated accordingly, by radionuclide, and by physical form, especially when the form is different, or when the radionuclide is different, or when there are different risks of contamination. The inventory should be maintained to document receiving, preparation, use and transfer and disposal. WHO suggests that production, use and storage of radiopharmaceuticals should be licensed at the national or regional level, should be subject to pharmaceutical and radioactive-material regulations. Thus, storage systems should be linked in with the facility's radiation-safety program and pharmaceutical quality system.

13.6 Disposal of Radiopharmaceuticals

Handling and disposal of radioactive waste and radiopharmaceuticals should be carried out in accordance with the relevant national regulations, as well as the half-life, physical and chemical characteristics of the waste, the radiopharmaceutical/radioactive waste and the activity. Biohazard waste, contaminated labware, vials and syringes, gloves, absorbent materials and unused radiopharmaceuticals are all considered radioactive waste. The simple goal is to avoid needless radiation exposure and contamination of the environment. Separation of waste by radionuclide and type, labelling, proper waste containment and monitoring. It may be possible to decay short-lived radionuclides in the store, if permitted. This is a method whereby radioactive waste is placed in a controlled facility for a period of time until the radioactivity level of the waste is acceptable for

release or disposal. If the radionuclide or waste is long-lived, or has not been decayed in storage, then an alternate path for authorized disposal must be developed for it. Mobile radioactive liquids may need special collection and disposal and contaminated solids may need special containment. Radioactive biological waste may be radioactive and contain a biological hazard as well and therefore, should be coordinated. Actions associated with the production, storage, monitoring and final disposal of waste should be documented. Radioactive waste shall NOT be disposed of in waste streams that are intended for normal disposal until radioactive waste release requirements are met. Similarly, radioactive materials should not be discharged to sinks or sewage systems unless so allowed by the applicable regulations and institutional procedures. The disposal needs are different for different jurisdictions and radionuclides. So, instead of general criteria for disposal, facilities need to follow the advice of their national radiation-protection authority and institutional radiation-safety officer. Radioactive waste management is a crucial aspect of the radiopharmaceutical life cycle from procurement, preparation, administration, disposal. The objective is to control radioactive materials during their working life and to ensure that undue exposure of workers, patients, public and environment are avoided.

13.7 Regulatory Guidelines for Radiation Safety

The structure of the state law, the rules of radiation safety, the requirements for pharmaceuticals, conditions for licensing and the rules in the institution are all effective in the regulation of radiopharmacy safety. Technical standards and guidance for national regulatory systems are also available from international bodies like the International Atomic Energy Agency (IAEA) and World Health Organization (WHO). Authorities in India for the handling of radioactive materials are governed by the framework set up by the competent national radiation-safety authorities and various requirements may include the authorization of the facility, training of staff, zoning of areas, monitoring of radiation levels, calibration of equipment, security of sources, management of radioactive wastes and documented procedures. There are both pharmaceutical and radiation requirements for radiopharmaceutical facilities. WHO also points out that the production, use and storage of radiopharmaceuticals are subject to the licensing of the national and/or regional authorities, and must be regulated in accordance with the regulations for pharmaceutical preparations and radioactive materials. Radiopharmaceuticals have unique requirements for quality assurance because of radioactive decay, a limited testing period, variable radiation levels, and special handling procedures. The WHO/IAEA good-practice guidance on radiopharmaceutical quality control states that these factors need to be incorporated into the radiopharmaceutical quality control system. The production of radiopharmaceuticals conforms to the Good manufacturing practice requirements and there are minimum Good manufacturing practice requirements for radiopharmaceuticals set by the WHO/IAEA. Radiation Safety Programs should thus include staff training, monitoring of staff, monitoring of the area, monitoring of contamination, preparedness for emergencies, monitoring of

equipment, and the documentation and periodic review of procedures. The basic principle is to limit radiation exposure to as low as reasonably practicable without sacrificing the diagnostic and/or therapeutic value. All the limits, conditions and disposals mentioned in the document are subject to change in the rules of the competent national authority and should always be compared with the rules in force.

Chapter Summary

A radiopharmaceutical is a medicine containing a radioactive element that is mainly used for diagnosis, therapy or physiological investigations. They are special and are subject to a simultaneous control of pharmaceutical quality and radiation safety. Radioactivity is the random transformation of an unstable atomic nucleus and radioactive decay has a decay constant and physical half-life. In this chapter the main particles that are covered are alpha particles, beta particles and gamma rays. The high ionization density and low penetration power of alpha particles makes them useful in some therapeutic applications, the intermediate penetration power of beta particles makes them useful in some therapeutic applications, and the high penetration power of gamma rays makes them useful in diagnostic applications. Iodine-131, technetium-99m, cobalt-60, and phosphorus-32 are some important medical radionuclides. Iodine-131 is a beta, gamma emitter, and has significant therapeutic use in the thyroid. Technetium-99m is a short-lived gamma ray emitter which has been used extensively in diagnostic imaging. A radionuclide of cobalt-60 is historically important for external radiation therapy and is selected as a therapeutic isotope: Cobalt-60. b) Phosphorus-32 is a radioactive isotope of cobalt-60, which emits β radiation and is selected as a therapeutic: Phosphorus-32. The use of radiopharmaceuticals must be safe and appropriate training, radiation level monitoring, prevention of radioactive contamination, radiation shielding, and proper handling of radioisotopes must be provided. Pharmaceutical conditions, protection from radiation and security should be provided during storage. Radioactive waste should be put in a segregated manner, labeled, stored, monitored and disposed of in accordance with the radionuclide and the relevant regulations. The international WHO/IAEA guidance places particular importance on the unique radioactive nature of radiopharmaceuticals, and also the short testing windows. Finally, the safe and effective use of radiopharmaceuticals requires the fusion of all the aspects of nuclear science, pharmaceutical quality, clinical practice, radiation protection and regulatory compliance.

Key Points

1. Radiopharmaceuticals are medicinal products containing radionuclides.
2. They are used for diagnosis, therapy, or physiological investigation.
3. Radioactivity results from spontaneous nuclear transformation.
4. The half-life is the time required for half of the radioactive nuclei to decay.

5. Radioactive activity is measured in becquerels (Bq).
6. Alpha particles consist of two protons and two neutrons.
7. Alpha radiation has high ionization potential and low penetration.
8. Beta particles are high-energy electrons or positrons.
9. Beta radiation is useful in selected therapeutic applications.
10. Gamma rays are electromagnetic photons with high penetrating ability.
11. Technetium-99m is an important diagnostic gamma-emitting radionuclide.
12. Iodine-131 emits both beta particles and gamma radiation.
13. Iodine-131 has important thyroid-related therapeutic applications.
14. Cobalt-60 is a major gamma-emitting therapeutic radionuclide historically used in external beam therapy.
15. Phosphorus-32 is a beta-emitting therapeutic radionuclide.
16. Radiation protection is based on minimizing unnecessary exposure.
17. Time, distance, andshielding are fundamental practical radiation-protection principles.
18. Radiopharmaceutical storage requires both pharmaceutical and radiation-safety controls.
19. Radioactive waste must be segregated and managed according to radionuclide characteristics and regulations.
20. Short-lived radionuclides may be managed by decay-in-storage where authorized.
21. Radiopharmaceutical quality control includes radionuclidic and radiochemical considerations.
22. WHO and IAEA provide international guidance for radiopharmaceutical quality and safety.
23. National regulatory authorities establish legally applicable radiation-safety requirements.
24. Radiopharmaceutical facilities require appropriate authorization and trained personnel.
25. Radiation safety and pharmaceutical quality must be integrated throughout the radiopharmaceutical lifecycle.

Review Questions

Short-Answer Questions

1. Define a radiopharmaceutical.

2. What is radioactivity?
3. Define radioactive decay.
4. What is meant by physical half-life?
5. What is a becquerel?
6. Name the three major types of radioactive emissions.
7. What are alpha particles?
8. What are beta particles?
9. What are gamma rays?
10. State two characteristics of gamma radiation.
11. Why is technetium-99m widely used in diagnostic imaging?
12. State the physical half-life of technetium-99m approximately.
13. What are the major applications of iodine-131?
14. Why is iodine-131 particularly useful in thyroid disorders?
15. What type of radiation is emitted by phosphorus-32?
16. State one major application of cobalt-60.
17. What is meant by radiation contamination?
18. State the three basic practical principles of radiation protection.
19. Why is shielding necessary when handling gamma-emitting radionuclides?
20. What is decay-in-storage?
21. Why must radioactive waste be segregated?
22. State two requirements for radiopharmaceutical storage.
23. What is radiochemical purity?
24. Why is quality control particularly important for radiopharmaceuticals?
25. Why must radiopharmaceutical facilities comply with regulatory requirements?

Long-Answer Questions

1. Define radiopharmaceuticals and discuss their pharmaceutical and medical importance.

2. Explain the basic principles of radioactivity and radioactive decay.
3. Describe alpha, beta, and gamma radiation and compare their properties.
4. Discuss iodine-131, including its characteristics, diagnostic applications, and therapeutic applications.
5. Explain the importance of technetium-99m in diagnostic nuclear medicine.
6. Describe cobalt-60 and its therapeutic applications.
7. Discuss phosphorus-32 and its therapeutic significance.
8. Explain the principles of safe handling of radiopharmaceuticals.
9. Discuss the proper storage requirements for radiopharmaceuticals.
10. Explain the principles of radioactive-waste disposal.
11. Discuss regulatory requirements and radiation-safety principles in radiopharmacy.
12. Compare iodine-131, technetium-99m, cobalt-60, and phosphorus-32.
13. Explain the importance of half-life in selecting and handling radionuclides.
14. Discuss the role of quality control in radiopharmaceutical preparation.
15. Explain the importance of time, distance, and shielding in radiation protection.

MCQs

1. A radiopharmaceutical contains:

A. Only a conventional drug

B. A radionuclide incorporated into a medicinal preparation

C. Only a vitamin

D. Only a contrast dye

Answer: B

2. The SI unit of radioactivity is:

A. Gray

B. Sievert

C. Becquerel

D. Coulomb

Answer: C

3. The time required for half of a radioactive sample to decay is called:

A. Biological life

B. Physical half-life

C. Shelf life

D. Expiry period

Answer: B

4. Alpha particles consist of:

A. Electrons only

B. Two protons and two neutrons

C. Photons

D. Neutrons only

Answer: B

5. Which radiation has the greatest penetrating ability among the three discussed?

A. Alpha

B. Beta

C. Gamma

D. All are equal

Answer: C

6. Technetium-99m is primarily used for:

A. Diagnostic imaging

B. Antacid therapy

C. Antibiotic treatment

D. Anaesthesia

Answer: A

7. The approximate physical half-life of technetium-99m is:

A. 6 hours

B. 8 days

C. 14 days

D. 5 years

Answer: A

8. Iodine-131 is particularly useful in the treatment of:

A. Thyroid disorders

B. Gastric ulcers only

C. Skin infections

D. Bacterial pneumonia

Answer: A

9. Iodine-131 emits:

A. Alpha radiation only

B. Beta and gamma radiation

C. Gamma radiation only

D. Neutron radiation only

Answer: B

10. Cobalt-60 is primarily associated with:

A. External radiation therapy

B. Antacid therapy

C. Vaccination

D. Antibacterial chemotherapy

Answer: A

11. Phosphorus-32 is primarily a:

A. Gamma emitter

B. Beta emitter

C. Alpha emitter only

D. Neutron emitter

Answer: B

12. The three fundamental practical principles of radiation protection are:

A. Heat, pressure, and humidity

B. Time, distance, and shielding

C. Dose, colour, and taste

D. Weight, volume, and density

Answer: B

13. Gamma radiation is:

A. A charged particle

B. A helium nucleus

C. Electromagnetic radiation

D. An electron only

Answer: C

14. Which radionuclide is widely used for diagnostic nuclear imaging?

A. Technetium-99m

B. Cobalt-60 only

C. Phosphorus-32 only

D. Radium-226 only

Answer: A

15. Which radionuclide is associated with thyroid-selective uptake?

A. Iodine-131

B. Cobalt-60

C. Phosphorus-32

D. Technetium-99m only

Answer: A

16. Decay-in-storage is particularly applicable to:

A. Authorized management of suitable short-lived radioactive waste

B. Ordinary pharmaceutical waste

C. All radioactive waste regardless of half-life

D. Non-radioactive waste only

Answer: A

17. Radiopharmaceutical quality control may include evaluation of:

A. Radiochemical purity

B. Colour only

C. Taste only

D. Tablet hardness only

Answer: A

18. A major concern with gamma-emitting sources is:

A. High penetrating radiation

B. Lack of energy

C. Complete absence of radiation

D. Low physical activity only

Answer: A

19. P32 is useful therapeutically mainly because it emits:

A. Beta particles

B. Gamma photons only

C. Alpha particles only

D. Infrared radiation

Answer: A

20. Radiopharmaceutical facilities must comply with:

A. Only pharmaceutical regulations

B. Only radiation regulations

C. Both applicable pharmaceutical and radioactive-material requirements

D. No regulatory requirements

Answer: C

UNIT V

MISCELLANEOUS COMPOUNDS

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Chapter 14

Expectorants and Emetics

Learning Objectives

After completing this chapter, the learner will be able to:

1. Define expectorants and emetics and explain their therapeutic significance in the management of respiratory and gastrointestinal conditions.
2. Classify expectorants and emetics and describe their mechanisms of action, important pharmaceutical properties, identification tests, assays, uses, and storage requirements.
3. Explain the pharmacological and pharmaceutical characteristics of potassium iodide, ammonium chloride, copper sulphate, and sodium potassium tartrate.
4. Differentiate between expectorant and emetic actions and apply relevant concepts to pharmaceutical analysis and safe use of these compounds.

14.1 Introduction to Expectorants and Emetics

Traditionally, pharmaceutical substances with different therapeutic effects are classified under the miscellaneous inorganic and pharmaceutical compounds, among which are expectorants and emetics.

Expectorants are substances that promote the removal of mucus and bronchial secretions from the respiratory tract and emetics are substances that stimulate the vomiting reflex. The two groups are important for their inorganic salts (with characteristic chemical properties, identification reactions and methods of their assay) in the pharmaceutical chemistry. Expectorants are generally helpful if there is too much or sticky mucous secretions in the respiratory tract that make it difficult to cough up and clear. They may do this in several different ways: increasing the quantity of secretions in the respiratory tract or changing the composition of the secretions, or by making them easier to cough up indirectly. Discussed potassium iodide and ammonium chloride – supposedly expectorants. The emetics act on the pathways of the emetic reflex (central or peripheral) or directly stimulate the gastric mucosa. Traditionally the following were noted as emetics: copper sulphate, sodium potassium tartrate but the therapeutic use of many of the traditional emetics has fallen considerably, as they are now replaced by more effective and safer alternatives. For the pharmaceuticals, knowledge of these compounds would entail knowledge of their chemical formulas, how they are prepared, physical and chemical properties, how they can be identified, how much they contain, what their use is and how they are stored. Overall classification of expectorants and emetics and difference between the main compounds discussed in this chapter is given in figure 14.1. This study is therefore not only significant for medicinal purposes, but also in the pharmaceutical analysis, quality control, compounding and safe handling. In today's clinical practice emphasis is placed on evidence-based use, as some of the traditional agents have been shown to be highly toxic and of low therapeutic value. It would, therefore, be useful for pharmaceutical students to know the extent of these compounds in the past as well as in the present. For the ideal identification and quantitative analysis, it is necessary to ensure the purity, potency and fulfillment of the pharmacopeial criteria. In this chapter Pharmacological concept is introduced along with the pharmaceutical chemistry with the aim of making the learner understand the correlation between pharmaceutical action and analytical assessment of all the compounds.

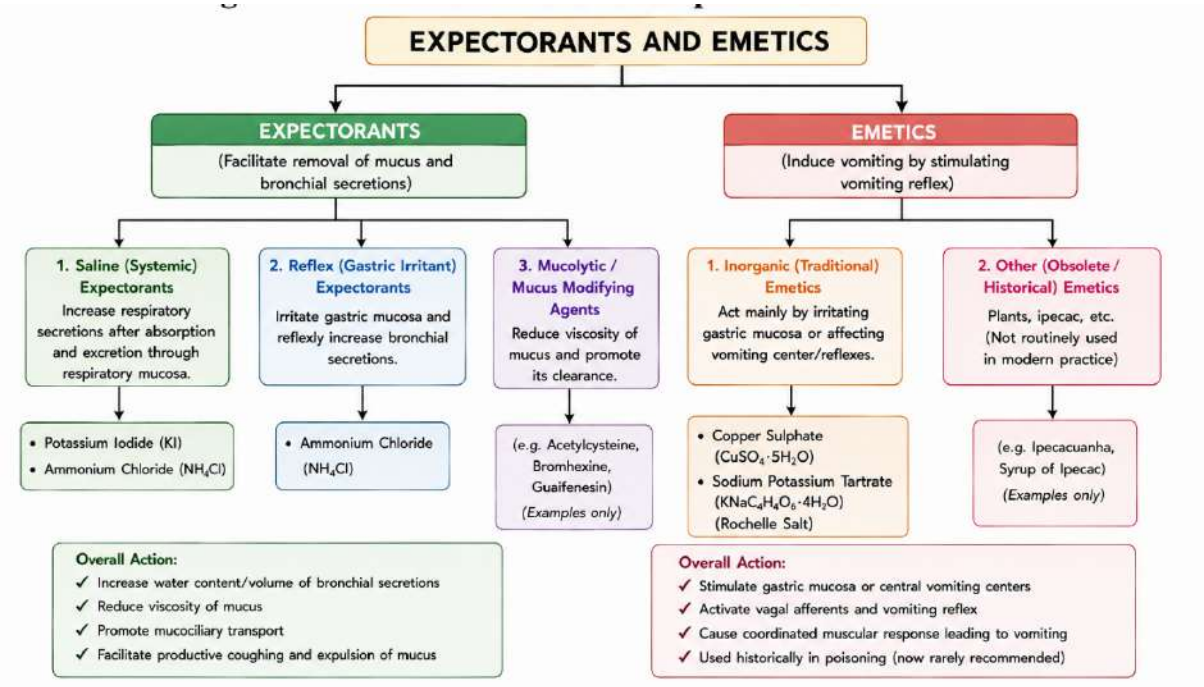

Figure 14.1 Classification of Expectorants and Emetics

14.2 Expectorants

Definition of Expectorants

Drugs which increase the amount or decrease the stickiness of bronchial secretions and facilitate their expectoration, causing the coughing to be more productive are called expectorants. They are normally used when the mucus is thick, sticky and difficult to remove from airways. The function of clearing respiratory secretions is essential to protecting the airway because buildup of mucus may cause airway blockage, which in turn can become a breeding ground for microorganisms. Therefore, expectorants should also be kept away from anti-tussive drugs which act on the cough reflex. Expectorants are not meant to suppress a cough, but to get rid of secretions by helping the cough. Common expectorants used in the past have been potassium iodide and ammonium chloride. For the first time, potassium iodide has been recognized as a systemic expectorant - the iodide ion passes into the blood stream and is then excreted in the respiratory secretions, which may then have an effect on bronchial secretion. Ammonium chloride has also been used for a long time as an expectorant and has been associated with reflex stimulation of respiratory secretion due to its irritant properties on the gastric mucosa. The effectiveness of the traditional expectorants is unclear and usage should be based on therapeutic considerations. From the point of view of pharmaceutical chemistry, expectorants are of significant importance because of their chemical properties, which may affect their identification, preparation, storage and assay. Potassium iodide, for instance, is very soluble in water, and undergoes characteristic reactions that are typical of the iodide ion; ammonium chloride is a water-soluble crystalline salt with characteristic reactions typical of both the ammonium ion and the chloride ion.

The selection of expectorants is dependent upon the therapeutic use, formulation properties, patient consideration and safety profile. In modern formulation can also be included substances, which directly influence the hydration or viscosity of the mucus as part of the expectorant therapy. The classical inorganic compounds, however, are still important in the education of medicine because of their illustration of the relation of inorganic chemistry and medicine. Students learn about their mechanism and analytical properties allowing them to determine the physiological action that pharmaceutical substances might have, and evaluate them with known chemical analysis techniques.

Mechanism of Action of Expectorants

The mechanism of action of an expectorant is to increase the production of respiratory secretions and to help clear mucous secretions. The normal respiratory mucous secretion is constantly formed in the epithelium and glands, and is thrown out towards the pharynx by the coordinated action of the cilia and coughing. If the secretions are too thick or too much, then the normal mucociliary clearance can be inadequate. It was believed in the past that expectorants act by either increasing the water content of respiratory secretions, decreasing the viscosity of the mucus or stimulating the secretion. Potassium iodide, the traditional systemic expectorant, was once considered to be a systemic expectorant. After absorption, iodide may be excreted via the respiratory glands, which may result in an increase in the fluidity and quantity of bronchial secretions. This helps the mucus to move and is easier to cough up. Ammonium chloride is considered to be a reflex expectorant. Ingestion can lead to gastric irritation and induce a reflex response which leads to greater production of respiratory secretions. Because of its metabolization to acidic products, ammonium chloride was once thought to be one of the systemic-acting acidifying agents and is responsible for its expectorant effect. Drinking enough water is an important aspect of the effectiveness of expectorant therapy—because of the effect water has on the thickness of the mucus. Once hydrated, it is easier to get rid of respiratory secretions. The overall explanation of how the expectorant might act on the body to cause secretions in the respiratory tract to be easier to cough up is illustrated in figure 14.2. A point to note is that expectorants do not always take away the cause of excessive mucous production. Do not work on symptoms but on the removal of secretions. Mucous substances in the respiratory tract are also now known to be a complex mixture of mucins, proteins, lipids, electrolytes, cellular material and microorganisms. Variations in mucous properties, like changes in the mucous rheology or hydration, may have important influence on its transport. Physiological effects of the pharmacological action of the traditional inorganic expectorants should be considered. They should also be considered for therapeutic use, including the dosage, length of therapy, contraindications, adverse effects and interactions. For example, potassium iodide may also cause adverse effects due to excess iodide if given in excess, and ammonium chloride may also cause gastrointestinal disturbances and irritation from excess doses. Therefore, understanding of the mechanism of action is important in order to enhance the therapeutic utility, and to uncover possible limitations and safety concerns.

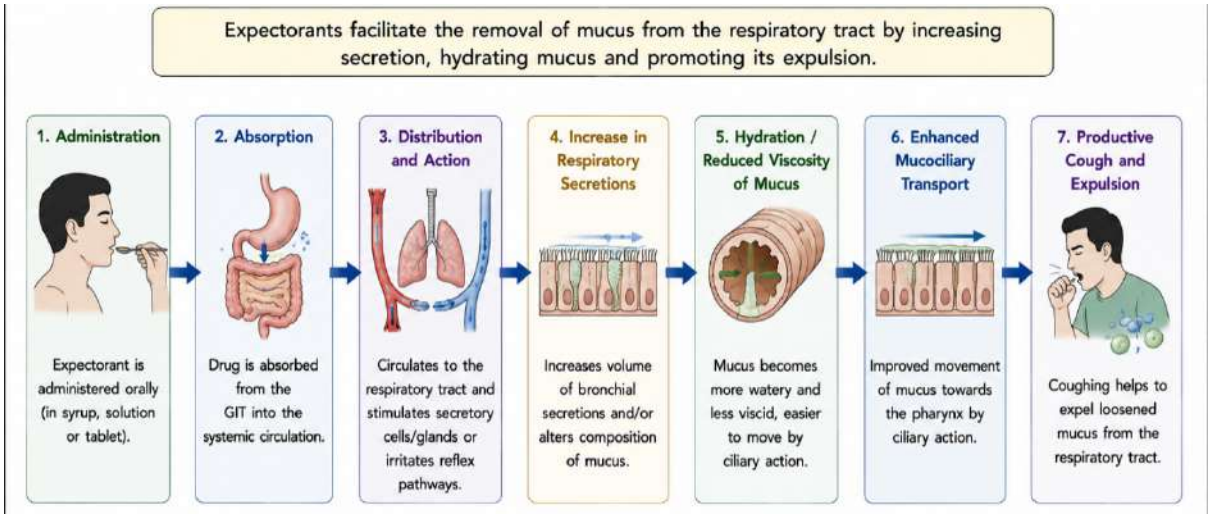

Figure 14.2 Mechanism of Action of Expectorants

Classification of Expectorants

There are different methods of administration, chemical types and mechanisms of action of expectorants. In a traditional pharmaceutical way of thinking, expectorants can be broken down into reflex acting expectorants, and systemic or secretory expectorants. Reflex-acting expectorants act by stimulating the gastric mucosa and this in turn stimulates the reflex increase in respiratory secretions. The components of this group include traditionally the ammonium chloride. Systemic expectorants are taken up into the bloodstream and then excreted by reaching their target organs through the respiratory glands; it is believed that they act in the bronchial secretions. The traditional classification of potassium iodide is in this category. Other classifications are saline expectorants, irritant expectorants and agents that alter the viscosity or hydration of mucus. It is helpful because it correlates the physiologic effects of a substance and its chemical properties. An inorganic iodide salt that is very soluble in water, such as potassium iodide, has unique chemical reactions. It has been used traditionally in formulations to increase mucous secretions in the respiratory tract. Ammonium chloride has been used for centuries to make it an expectorant; the traditional reflex action is employed here as an inorganic ammonium salt. Most of these can be classified as either antispasmodics or anti-inflammatory, and are also used as pharmaceuticals; the other emetics are also discussed later, and the classification and pharmaceutical uses of these compounds are summarized in Table 14.1, so that they can be compared with regard to chemical identity, category, and principal applications. In modern medicine, expectorants are frequently synonymous with medications that will induce expectoration (get rid of mucus), but they are not necessarily intended to make the mucous discharge increase. This difference is important as rapid secretion may mean it is not therapeutic, if not removed. Modern agents could work by increasing the water content of the mucus, decreasing its viscosity or enhancing the mucociliary transport. Classical inorganic compounds, however, are good to use as teaching aids. Students should recognize chemical formula and the principal pharmaceutical

properties of the principal expectorants; have knowledge of their traditional mechanism and know how they differ from antitussive drugs. Some substances can have similar therapeutic effects and be classified in different ways because of the different physiological mechanisms. Pharmaceutical analysis includes also the identification and the assay of such compounds for confirmation of identity and strength. Thus, classification is not just a matter of memory, but should be considered as a means to correlate the structure and physicochemical properties of the chemical with its mode of action, its preparation as a pharmaceutical product and its therapeutic use.

Table 14.1. Expectorants and Emetics: Classification, Properties and Uses

Drug/Compound	Category	Chemical Formula	Key Properties	Principal Uses
Potassium Iodide	Expectorant; inorganic salt	KI	White, crystalline or granular solid; freely soluble in water; stable under appropriate storage conditions	Used as an expectorant and as an iodine source; may be used in selected thyroid-related indications under medical supervision
Ammonium Chloride	Expectorant; systemic acidifying salt	NH_4Cl	White crystalline powder or colorless crystals; freely soluble in water; saline taste	Used as an expectorant and, in appropriate formulations, as a systemic acidifying agent
Copper Sulphate	Emetic; inorganic copper salt	$CuSO_4 \cdot 5H_2O$	Blue crystalline substance; soluble in water; produces characteristic reactions for copper and sulphate ions	Historically used as an emetic; routine use for inducing vomiting is now generally avoided because of toxicity concerns

Sodium Potassium Tartrate	Emetic; inorganic/organic salt	$KNaC_4H_4O_6 \cdot 4H_2O$	Colorless or white crystalline material; soluble in water; commonly known as Rochelle salt	Historically used as an emetic and in pharmaceutical preparations; present-day use as an emetic is limited
Expectorants – General	Agents promoting removal of respiratory secretions	—	May increase bronchial secretion or facilitate clearance of mucus	Used to assist the removal of excessive or tenacious respiratory mucus
Emetics – General	Agents capable of inducing vomiting	—	Produce vomiting through gastrointestinal or central mechanisms	Historically used to evacuate gastric contents; modern poisoning management generally favors evidence-based decontamination and supportive care

Potassium Iodide

Synonyms, Category and Chemical Formula

Potassium iodide is an inorganic compound that consists of potassium and iodide ions. It is commonly known as potassium iodide and it belongs to the systemic expectorants and inorganic salts, in general. In other pharmaceutical uses, the compound has been used for a few other uses, especially production of iodide. Of its chemical reactions, the most important is with the iodide ion, and it undergoes typical oxidation-reduction and precipitation reactions.

Preparation

Potassium iodide can be easily obtained by the reaction of iodine with suitable potassium salts, after purification and crystallization. The pharmaceutical grade material should conform to the appropriate

specifications for identity, purity and content. The manufacturing process is designed in a way that minimises the contamination of the product by the presence of iodate, carbonate, chloride and other impurities.

Properties

Potassium iodide is sold as a white or nearly white (crystalline) powder or crystals. Extremely soluble in water, and polar solvents. Aqueous solutions are normally neutral to slightly alkaline depending upon the conditions. Potassium iodide is fairly stable in dry conditions, and can oxidize to iodine in poor conditions. The colour change/break down may be as a result of exposure to light, oxidising agents or air.

Identification

Potassium and iodide ions need to be detected to identify them. The iodide ion can be detected by reaction with suitable oxidising agents to liberate iodine which can be used in colour reaction and/or with starch. Pharmacopoeial flame or precipitation test can be used to detect the presence of potassium in the sample.

Assay

The quantitative determination of iodide is the basis for this test for potassium iodide. According to the official procedure in the Pharmacopoeia, classically the analysis of the substance can be carried out by oxidation-reduction or precipitation methods. The method of analysis should be accurate for the amount of potassium iodide present, and should be able to differentiate it from any possible impurities that may contain iodide.

Uses and Storage

Potassium iodide is used as an expectorant for many years and a source of iodide. It also has a couple medical uses in a controlled clinical setting. It should not be used for long time or wrongly used as it may affect health adversely. Potassium iodide should be stored in a tightly closed container away from extreme moisture, incompatible oxidizing agents and light.

Ammonium Chloride

Synonyms, Category and Chemical Formula

Ammonium chloride is an inorganic compound made up of ammonium and chloride ions. The compound's chemical formula is NH_4Cl. It has been traditionally classified as a systemic acidifying salt and expectorant. The compound is also chemically important as it shows characteristic reactions of ammonium and chloride ions.

Preparation

Ammonium chloride can be synthesized by the reaction of ammonia with hydrochloric acid, which is then concentrated and crystallized. By-products of other chemical processes may be produced during industrial manufacturing processes which can be recovered as ammonium chloride. The purified and quality tested material is used for pharmaceutical use.

Properties

Ammonium chloride, a white crystalline powder or white crystalline, is available. The ammonium ion is highly soluble in water and as it undergoes hydrolysis it gives an acidic solution. The compound is stable when stored in normal conditions, away from excess water. Ammonium chloride volatilizes and decomposes to ammonia and hydrogen chloride on strongly heating.

Identification

To detect the presence of the ammonium ion, it can be reacted with the suitable alkali to release ammonia gas and then warmed. The presence of free ammonia can be detected by smell and/or by its reaction with suitable indicator paper. Precipitation with silver ions to form the characteristic precipitate AgCl can be used to detect chloride in the proper conditions.

Assay

The quantitative analytical method is used in assay procedures to find out the amount of ammonium chloride present. As appropriate, using acid-base or other validated methods may be used. The test is used to determine the quality and potency of a pharmaceutical product.

Uses and Storage

Ammonium chloride has been employed in the past as systemic acidifying and expectorant. The expectorant action of reflex stimulation of respiratory secretions is related. Too much can cause irritation to the digestive system or upset the body; use the correct amount. Should be kept in a well-closed container in a dry place and away from contamination and excess moisture.

14.3 Emetics

Definition of Emetics

Emetics: Drugs that activate pathways that cause vomiting. Vomiting is a physiological process that is regulated by the gastrointestinal tract, by vomiting centres in the brainstem, by visceroafferent pathways and by the diaphragm and abdominal wall muscles. Emetics have been used in the past to treat some poisonings and to induce vomiting from the ingestion of undesirable substances. However, the regular use of therapeutic emesis is now no longer used, as it may lead to complications like

aspiration, electrolyte imbalances, mucosal damage or delayed treatment of poisoning. Examples of traditional pharmaceutical emetics are copper sulphate and sodium potassium tartrate. Copper sulphate being a gastric mucosa irritant causes vomiting at high concentrations. In addition, sodium potassium tartrate has a gastrointestinal effect and was traditionally reported to be an emetic. These compounds are now only of historical and medicinal chemistry importance as emetics. Treatment of modern poisonings is based on evidence-based practices and in most cases, the general guideline is not to consider inducing vomiting as a therapeutic option. However, in the field of pharmaceutical analysis these compounds are still valuable examples for the study of inorganic salts, identification reactions, assay methods and storage conditions. Copper sulphate is a blue crystalline compound which contains the copper ions and sulphate ions, while sodium potassium tartrate is a double salt of sodium, potassium and tartrate ions. The physical properties are determined by their chemical properties, their solubility, their reactions and its analytical properties. Emetics should also be separated from substances which cause vomiting as a side effect. Emetic = induced vomiting, Nausea/Vomiting = toxicity/intolerance to the drugs. It's important to be aware of the difference in the world of pharmaceutical practice. Pupils should also be aware that historic uses of medicines are not necessarily indicative of current clinical guidance. Always take into account the safety profile, therapeutic index, availability of safer alternatives and modern clinical guidelines. Therefore, emetic study in pharmaceutical chemistry should be focused on the chemical identity of emetics, classical mechanism of action, analytical characteristics and historical background of emetics and their application in routine clinical use should be remembered.

Mechanism of Action of Emetics

The emetic reflex is a complex protective reflex which expels potentially harmful material from the upper gastrointestinal tract. It is a process which involves activation of sensory receptors, afferent neural pathways, central vomiting pathways and motor responses. It can be peripheral - acting directly on the gastrointestinal tract - or central - acting directly on the central nervous system - or both. The significant action of the classical inorganic emetics with respect to vomiting is through the action on the mucosa of the gut. The stimulation of sensory receptors in the stomach by acoustic stimulation of them leads to the activation of afferent signals that go to the CNS, which in turn participates in the activation of the vomiting reflex. When activated, the coordinated response includes glottis closure, abdominal contraction, movement of the diaphragm, and relaxation of the upper GI tract and the speeding up of gastric contents. This varies by the substance, dosage, and method of delivery, and individuals' health. Copper sulphate has a special historical status as an emetic, thus being a unique historical germicide. But it has proved toxic and treatment of poisoning rarely calls for its use as an emetic. Sodium potassium tartrate used to be used as an emetic (something that causes vomiting) but isn't much used these days. The vomiting reflex consists of several stages: (1) stimulation of the receptors in the peripheral or central nervous system; (2) integration of the nerves; (3) gastric and

muscular responses (see figure 14.3). This mechanism can be of importance as vomiting can not be considered a purely local stomach phenomenon but is linked up between the gastrointestinal tract and the central nervous system. The excessive or persistent vomiting may lead to dehydration, electrolyte disturbances, metabolic changes, aspiration and gastrointestinal tract injury. So, there's no therapy that must cause vomiting. Modern medicine endeavors to prevent harm, not to stimulate the emetic reflex indiscriminately, but to use the right treatment of disease. That it is still remarkable that the classification of emetic agents is the same as it was then and that the systemic reaction to which the body responds to chemical irritation can be known. Students of Pharmacy should also understand the difference between emetic and antiemetic; they act by blocking emetic centers (transmitter receptors and central pathway) that prevents the occurrence of nausea and vomiting.

Classification of Emetics

There are various kinds of emetics, depending on how they cause vomiting. They have been traditionally divided into peripherally acting emetics and centrally acting emetics. Peripheral emetics act on receptors in the GIT that lead to afferent signals which activate the vomit centre. Copper sulphate is an example of peripheral irritant emetic. Centrally acting emetics have a direct or indirect effect on the structures of the central nervous system involved in the vomiting response. Other classifications are possible – based on the chemical nature of the emetics (inorganic salts, organic compounds). Examples of inorganic compounds from history are sodium potassium tartrate and copper sulphate. It helps to classify to understand what should be seen, what should be expected and any side effects. Peripherally acting irritants can produce amazing gastrointestinal irritation and tissue damage and centrally acting irritants can lead to neurological effects. From the history of emetics in poisoning, there is a lesson to be learned in pharmaceutical and clinical practice: A medicine can be expected to have a predictable effect but because of safety issues, it may not be available for everyday use. Specific antidotes (in some instances with activated charcoal) and supportive treatment and procedures under the direction of a specialist are preferred in modern toxicology over routine induction of vomiting. Therefore, it is crucial for the pharmaceutical students to understand the difference between the old and new classification. The chemistry of inorganic salts is illustrated by the emetic compounds that are the subject of this chapter, and are also important from an analytical point of view. Copper sulphate has characteristic reaction of Copper ion and that of sulphate ion, sodium potassium tartrate has characteristic reaction of double salt. They are pure and can be tested by suitable pharmacopoeial tests for their identity. The classifications also provide a logical linkage between the chemical structure and the physiological activity. Pharmaceutical properties may be affected by the solubility, ionic nature, stability and reactivity of a substance, as may be its analytical determination. Thus, learning classification of emetics enables the learners to correlate the study of medicinal chemistry, inorganic chemistry, pharmacology and pharmaceutical analysis as a whole and not as a part.

Copper Sulphate

Synonyms, Category and Chemical Formula

Copper sulphate is an inorganic copper salt which has traditionally been linked with its emetic properties. The hydrated form of copper sulphate is more prevalent since it is more stable.A more stable form of copper sulphate is the hydrated form, $CuSO_4 \cdot 5H_2O$. Also known as blue vitriol. The compound is very blue in colour and reacts with copper and sulphate ions.

Preparation

Copper sulphate can be obtained by adding copper oxide to sulphuric acid under suitable conditions to form copper sulphate solution, filter the solution and crystallise it. The crystals are formed from water solution under controlled conditions, and are called hydrated crystals. The pharmaceutical grade material is tested for quality control for purity and correct hydration level.

Properties

Copper sulphate pentahydrate is a blue crystal. Soluble in water, it forms blue solutions in water as a result of hydrated copper ions. It loses water of crystallization on heating, then gradually turns colour and finally it becomes anhydrous copper sulphate. The compound has the typical reactions of a copper II compound with a variety of reagents.

Identification

There are several characteristic reactions by which copper can be identified, and which can be used to produce precipitates or coloured complexes. Sulphate can be detected by precipitation with an appropriate barium salt in the presence of an appropriate acid to form an insoluble barium sulphate precipitate. The reactions can be used to substantiate the presence of the compound.

Assay

An appropriate analytical method (complexometric, iodometric or other standard method) may be used to determine the amount of copper sulphate. The assay selected should be sensitive to the amount (or the amount of copper sulphate in the solution).

Uses and Storage

Copper sulphate had been used as an emetic and there were many non-therapeutic uses as well. Copper is highly toxic, and is not suitable for use as a regular self-administered emetic. It should be stored in a tightly closed container, in a safe place where it's protected from moisture, contamination and handled according to proper safety procedures.

Sodium Potassium Tartrate

Synonyms, Category and Chemical Formula

Sodium potassium tartrate is a double salt of sodium and potassium which is formed from tartaric acid. It is also known as Rochelle salt, and can be written as $KNaC_4H_4O_6·4H_2O$ (the tetrahydrate form). It used to be a classified emetic and is also considered as a chemical reagent.

Preparation

Sodium potassium tartrate can be prepared by neutralisation of tartaric acid (or an appropriate "acid tartate") with sodium hydroxide or potassium hydroxide or its salts, followed by concentration and crystallisation. The hydrated crystals are formed by a process known as controlled crystallization.

Properties

It exists in the form of a white or colourless crystal and it is soluble in water. It has the typical properties of double salt containing tartaric acid. It is known to lose water of crystallization on heating and it also is known to further decompose at higher temperatures. Aqueous solution of it can undergo typical tartrate reactions.

Identification

Tests for potassium, sodium and tartrate ions are used for identification. Tartrate can react with appropriate reagents to give characteristic reactions and sodium and potassium can be identified by appropriate qualitative tests. The total results are used to describe what the substance is.

Assay

The sodium potassium tartrate assay is based upon the appropriate pharmacopoeial or analytical method. Quantitative methods can be used to determine the amount of tartrate and/or specific ions. Analytical Control is a technique implemented to ensure the material complies to the specifications.

Uses and Storage

Sodium potassium tartrate has found use as an emetic in the past and in pharmaceutical and chemical formulations. It has only limited modern pharmaceutical use as a purgative. Should be stored in a well closed container in a dry location away from contamination and excess moisture.

Chapter Summary

Two groups of miscellaneous pharmaceutical compounds that have different physiological actions are expectorants and emetics. Expectorants increase production of respiratory secretions; they increase the hydration, the viscosity, or the ability to cough up the secretions. Typical examples of traditional compounds are potassium iodide and ammonium chloride. Potassium iodide, KI, is an inorganic salt compound of iodine and is a systemic expectorant and source of iodine during olden times. NH_4Cl has

been traditionally considered a reflex expectorant and systemic acidifying salt. They also have pharmaceutical importance in the aspects of identification, purity, preparation conditions, chemical properties, assay and storage conditions, as they are constituents of the pharmaceutical quality control. Emetics: Agents which stimulate pathways in the periphery or in the central nervous system that trigger vomiting. Examples include copper sulphate and sodium potassium tartrate. The crystal form of Copper Sulphate Pentahydrate, $CuSO_4 \cdot 5H_2O$ is blue, and has characteristic copper and sulphate reactions. The sodium potassium tartrate, or Rochelle salt, is a double salt of sodium, potassium and tartrate ions. These compounds have historical significance and the use of emetics in routine treatment of emesis has to a large extent now been replaced by safer, better evidence-based approaches. Pupils should therefore differentiate between historical uses in medicine and modern day uses. Overall the chapter demonstrates how the chemical composition, physicochemical properties, analytical identification and assay, mechanism of action and therapeutic application of the drug are inter-dependent and how each of these factors is related to safety. The insight gained in these relationships allows pharmaceutical professionals to critically assess inorganic medicinal compounds and to use the principles of pharmaceutical analysis and safe handling.**Key Points**

- Expectorants facilitate the removal of mucus and respiratory secretions.
- Potassium iodide (KI) is a traditional systemic expectorant and iodide-containing inorganic salt.
- Ammonium chloride (NH_4Cl) is traditionally classified as a reflex expectorant and systemic acidifying salt.
- Expectorants should be distinguished from antitussives, which suppress coughing.
- Adequate hydration supports effective respiratory mucus clearance.
- Emetics are substances that induce vomiting by activating pathways involved in the vomiting reflex.
- Copper sulphate is a classical peripheral irritant emetic with historical pharmaceutical importance.
- Sodium potassium tartrate, or Rochelle salt, is a traditional inorganic emetic.
- Copper sulphate pentahydrate has the formula $CuSO_4 \cdot 5H_2O$.
- Sodium potassium tartrate tetrahydrate may be represented as $KNaC_4H_4O_6 \cdot 4H_2O$.
- Identification tests are based on characteristic reactions of the constituent ions.
- Assay procedures determine the quantity and purity of pharmaceutical substances.

- Modern poisoning management generally does **not** recommend routine induction of vomiting.
- Proper storage protects pharmaceutical substances from moisture, light, contamination, and incompatible substances.
- Pharmaceutical knowledge should integrate chemical properties, mechanism, therapeutic use, analytical evaluation, and safety.

Review Questions

1. Define expectorants and explain their pharmaceutical importance.
2. Describe the general mechanism of action of expectorants.
3. Classify expectorants with suitable examples.
4. Discuss the synonyms, category, formula, preparation, properties, identification, assay, uses, and storage of potassium iodide.
5. Describe the pharmaceutical properties and uses of ammonium chloride.
6. What are emetics? Explain their mechanism of action.
7. Classify emetics according to their mechanism of action.
8. Discuss the chemistry and pharmaceutical applications of copper sulphate.
9. Write a detailed note on sodium potassium tartrate.
10. Differentiate between expectorants and emetics.
11. Explain the importance of identification and assay of pharmaceutical inorganic compounds.
12. Why has the routine therapeutic use of traditional emetics declined?
13. Describe the safety considerations associated with emetic compounds.
14. Explain the relationship between mucus hydration and expectorant action.
15. Discuss the importance of proper storage of pharmaceutical inorganic salts.

MCQs

1. Which of the following is traditionally classified as an expectorant?

A. Copper sulphate

B. Potassium iodide

C. Sodium chloride

D. Calcium carbonate

Answer: B. Potassium iodide

2. The chemical formula of potassium iodide is:

A. KCl

B. KI

C. KIO_3

D. K_2I

Answer: B. KI

3. Ammonium chloride has the formula:

A. NH_4OH

B. NH_4NO_3

C. NH_4Cl

D. NaCl

Answer: C. NH_4Cl

4. Which compound is traditionally known as blue vitriol?

A. Copper sulphate

B. Sodium potassium tartrate

C. Potassium iodide

D. Ammonium chloride

Answer: A. Copper sulphate

5. Copper sulphate pentahydrate is represented by:

A. $CuCl_2$

B. $CuSO_4$

C. $CuSO_4 \cdot 5H_2O$

D. $CuCO_3$

Answer: C. $CuSO_4 \cdot 5H_2O$

6. Rochelle salt is another name for:

A. Ammonium chloride

B. Sodium potassium tartrate

C. Copper sulphate

D. Potassium iodide

Answer: B. Sodium potassium tartrate

7. The primary purpose of an expectorant is to:

A. Suppress all coughing

B. Increase mucus clearance

C. Induce sleep

D. Reduce gastric acidity

Answer: B. Increase mucus clearance

8. Which compound contains an iodide ion?

A. KI

B. NH_4Cl

C. $CuSO_4$

D. $KNaC_4H_4O_6$

Answer: A. KI

9. Emetics primarily produce:

A. Diuresis

B. Vomiting

C. Sedation

D. Bronchodilation

Answer: B. Vomiting

10. Which of the following is a historical emetic?

A. Potassium iodide

B. Ammonium chloride

C. Copper sulphate

D. Sodium bicarbonate

Answer: C. Copper sulphate

Chapter 15

Haematinics

Learning Objectives

After completing this chapter, the learner will be able to:

1. Define haematinics and explain their importance in the prevention and management of iron-deficiency anaemia.
2. Describe the chemical properties, preparation, identification, assay, pharmaceutical uses, and storage of ferrous sulphate and ferrous gluconate.
3. Explain the processes of iron absorption, transport, storage, and utilization in haemoglobin formation.
4. Classify commonly used haematinic agents and discuss their pharmaceutical applications.

15.1 Introduction to Haematinics

Definition of Haematinics

Haematinics are medicines that help your body make blood cells – particularly red blood cells – by helping to supply nutrients that your body needs to make haemoglobin and red blood cells. The Greek word haema means blood and is used generally for agents used for the prevention and treatment of nutritional deficiencies related to anaemia. The most important haematinic nutrient is iron because it is taken up by the protein haemoglobin, which carries oxygen in the red blood cells. Folic acid and Vitamin B_{12} are other haematinic nutrients which play a role in DNA synthesis and normal maturation of the erythroid precursor cells. In the pharmaceutical practice, iron-containing preparations are of

particular importance as iron-deficiency anaemia is still a widespread nutritional disorder in the world. There are two forms of haematinics - oral and parenteral. The oral forms of iron include ferrous sulphate, ferrous gluconate and iron salts/complexes. The preparation varies in a nuanced way in terms of its iron content, tolerability, solubility and absorption. So preparation will depend on the severity of deficiency, patient's tolerance to the drugs, clinical considerations and therapeutic need. Treatment of anaemia should be directed towards correction of the underlying cause of the anaemia and not just towards increasing the haemoglobin concentration. Iron deficiency can happen due to a low iron diet, increased need (e.g., growth and production in women), chronic blood loss, impaired intestinal absorption or a mix of these conditions. Therefore a correct diagnosis is crucial prior to supplementation. The pharmaceutical chemistry component of haematinics is significant because of the following: (i) their chemical composition has an impact on their stability, solubility, elemental iron content, identification tests, assays and storage conditions; and (ii) they are used in the manufacture of pharmaceutical products like tablets, capsules and injections. Knowledge of these is significant in the formulation of pharmaceutical products to ensure that they will contain the proper amount of the active ingredient during the time on the shelf (shelf-life) and be stable. Therefore, haematinics can be regarded as a bridge between inorganic and organic pharmaceutical chemistry/pharmacology, nutrition and therapy.

Importance in Anaemia Management

The contents of haematinics are essential for normal erythropoiesis and they are used in the management of nutritional and/or deficiency anaemias. Of particular importance is iron, which is utilised as a component of haemoglobin in circulating erythrocytes, about two thirds of the body's iron is used in this manner. Where there is iron deficiency, haemoglobin production is decreased and the red cells are smaller and without haemoglobin. The iron deficiency can lead to iron-deficiency anaemia which may lead to fatigue, weakness, reduced exercise tolerance, pallor, headache and reduced concentration. In the setting of chronic iron deficiency, children can also be affected by the disease processes having a negative impact on normal cognition and development. The goal of haematinic therapy is thus to replenish the body's stores of nutrients and promote the production of normal red blood cells. Iron salts (typically as an oral medication) are administered when iron deficiency is confirmed and the iron absorption in the gastrointestinal tract is adequate. Ferrous salts are commonly selected, as a general rule, ferrous iron is more absorbable in the gastrointestinal tract than ferric iron. The main site of absorption is in the proximal small intestine with regulation according to the body's iron requirements. The amount of iron taken up will bind to transferrin in plasma, travel to tissues for storage in storage proteins or for use in the production of haemoglobin and enzymes. Iron absorption, transport, utilization & storage are very specific and detailed and is illustrated in Figure 15.1 which also emphasizes the important role of iron availability regulation to ensure normal haemoglobin production. Appropriate use of haematinics – too much and when not

necessary can have unwanted effects, and in some cases excessive levels of iron. Gastrointestinal effects are common and are experienced by patients upon oral administration of iron, such as stomach discomfort, nausea, constipation or diarrhoea. Poor tolerability can impact on adherence, and therefore treatment effectiveness. Hence, treatment should take into account therapeutic needs and patient tolerance. If oral iron is not tolerated or if there are severe blood losses or iron deficiencies, iron can be administered parenterally or from an appropriate medical supervision if it is not given orally. A good measure of the effectiveness of treatment is a clinical improvement and appropriate laboratory parameters. Note: a normal level of haemoglobin doesn't indicate a normal iron level in the body. Therefore, if it is required, enough treatment time may have to be given to replenish the depleted reserves. So, haematinics are no longer just a way of raising haemoglobin, they are integral parts of the management of certain nutritional deficits and their causes.

15.2 Ferrous Sulphate

Synonyms

Iron(II) sulphate or ferrous sulfate is also known as ferrous sulphate. The common hydrated form is ferrous sulphate heptahydrate (FeSO4.7H2O) which is used in pharmaceuticals. This is one of the oldest and commonly used oral iron tablets because of its availability, iron efficiency in treating iron-deficiency and also because of its low cost.

Category

Ferrous sulphate is in the group of medicines called haematinics and iron medicines. It supplies ferrous (Fe2+) ions which can be absorbed in the gut, and then incorporated into biological molecules like haemoglobin.

Chemical Formula

The formula of ferrous sulphate heptahydrate is $FeSO_4 \cdot 7H_2O$. The formula of anhydrous ferrous sulphate is $FeSO_4$. The iron content of a preparation is dependent on the form of the iron in the preparation and its salt content.

Preparation

Ferrous sulphate can be prepared by controlled reaction of the iron or some compound containing iron with dilute sulphuric acid and it is then purified and crystallised. Oxidation needs to be controlled in the pharmaceutical manufacturing industry, as ferrous ions can be oxidized to ferric ions if the conditions are right (oxygen and moisture). The material is processed in an effort to render it as pure and strong as necessary for pharmaceutical uses.

Properties

Ferrous sulphate heptahydrate is found mostly in the form of a pale green or bluish-green crystalline compound. Water-soluble and forms an AQUEOUS SOLUTION, containing ferrous ions. Ferrous salts may slowly turn to ferric salts in the presence of air, and can discolor. Heating can cause loss of water of crystallization. The compound must hence be protected from the adverse environmental impacts.

Identification

The tests are carried out to confirm the presence of a ferrous ion and the presence of a sulphate ion and these tests are used in the identification of ferrous sulphate. Ferrous ions will precipitate or colour a suitable reagent(s). The presence of sulphate will be confirmed by precipitating it with barium ions under the correct acidity to form barium sulphate (which is insoluble in water).

Assay

$FeSO_4$ assay is a quantitative estimation of the amount of Fe or $FeSO_4$. Ferrous ions can be oxidized to ferric ions and thus redox titration procedures can be used. The analytical method should be carried out under controlled conditions to keep the extent of oxidation to a minimum prior to or during analysis.

Uses

Ferrous sulphate is a mainstay drug for the prevention and treatment of iron-deficiency anaemia. It may also be used when iron supplementation is necessary when there is an increased physiological demand, as long as iron deficiency or increased demand has been determined appropriately.

Storage

Ferrous sulfate must be kept in a well-closed container, away from high moisture and conditions which favor oxidation. Chemical stability and pharmaceutical quality are ensured with proper packaging.

15.3 Ferrous Gluconate

Synonyms

Iron (II) gluconate, also known as ferrous gluconate, is a chemical compound that contains iron.Ferrous gluconate, or iron (II) gluconate, is a chemical compound that contains iron. It is an iron salt of gluconic acid that is used as an oral haematinic drug. It contains iron in absorbable form for the GI tract for use in haemoglobin synthesis, similar to other ferrous salts.

Category

Ferrous gluconate is an oral iron haematinic. It is used to help treat people who don't have enough iron in their body or who need more iron. The clinical significance is limited to prevention of iron deficiency and treatment.

Chemical Formula

Ferrous gluconate is usually written as $Fe(C_6H_{11}O_7)_2$, which represents the iron(II) salt of gluconic acid. Pharmaceutical preparations can differ in composition with regard to formulation and moisture content.

Preparation

The synthesis of ferrous gluconate can be carried out by a controlled reaction between a suitable ferrous compound and gluconic acid or a source of gluconates. This yields the cleaned salt which is available to produce a medicine grade product. Manufacturing controls must be in place to ensure proper oxidation state and to be used to insure elemental iron uniformity.

Properties

Ferrous gluconate is typically supplied in the form of a light greenish or yellowish powder or as crystals, in tablet or capsule form. Soluble in various amounts in water and is taken orally. Like other ferrous salts, can oxidize under conditions. Moisture, oxygen, pH and formulation ingredients will thus influence its chemical stability.

Identification

The identification can include the identification of the ferrous ion by the use of appropriate qualitative reactions, and confirmation of the gluconate component by suitable analytical procedures. Under certain conditions, the ferrous ion will react with some reagents to produce tests characteristic of the ferrous ion, and the identity of the organic anion can be determined by instrumental or chemical means.

Assay

Ferrous gluconate is estimated in the assay to find out the amount of iron or ferrous gluconate present in the pharmaceutical material. Redox, complexometric methods and instrumental methods are suitable for application, depending on the official analytical method. Consistency of dosage and pharmaceutical quality is crucial, and this is done through assay procedures.

Uses

Ferrous gluconate is an iron supplement that is taken by mouth and used to prevent and treat iron-deficiency. It can be used when an alternative oral iron salt has been indicated due to gastrointestinal tolerance and/or adherence problems among individual patients.

Storage

Ferrous gluconate is typically packaged in a tightly sealed container and stored away from excessive moisture, heat and conditions that may promote oxidation. The storage conditions should be related to the requirements of the final pharmaceutical product.

15.4 Pharmaceutical Applications of Haematinics

The haematinics have wide applications in the prophylaxis and/or therapy of nutritional anaemias and disease states that may have increased demand for blood formation. Iron preparations are of particular importance because iron plays a key role in the production of haemoglobin, the transportation of oxygen, metabolic processes and certain enzyme reactions. Ferrous salts, such as ferrous sulphate and ferrous gluconate, are usually administered orally in cases of iron deficiency (when absorption is good). These preparations are formulated with a form of Fe that can be absorbed in the gut then transported to tissues. The iron taken up is either bound to haemoglobin in developing erythrocytes or is bound to ferritin and/or haemosiderin for later use. Figure 15.2 illustrates the importance of iron in the formation of haemoglobin and how absorbed iron is used in the formation of haemoglobin in developing red blood cells and how it ends up in transporting oxygen. The use of haematinics in the pharmaceutical industry also goes beyond just iron supplements. If a higher nutrient requirement is determined, then nutrients can be included in nutritional formulations, therapeutic and preventive supplementation programmes. The use of haematinics, however, should be directed by a proper evaluation of the cause of anaemia. There is no evidence of any benefit from iron supplementation for non-iron anaemias (e.g. vitB12, folate deficiency, chronic disease, inherited haemoglobin deficiencies etc.) so a laboratory assessment is necessary before long-term iron supplementation. There are differences in the levels of elemental iron, the amount needed and the gastrointestinal tolerability and formulation between the various iron preparations. Ferrous sulphate has been proven to be effective and inexpensive, while ferrous gluconate is the other oral preparation that is available. Other iron preparations include iron complexes and parenteral preparations for use in particular clinical situations. In Table 15.1, the haematinics which are commonly used are compared with respect to their chemical nature, their main characteristics and their pharmaceutical applications. Haematinics may be combined with folic acid, vitamin B_{12}, vitamin C or other nutrients when clinically appropriate, and where combinations are logical and suggested by the nutritional status of the person. Therapeutic effectiveness depends on the amounts, purity, stability and uniformity of the elemental iron content, which are part of pharmaceutical quality control. It is also essential to ensure proper storage, as some iron salts can be affected by oxidation and by the environment. For this reason, it is

necessary to combine pharmacological knowledge, pharmaceutical chemistry, nutrition, analytical quality control and suitable clinical evaluation in pharmaceutical applications of haematinics.

Table 15.1. Comparison of Common Haematinics

Haematinic Agent	Category	Chemical Formula	Major Nutrient/Active Component	Key Properties	Principal Pharmaceutical Uses
Ferrous Sulphate	Oral iron haematinic	$FeSO_4 \cdot 7H_2O$	Elemental iron (Fe^{2+})	Pale green/blue-green crystalline material; soluble in water; susceptible to oxidation	Prevention and treatment of iron-deficiency anaemia
Ferrous Gluconate	Oral iron haematinic	$Fe(C_6H_{11}O_7)_2$	Elemental iron (Fe^{2+})	Pale greenish/yellowish material; suitable for oral administration; relatively well tolerated by some patients	Prevention and treatment of iron deficiency
Ferrous Fumarate	Oral iron haematinic	$FeC_4H_2O_4$	Elemental iron (Fe^{2+})	Reddish-orange to brown powder; relatively high elemental iron content	Treatment and prevention of iron-deficiency anaemia
Folic Acid	Vitamin haematinic	$C_{19}H_{19}N_7O_6$	Folate (Vitamin B_9)	Yellow or orange-yellow crystalline powder; sparingly soluble in water	Prevention and treatment of folate-deficiency anaemia; supplementati

					on during increased requirements
Cyanocobalamin	Vitamin haematinic	$C_{63}H_{88}CoN_{14}O_{14}P$	Vitamin B_{12}	Red crystalline compound; cobalt-containing vitamin; water-soluble	Prevention and treatment of vitamin B_{12} deficiency and associated megaloblastic anaemia
Iron–Folic Acid Combination	Combination haematinic	—	Iron + folate	Provides two nutrients required for normal erythropoiesis	Prevention and treatment of nutritional anaemia when both nutrients are indicated
Parenteral Iron Preparations	Injectable iron haematinics	Varies with preparation	Iron	Designed for administration when oral iron is unsuitable, ineffective, or inadequately absorbed	Treatment of iron deficiency in selected patients under medical supervision

Chapter Summary

Haematinics are drugs which help the body to make red blood cells particularly for the prevention or treatment of nutritional anaemias. Iron is the most important haematinic nutrient as it is a component of haemoglobin and needed for transport of oxygen. Oral iron preparations are important such as ferrous sulphate and ferrous gluconate. There are several widely used and effective ferrous sulphate heptahydrate ($FeSO_4 \cdot 7H_2O$) which are available and affordable. Ferrous gluconate is an iron(II) compound of gluconic acid which can be used as an alternative iron(II) compound that can be taken orally. Both of them can be quantitatively analysed by appropriate methods and both of them give characteristic identification reactions. Iron is absorbed in the small intestine, predominantly in the proximal small intestine and is regulated tightly in the small intestine. Transferrins bind to iron ions and transport them into tissue where they are incorporated into developing erythrocytes and into the

haemoglobin. Excess iron is stored in the primary form of ferritin and haemosiderin. Hypochromic microcytic anaemia may be due to iron deficiency. Therefore, the treatment of a haematinic should not just be to raise the haemoglobin concentration, but also to restore the iron stores and to treat the underlying cause of iron-deficiency anaemia. Oral preparations of iron can also have gastrointestinal side effects and treatment should be individualized based on the therapeutic indication and the risk of gastrointestinal upset. In addition to the haematinic nutrients, there are other vitamins that are also crucial to normal erythropoiesis and these should be considered in the evaluation of anaemia, for example, folic acid and vitamin B_{12}. Safe, stable and effective haematinic preparations can only be assured by the proper storage, identification, assay and quality control of pharmaceutical products.

Key Points

- Haematinics support normal erythropoiesis and haemoglobin formation.
- Iron is the most important nutrient associated with haemoglobin synthesis.
- Ferrous sulphate is a widely used oral iron preparation.
- Ferrous sulphate heptahydrate has the formula $FeSO_4 \cdot 7H_2O$.
- Ferrous gluconate is another commonly used oral iron salt.
- Ferrous gluconate supplies iron in the ferrous oxidation state.
- Iron is absorbed mainly in the proximal small intestine.
- Absorbed iron is transported primarily by transferrin.
- Iron is stored mainly as ferritin and haemosiderin.
- Iron is incorporated into haemoglobin during erythrocyte formation.
- Iron deficiency can produce microcytic, hypochromic anaemia.
- Haematinic therapy should be directed toward the underlying cause of deficiency.
- Oral iron preparations can cause gastrointestinal adverse effects.
- Identification and assay are important for pharmaceutical quality control.
- Proper storage protects iron preparations from moisture, oxidation, and contamination.

Review Questions

1. Define haematinics and explain their importance in anaemia management.
2. Describe the role of iron in haemoglobin synthesis.

3. Explain the absorption, transport, and storage of iron in the body.
4. Discuss the synonyms, category, formula, preparation, properties, identification, assay, uses, and storage of ferrous sulphate.
5. Write a detailed note on ferrous gluconate.
6. Compare ferrous sulphate and ferrous gluconate.
7. Explain the pharmaceutical applications of haematinic agents.
8. Describe the importance of elemental iron content in iron preparations.
9. What are the major causes of iron deficiency?
10. Explain the role of transferrin and ferritin in iron metabolism.
11. Why are ferrous salts commonly used as oral iron preparations?
12. Discuss the quality-control requirements for haematinic preparations.
13. Explain the relationship between iron deficiency and haemoglobin formation.
14. Describe the common adverse effects associated with oral iron therapy.
15. Classify commonly used haematinic agents.

MCQs

1. Haematinics are primarily used to:

A. Reduce gastric acidity

B. Promote blood formation

C. Suppress cough

D. Increase urine output

Answer: B. Promote blood formation

2. The most important mineral required for haemoglobin synthesis is:

A. Calcium

B. Sodium

C. Iron

D. Potassium

Answer: C. Iron

3. Ferrous sulphate heptahydrate has the formula:

A. $FeCl_3$

B. $FeSO_4 \cdot 7H_2O$

C. $Fe_2(SO_4)_3$

D. $FeCO_3$

Answer: B. $FeSO_4 \cdot 7H_2O$

4. Ferrous gluconate is classified as a:

A. Haematinic

B. Antacid

C. Laxative

D. Antiseptic

Answer: A. Haematinic

5. Iron is incorporated into which major protein?

A. Albumin

B. Haemoglobin

C. Collagen

D. Keratin

Answer: B. Haemoglobin

6. The major plasma protein responsible for iron transport is:

A. Albumin

B. Transferrin

C. Ferritin

D. Globulin

Answer: B. Transferrin

7. The principal intracellular storage protein for iron is:

A. Transferrin

B. Ferritin

C. Haemoglobin

D. Myoglobin

Answer: B. Ferritin

8. Iron deficiency classically produces:

A. Macrocytic anaemia

B. Microcytic hypochromic anaemia

C. Hemolytic anaemia only

D. Aplastic anaemia

Answer: B. Microcytic hypochromic anaemia

9. Ferrous sulphate is mainly administered for:

A. Iron deficiency

B. Calcium deficiency

C. Iodine deficiency

D. Vitamin C deficiency

Answer: A. Iron deficiency

10. Which of the following is an important consideration during oral iron therapy?

A. Gastrointestinal tolerability

B. Increased vision

C. Reduced body temperature

D. Increased salivation

Answer: A. Gastrointestinal tolerability

Chapter 16

Poisons and Antidotes

Learning Objectives

After completing this chapter, the learner will be able to:

1. Define poisons and antidotes and explain the general principles involved in poisoning and its management.
2. Classify antidotes into physical, chemical, physiological, and mechanical categories with suitable examples.
3. Describe the chemical properties, preparation, identification, assay, uses, and storage of sodium thiosulphate.
4. Explain the general principles of poisoning management and the pharmaceutical applications of important antidotes.

16.1 Introduction

Poisoning is an important medical and public health problem that can happen when a person is exposed to a substance that can cause a harmful biological effect when absorbed, breathed in, injected or taken into the body. A poison can be a pharmaceutical drug, household chemical, a pesticide, an industrial chemical, a plant product chemical, an environmental contaminant or another chemical

agent. The effectiveness of a poisonous material depends on the type of material, its concentration, dosage, route of exposure, duration of exposure, formulation and susceptibility of the individual. Poisoning can manifest itself locally, on a systemic level, or both. Symptoms range from mild gastrointestinal or neurological to respiratory failure, cardiovascular collapse, convulsions, coma and death. The treatment of poisoning is thus a time-sensitive medical emergency, which necessitates a rapid and correct appraisal and supportive treatment. Locally available antidotes, depending on the pattern of poisonings and the healthcare needs, and some poisonings may require specialised assessment, as highlighted by WHO. Substance that neutralizes, diminishes or counteract the harmful effects of a particular toxin (physically, chemically, physiologically or otherwise). Antidotal therapy is just one part of the treatment of poisoning, though. Mediations include stabilizing airway, breathing and circulation, assessing the extent of exposure, decontamination (if needed), supportive treatment, and administration of a specific antidote (if available and clinically appropriate). However, it must be kept in mind that poisoning cannot be managed unless it is assumed that a particular type of poisoning or dose is not dangerous if there is no immediate effect. The current poison-control guidelines also state that it is not a routine practice to induce vomiting after ingestion of a substance that might be toxic. It is thus advisable for the pharmaceutical student to know about both chemical and clinical aspects of poisons and antidotes. The study of antidotes is of special interest to pharmaceutical chemistry as many of the antidotal substances possess unusual chemical reaction and analytical properties. For instance, sulphur containing inorganic compounds are important, such as sodium thiosulphate, which can be used to treat cyanide poisoning. The chapter this way incorporates toxicology, pharmaceutical chemistry, analytical methods and principles of emergency management.

16.2 Poison

Definition of Poison

A poison is a substance that due to its ingestion in sufficient amounts can produce a harmful physiological or pathological effect and which can cause serious illness and/or death of the host. In addition to the toxicity of a substance, the idea of poisoning is associated with the dosage, the mode of exposure, the period of exposure, and the setting of the exposure. The concept that dose is tightly coupled with toxicity is illustrated by the following: a therapeutic dose may be good while an excessive dose may be bad. Poison exposure can happen when you swallow, breathe in, inject, touch with skin, put in your eyes, or are bitten or stung by poisonous arthropods. Poison control recognizes that not every exposure to poisons is a clinical poison exposure, that is why it is described as a poison exposure. There are several ways to classify poisons: by source, chemical nature, target organ, mechanism of toxicity and route of exposure. These may range from corrosive material, pesticides, toxic metals, solvents, gases, overdose of drugs but can also be biological toxins. Some poisons have a local effect and some enter the blood stream and have a systemic effect. The clinical features are

related to the mechanism of toxicity. Some will interfere with cellular respiration, some will interfere with neurotransmission and some will damage the liver, kidneys, heart or blood-forming systems. Poisoning needs to be duly considered with regards to the patient's symptoms and available history of exposure, so it can be identified. Key information should contain the name of the substance, approximate quantity, exposure time, exposure route, formulation and any first-aid action that may have been taken. Where possible, the original product container/packaging should be retained as it may provide health care practitioners with useful information. A basic part of the study of toxicology and antidotal therapy in pharmaceutical education is the knowledge of what is a poison. It also reiterates the importance of proper dosage, labelling, storage, handling and administration of pharmaceuticals for safe practice. Many poisonings can be prevented if the items are stored properly, packaged in child-resistant containers, labelled and incompatible chemicals are not mixed together and disposed of properly. If you think someone may have been poisoned, a health care professional or a poison-control service should assess the situation, don't try to treat it with remedies that you read about at home.

General Principles of Poisoning

Treatment of poisoning involves prompt recognition, stabilization, determination of the cause of the poisoning, supportive treatment, and specific treatment when it is indicated. Assessment and stabilization of the patient's airway, breathing and circulation are the first priorities. In severe poisoning, consciousness, respiratory, cardiovascular and neurological function can be affected so that immediate supportive care is important. Vital signs, level of consciousness, oxygenation, circulation and related clinical parameters should be monitored continuously, depending on the severity of the exposure. The second rule is the identification of the poison and an estimation of the route, approximate dose, time and circumstances of exposure. The container, label, medication strip or safety data information can be used to help identify it. If the substance is not known, clinical data and proper laboratory tests can be used to limit the choices. Decontamination is only considered after an exposure when it is appropriate for that exposure. If the skin is exposed, contaminated clothes can be removed and the area washed with running water; if the eyes are exposed, it is generally important to flush the eyes immediately. Inhalational exposures will also involve moving away from the contaminated environment and access to fresh air when it is safe to do so. The ingestion of vomit should not be routinely done because aspiration and further damage of tissues can occur. Treatment will vary depending on the substance involved, and will involve supportive treatment, increased elimination, antidotes or specialist treatment. Only use an antidote when the indication for its use is known as inappropriate use of antidotes can be harmful. Some antidotes have a time sensitivity and therefore should be easily available in a facility dealing with poisoning emergencies," says the WHO. Routine checking is necessary as poisoning can worsen over time and some effects of poisoning can be delayed. Another important principle is prevention which encompasses safe storage of medicines

and chemicals, appropriate labelling, and appropriate occupational precautions and public education. Overall, there is no universal protocol for the management of poisoning; treatment depends on type of poison and clinical condition.

16.3 Antidotes

Definition of Antidotes

An antidote is a substance or therapeutic agent that neutralizes, prevents or reverses the toxic effect of a poison. Antidotes can be used directly to combat the toxic substance or indirectly to change the physiological effects caused by the poison. Their mechanisms are hence very different. Some antidotes bind or adsorb toxic agents, thus preventing their absorption; others chemically neutralize poisons; some block the toxic action at receptors or at physiological systems; some promote elimination or detoxification of toxic agents. Antidotal treatment is generally specific or relatively specific, should be distinguished from general supportive treatment. For example, treatment of oxygen, fluids, airway management and treatment of seizures may be included in the care of the poisoned person but not included as conventional chemical antidotes. Antidotes will be selected based on the suspected or confirmed poisons, the degree of ill health, the timing of the exposure, contraindications, and available evidence. In many cases of poisoning, supportive management forms the basis of treatment; there are no specific antidote for many of the common cases of poisoning. Selected antidotes are included in the WHO Model List of Essential Medicines and as such the availability of these medicines should be based on the pattern of poisoning and clinical needs in the different regions. The thiosulphate ion, $NaS2O3$ is an anti-dotal agent of great importance in the treatment of cyanide poisoning. It adds some sulphur for the enzymes to convert cyanide to the much less toxic thiocyanate. Hydroxocobalamin, naloxone, atropine, and chelating agents are other drugs that are commonly used as antidotes in cases of cyanide poisoning, opioid toxicity, certain cholinergic poisonings, and some heavy metal exposures, respectively. Antidotes used are dependent upon the mode of action of the poison, not just its name. The student of the pharmaceutical profession should remember that an antidote will not remove all the toxic effects at once, and that treatment with an antidote should be supplemented with supportive and definitive treatment. A wrong choice or delay in administration may have a negative effect on the efficacy, while additional administrations may represent an additional risk. In any case, antidotes should be administered in accordance with the appropriate clinical supervision. Antidotes are used in the pharmaceutical practice: in emergency preparedness, hospital pharmacy, drug information services, poison-control systems and safe medication management.

Importance of Antidotal Therapy

The antidotal treatment is of importance because some poisons exhibit a predictable biochemical or physiological action and this can be specifically treated with the use of appropriate antidotes. Treatment of an antidote can make the difference in reducing morbidity and mortality, if one is available. Poisoning cases where the toxic action is rapid and/or where the toxic action causes irreversible cell damage are particularly significant in the need for prompt treatment. WHO guidance acknowledges the importance of having suitable access to antidotes in health care facilities to address poisoning as a time-dependent emergency. There are several ways in which antidotes can work. A chemical antidote may specifically bind to the toxin, a physiological antidote may act on the receptor/organ system level of a specific toxin. A physical antidote can be used to decrease absorption by adsorption or something else, and a mechanical intervention can be used to remove or isolate the toxic material. Factors that contribute to the clinical benefits of an antidote include: obtaining the right identification, timing, having an antidote available and safe administration. Not all poisonings need to be treated with an antidote; and many poisons do not have an antidote. Thus, supportive care continues to be an essential component. Also some antidotes have detrimental side effects and contraindications, so the potential benefit must be weighed against the potential harm. For instance, sodium thiosulphate is known to form part of the treatment of cyanide-poisoning. The FDA says sodium thiosulphate is on the list of products that can be used in a chemical emergency in the event of cyanide poisoning. The other component of antidotal treatment is the pharmaceutical supply component. Hospitals should be well prepared with essential anti-venom, have storage areas, staff well trained and have the necessary protocols for speedy access to materials for poison cases. The availability of antidote should be assessed based, among other things, on the epidemiology of poisonings and the health-care needs in the area, in line with WHO guidelines. Pharmacy workers are knowledgeable about antidotes for emergency preparedness; ordering and inventorying, identifying formulations, checking for expiry dates, and drug information. Last, an antidote must be administered within the context of a “poison-management plan” which includes initial diagnosis, supportive care, toxicology consultation, monitoring and follow-up.

16.4 Classification of Antidotes

Antidotes can be classified into those that work by the mechanism of action to neutralize the toxic agent. Traditionally they have been divided to the physical, chemical, physiological and mechanical antidotes. These are the physical countermeasures which block or prevent the poison from being absorbed. Examples include adsorbent substances that can bind to some toxins in the digestive tract and prevent them from getting into the blood stream. An adsorbent's effectiveness is dependent on the type of poison and when it is fed. Chemical antidotes work by binding to the toxic substance and changing the toxic substance into less toxic and/or more easily excreted form. One of the examples of that more relevant is the detoxification of cyanide to thiocyanate, in the presence of sodium thiosulphate. Chemical antidotal agents are also chelating agents, that is agents which bind certain

metal ions and facilitate their elimination. Physiological antidotes are not necessarily chemical compounds, but rather agents which, in some way, neutralize or block the action of the poison on the physiology. For instance, naloxone blocks the action of opioids and atropine blocks the relevant muscarinic effects of cholinergic toxicity. Mechanical antidotal treatment involves either the removal of the poison from the body, or the prevention of the poison entering the body. These include proper decontamination, change of contaminated clothing, washing of exposed tissues and some gastrointestinal decontamination – which should only be done under expert guidance. These are the four types that have been found to be helpful in educational contexts; some agents or interventions might be structurally similar. The main groups of antidotes and representative examples are presented along with the general mechanism of action in Table 16.1. Always choose an antidote according to the type of poison and clinical situation. A professional/expert evaluation should not be replaced by any classification system. Other Toxic(s) require repeated doses and some Poisons have no antidote and supportive therapy is the only remedy. Antidotes should therefore not be considered as part of a course of treatment for poisoning, but rather as part of a poisoning-management plan. The students can relate this to the therapeutic use and comprehend why they employ various antidotal substances for different types of toxic exposures.

Table 16.1. Classification of Antidotes with Examples

Class of Antidote	**Principle/Mechanism of Action**	**Examples**	**Representative Poison/Toxicity**	**Pharmaceutical Significance**
Physical Antidotes	Reduce absorption or interaction of the poison through physical processes such as adsorption or dilution	Activated charcoal; suitable irrigation agents	Selected orally ingested poisons; skin/eye exposures	Help prevent further absorption or tissue contact when appropriately indicated
Chemical Antidotes	React chemically with the poison or facilitate its conversion into a less toxic compound	**Sodium thiosulphate**; selected chelating agents	Cyanide; selected heavy-metal poisonings	Directly modifies or facilitates detoxification of the toxic substance
Physiological	Oppose or reverse the	**Naloxone**,	Opioid toxicity;	Provide

Antidotes	physiological/pharmacological effects of the poison, often through receptor antagonism	**atropine**, **hydroxocobalamin**	cholinergic poisoning; cyanide poisoning	mechanism-specific reversal of important toxic effects
Mechanical Antidotes	Remove the toxic substance or interrupt further exposure by physical intervention	Removal of contaminated clothing; skin/eye irrigation; selected clinical decontamination procedures	External chemical exposure; selected ingestions	Limits continued exposure and reduces additional absorption
Chelating Antidotes	Form stable complexes with selected metal ions, reducing their biological availability and facilitating elimination	Dimercaprol, EDTA, penicillamine	Arsenic, lead, mercury, or other selected metal toxicities	Important in the management of specific heavy-metal poisonings
Enzyme/Metabolic Antidotes	Alter the metabolism or detoxification pathway of the poison	Sodium thiosulphate; fomepizole	Cyanide; methanol/ethylene glycol poisoning	Interrupt toxic metabolic pathways or enhance detoxification

Physical Antidotes

Physical antidotes counteract the poison by simply physically removing it or blocking it out, without chemically altering the substance or antagonizing the receptor. They can be primary adsorption, diluting, coating or preventing further adsorption. Toxic chemicals may, in the gastrointestinal tract, be bound by adsorbent substances which will limit the amount that is absorbed into the blood stream. The effectiveness of a physical antidote is greatly dependent on the physicochemical properties of the antidote and the poison. The extent of adsorption is related to molecular size, polarity, solubility, surface area, time or presence of foodstuff or other material. Therefore, there are poisons for which physical antidotal treatments are not always effective. One of the keys to poisoning management is to

apply a treatment based on the particular poison used and not as a standard treatment. External exposures also can be physically decontaminated. Removing the contaminated clothing exposes skin, which will reduce the continued absorption from the skin, such as after washing. If eyes are irrigated with water as soon as possible after exposure, it can be hoped that the toxic material will be flushed from the eyes, thus reducing injury to the tissues. These interventions are especially time-dependent as prolonged contact may cause further damage to the tissues. Poison control recommendations are to immediately flush all skin and eye exposures and move the person to fresh air if they have been released by inhaling the product and they are safe. But physical antidotes are not effective for tissue penetration of toxins, and early intervention may be crucial. They are also not a substitute for airway support, cardiovascular stabilization or specific antidotal treatment, if required. They are mostly used pharmaceutically to reduce the contact or the absorption of the toxic substance. The use of physical antidotes is recommended if it is known from toxicological information that they work; they might not work for some poisons and some decontamination may make the injury worse. For example, as soon as a poison has been swallowed, making a victim vomit is not desirable as this may result in further aspiration of the poison in the person's stomach or in the person swallowing more corrosive material. As such, physical antidotal therapy is best viewed as a targeted support measures intervention and not as an antidotal therapy for all poisonings.

Chemical Antidotes

Chemical antidotes neutralize poisons either by acting directly with the poison or by biochemically altering the poison. These may be precipitation reactions, complex formation reactions, oxidation-reduction reactions or conversion of a harmful substance to a less harmful substance. One such example is chelating agents, which are able to form stable complexes with certain metal ions, decreasing their interaction with biological tissues and, hence, their elimination rate. Another important chemical antidote is sodium thiosulphate which is used in the detoxification of cyanide by providing sulphur for its enzymatic conversion to thiocyanate. This reaction will help to lower toxic effects of cyanide and promote its removal. Sodium thiosulphate is known to be a cyanide-poisoning management product. Chemical antidotes are specific as the antidote will only work for a specific chemical and reaction. These should be applied only if the suspected poison and clinical indications are well-founded. An incorrect chemical antidote may be ineffective and/or harmful. The use of chemical antidotes is also a testament to the importance of pharmaceutical chemistry in toxicology. Solubility, oxidation state, reactivity, and compatibility with other therapeutic agents influence preparation and use as well as their molecular structure, and their stability. In emergency situations, quick availability of properly prepared antidotes is essential as some toxic reactions are irreversible with time. WHO recommends that some an

tidotes be administered immediately and be easily available in the facilities where poisoning is being managed. Depending on the toxic agent, chemical antidotes can be used as the sole treatment, in conjunction with supportive treatment and other antidotes. They should always be used with clinical monitoring as reversal of the toxic mechanism does not automatically reverse the organ damage caused by the toxic mechanism. The knowledge of chemical antidotes therefore requires knowledge of principles of chemical reactions, pharmacology, toxicology, analytical chemistry and practice. Students should be given special emphasis that antidotal therapy is poison specific and that there is no universal chemical antidote to all poisons.

Physiological Antidotes

Physiological antidotes: These are substances that will have a physiological or even a pharmacological effect different from the poison itself, but that will, in any way, react chemically with the poison. They work through the receptor antagonism, functional antagonism, and/or restoration of physiological balance. These agents come into particular importance when there are over- or under-stimulations of certain neurotransmitter systems, such as poisoning. Naloxone is an opioid receptor antagonist which can quickly reverse opioid central nervous system and respiratory depression, for instance. Some cholinergic poisonings may warrant the use of atropine, as it will block the muscarinic symptoms (salivation, bronchoconstriction, bradycardia, and heavy secretions). Other physiological measurements are used to activate cardiovascular, neurological or respiratory activity for the purpose of metabolizing the toxin or eliminating it. The advantage of physiological antidotes is that they can reverse the biological effects of a poison even though it is not chemically possible to neutralize the effect. Often these are not successful in ridding the body of the toxic substances. Thus, more monitoring may be needed because the duration of action of the antidote could be less than the toxic substance. It may be that the antidote has become outdated or there may still be plenty of poison in the body, causing another bout of toxicity. Especially when taking tablets with long acting drugs, drugs with a sustained release will be important. Special care should also be taken to ensure that the physiological antidotes are used appropriately, that some may have undesirable effects if administered in excess, or if a different physiological antidote is administered. The choice of drugs is based on the suspected mechanism of toxicity, clinical presentation and patient specific factors. There are examples of the relationship between receptor pharmacology and toxicology in the pharmaceutical realm, such as physiological antidotes. Sometimes a drug meant for therapeutic purposes can also be used to treat the effects of another substance (such as a poison), and therefore be an antidote. Thus, classification of the physiological antidotes can be of value in the recognition of the pharmacological treatment of various poisoning syndromes. However, supportive care is still necessary, especially if the poisoning has involved the respiratory system, led to a decrease in blood pressure, seizures or altered mental status. The selection of the antidote depends upon the suspected toxin and the clinical advice available, and is expected to be made by qualified clinicians.**Mechanical Antidotes**

Mechanical antidote: Remove, isolate, dilute or interrupt the toxic substance (not through chemical neutralization or through pharmacologic antagonism). They do this as a means to prevent further exposure or to reduce the amount of poison that can be absorbed. These include changing contaminated clothing, washing exposed skin, flushing out the eyes and getting away from contaminated air. For external or inhalational exposures this is particularly significant as the dose to the patient may be increased if contact is continued. Chemical contact in the eyes is indicated by flushing immediately and in skin contact, affected clothing should be removed before flushing. Some procedures in healthcare may also be included in mechanical methods, but are only indicated for certain substances and should not be routinely performed. The method chosen will depend on the type of toxic substance, time since exposure, clinical condition, risk of aspiration and experience. Mechanical interventions are likely to be most beneficial if done early as their goal is to avoid additional contact or absorption. They can not remove toxicity but already present. Stabilization, monitoring and specific antidotal therapy should, therefore, be used in conjunction with them, when appropriate. Mechanical measures are particularly important in mass-casualty or occupational poisoning since it is to prevent secondary poisoning of patient and healthcare worker. If the toxic substance is still on the clothing or skin, it is important to wear the proper personal protective equipment and contamination-control measures. It is important to remember therefore that the toxicological concept of 'withdrawal from the source of exposure' can be as critical as treatment of the physiological effects of exposure. Pharmaceutical practitioners can participate in the management of poisoning by applying the correct principles of decontamination, making available materials and providing accurate information about the pharmaceutical or chemical product involved in the poisoning. Treatment with mechanical interventions, as with other antidotal treatments, should be individualized based on the specific circumstances of the exposure and the toxicological guidelines.

16.5 Sodium Thiosulphate

Synonyms

Sodium thiosulphate can also be referred to as sodium thiosulfate or hypo (in some photographic applications). It is the inorganic salt of sulphur present in sodium salt, which has a great application in the field of chemistry and pharmacology..

Category

Sodium thiosulphate is classified as inorganic sulphur containing Compound and Chemical antidote. It is particularly known for its part in the management of cyanide-poisoning.

Chemical Formula

The pentahydrate is the form that is generally found, $Na_2S_2O_3 \cdot 5H_2O$. The anhydrous form of the compound is $Na_2S_2O_3$.Preparation

Chemically sodium thiosulphate can be made under controlled conditions from sulphur containing compounds and sodium salts. Purified and standardized to meet the requirements for identity, purity and strength of pharmaceutical material.**Properties**

Sodium thiosulphate pentahydrate is generally obtained as a colorless or white crystalline substance. It is readily soluble in water and produces a clear aqueous solution. The hydrated compound can lose water of crystallization under appropriate environmental or thermal conditions. Thiosulphate ions participate readily in oxidation-reduction reactions and can be oxidized to sulphate under suitable conditions.

Identification

Identified by the typical reactions for the thiosulphate and sodium ions. Thiosulphate can be reacted with appropriate oxidising or acidifying agents to give characteristic products. Conventional qualitative tests can be used for the identification of the sodium. There are official pharmaceutical procedures that give standardized identity tests.

Assay

Sodium thiosulphate is a quantitative reactant with iodine which can be used in the iodometric titration method to determine the amount of thiosulphate. When thiosulphate is reacting with the iodine, it is being oxidised to tetrathionate and iodine is being reduced to iodide. Starch indicator can be used to detect the end point, under suitable analytical conditions.

Uses

An important use of sodium thiosulphate in the management of cyanide poisoning is to supply sulphur for enzymatic conversion of cyanide to thiocyanate. According to FDA, sodium thiosulphate is a medication used to treat cyanide poisoning. It also has some non-antidotal chemical and pharmaceutical uses.

Storage

Sodium thiosulphate should be stored in a well closed container, avoiding excess moisture, heat, contamination and incompatible substances. Pharmaceutical formulations must be stored as per their storage conditions.

Mechanism of Action

Sodium thiosulphate is a source of sulphur for enzymatic detoxification of cyanide. Cyanide disrupts cellular respiration by binding to cytochrome oxidase in mitochondria and stopping the cells from being able to use oxygen effectively. Cyanide can be transformed into thiocyanate, a much less toxic substance, which may be excreted by the kidneys, with the appropriate sulphur-donor pathways.

Sodium thiosulphate does not just capture cyanide, but also provides an important antidotal effect by facilitating the body's enzymatic process of cyanide detoxification. Sodium thiosulphate is listed as an antidotal agent in cyanide poisoning by WHO and the use of sodium thiosulphate in cyanide management protocols are described. Antidotal treatment will depend on the clinical situation and patient parameters, formulation and approved treatment guidelines. The treatment of cyanide poisoning should be done by trained health care professionals in a suitable emergency room, as it can develop very quickly. Sodium thiosulphate may be included in a complete antidotal regimen when required, but cannot be used in place of assistance with the airway, oxygenation, cardiovascular management or other emergency care. The mechanism illustrates the relationship of biochemical detoxification to toxicology: Giving the organism a suitable sulphur donor that enables cyanide to take a less toxic metabolic route. The pharmaceutical chemistry importance of the thiosulphate ion is that it can be oxidized and reduced and it is used as a basis for its analytical determination. In this instance, chemical reactivity and biological action go hand in hand, and sodium thiosulphate is an example of a compound that has a direct connection to its chemical properties in its pharmaceutical applications.

16.6 Pharmaceutical Applications of Antidotes

Antidotes play a significant role in emergency medicine, hospital pharmacy, toxicology services, poison-control and pharmaceutical preparedness. Their main role is to alleviate and/or neutralise the harmful effects of certain substances, but they must be used correctly, i.e. if the poisoning has been correctly identified, if they are available in time, if they are formulated appropriately and the administration is carried out by trained personnel. Sodium thiosulphate is an established example as being an important component of cyanide-poisoning management and is also listed among the products used in chemical emergencies. Other antidotal drugs act on specific mechanisms of toxicity, including opioid receptor antagonism, cholinergic toxicity and metal-ion binding. Antidotes can then be grouped into those that work physically, chemically, physiologically, and/or mechanically. The management of antidote stocks is also a part of the pharmaceutical application. Hospitals should decide which antidotes to keep on hand based on the local experience of the incidence of poisonings, the types of patients they see, the available emergency-service resources, and the requirements of the regulatory bodies. WHO guidance explicitly specifies that there is a need to ensure that the availability of antidote will correspond to the epidemiology of the location and that some antidotes may require early availability since treatment could be time sensitive. Pharmacy staff can be involved in procurement, in- and out-of-stock management, storage, expiry management, preparation, dispensing and supporting with drug information. The need for the proper storage is particularly important, because antidotes may be required on a sudden basis during an emergency and must be chemically stable, as well as clinically usable. There should also be clearly-defined instructions on indication and contraindication, preparation, administration, monitoring, and emergency access to

antidotes. Pharmaceutical applications include both hospital therapy and the prevention of illness and injury by pharmaceuticals, in emergency preparedness, and in the management of accidental exposures to pharmaceuticals, agricultural chemicals, industrial substances or environmental poisons. It is important to note that antidotes are not to be considered as an alternative to prevention. Poisoning can be prevented by the use of labels, proper storage, child-resistant packaging, safe handling, proper disposal and education. If poisoning happens, it is important to have an expert assess the situation to determine the appropriate treatment since the right treatment will depend on the exposure situation and the type of substance involved. Guidance for the management of poisoning today recommends that help should be sought as soon as possible, not after symptoms have appeared or home remedies have been tried and not verified. Therefore, the pharmaceutical use of antidotes can be expanded to include not only their therapeutic properties, but also their quality, availability, storage, safe administration, and incorporation into a broader approach to poison and poisoning management.

Chapter Summary

Poisons are toxic, harmful chemicals when inhaled at high concentrations or ingested which produce harmful biological effects; antidotes are chemicals that will neutralize the biological effects of certain poisons by physical, chemical, physiological or mechanical action. Exposure to any of the chemicals through ingestion, inhalation, injection, contact or eye exposure can lead to poisoning which may manifest with mild or severe effects that can involve breathing, heart and brain. Management involves rapid assessment and stabilisation of airway, breathing and circulation, recognition of the toxic chemical and decontamination if necessary, supportive management and specific antidotal therapy as available. If the patient presents with altered mental status, is unconscious and not breathing, vomiting should be induced for most poisonings. Physical antidotes decrease the absorption of a substance by physical means, chemical antidotes will neutralize or alter a toxic agent, physiological antidotes will counteract the toxic effects pharmacologically, and mechanical antidotes will remove or interrupt the absorption of a toxic agent. Sodium thiosulphate aid in the conversion of cyanide to the less toxic thiocyanate, making it an important chemical antidote in cyanide poisoning. Pharmaceutical chemistry of thiosulphate ion is related to its reactivity and its suitability for iodometric assay. For certain poisonings antidotal therapy must be administered in a timely fashion, thus the need for appropriate stock, storage, accessibility and trained personnel in the hospital. WHO advises use of the availability of antidote to be proportional to real local poisoning patterns and local health requirements. Generally the chemistry of poisons and antidotes is a combination of pharmaceutical chemistry, analytical chemistry, toxicology, pharmacology and emergency medicine and public health. All pharmaceutical personnel must realize that antidotes are very specific and must be used for the indications available and not as a blanket antidote for poisoning.

Key Points

- A **poison** is a substance capable of producing harmful biological effects when exposure is sufficient.
- Poisoning may occur through ingestion, inhalation, injection, skin contact, or eye exposure.
- Poisoning is a time-sensitive medical emergency.
- Initial management emphasizes stabilization of airway, breathing, and circulation.
- The identity, amount, route, and timing of exposure are important in poisoning assessment.
- Antidotes counteract or reduce the toxic effects of specific poisons.
- Antidotes may be classified as physical, chemical, physiological, or mechanical.
- Physical antidotes reduce absorption or continued exposure.
- Chemical antidotes interact chemically with toxic substances or facilitate detoxification.
- Physiological antidotes oppose toxic effects through pharmacological mechanisms.
- Mechanical interventions physically remove or interrupt exposure.
- **Sodium thiosulphate** is an important chemical antidote for cyanide poisoning.
- Sodium thiosulphate pentahydrate has the formula $\mathbf{Na_2S_2O_3 \cdot 5H_2O}$.
- Sodium thiosulphate can be assayed by **iodometric titration**.
- Sodium thiosulphate promotes conversion of cyanide to the less toxic thiocyanate.
- Antidotes should be administered according to appropriate clinical indications.
- Routine induction of vomiting after poisoning is not recommended.
- Appropriate antidote availability and storage are important components of hospital preparedness.

Review Questions

1. Define a poison and explain the factors that influence its toxicity.
2. Describe the general principles of poisoning management.
3. Define an antidote and explain its importance in toxicology.
4. Classify antidotes with suitable examples.
5. Differentiate between physical and chemical antidotes.

6. Explain the mechanism of physiological antidotes.
7. What are mechanical antidotes? Give suitable examples.
8. Discuss the synonyms, category, formula, preparation, properties, identification, assay, uses, and storage of sodium thiosulphate.
9. Explain the mechanism of action of sodium thiosulphate in cyanide poisoning.
10. Describe the importance of antidote availability in hospitals.
11. Explain the role of pharmaceutical professionals in antidote management.
12. Why should poisoning cases not be treated by inducing vomiting routinely?
13. Discuss the importance of early recognition and supportive treatment in poisoning.
14. Explain the role of chemical antidotes in toxicology.
15. Differentiate between a poison and an antidote.

MCQs

1. A substance capable of producing harmful biological effects when present in sufficient quantity is called a:

A. Nutrient

B. Poison

C. Preservative

D. Buffer

Answer: B. Poison

2. Antidotes are primarily used to:

A. Increase drug absorption

B. Counteract toxic effects

C. Increase appetite

D. Reduce drug stability

Answer: B. Counteract toxic effects

3. Which of the following is a chemical antidote?

A. Sodium thiosulphate

B. Water

C. Oxygen only

D. Normal saline

Answer: A. Sodium thiosulphate

4. Sodium thiosulphate pentahydrate has the formula:

A. Na_2SO_4

B. $Na_2S_2O_3 \cdot 5H_2O$

C. $NaHSO_4$

D. Na_2CO_3

Answer: B. $Na_2S_2O_3 \cdot 5H_2O$

5. Sodium thiosulphate has an important antidotal application in:

A. Cyanide poisoning

B. Iron deficiency

C. Hyperacidity

D. Constipation

Answer: A. Cyanide poisoning

6. The major detoxification product formed from cyanide through the thiosulphate pathway is:

A. Sulphide

B. Thiocyanate

C. Sulphate

D. Carbonate

Answer: B. Thiocyanate

7. Sodium thiosulphate can be assayed by:

A. Iodometric titration

B. Gravimetric calcium assay

C. Flame photometry only

D. Acid digestion only

Answer: A. Iodometric titration

8. Which category of antidote acts through receptor antagonism or physiological opposition?

A. Physical

B. Chemical

C. Physiological

D. Mechanical

Answer: C. Physiological

9. Removal of contaminated clothing and washing exposed skin represent primarily:

A. Mechanical decontamination

B. Chemical neutralization

C. Receptor antagonism

D. Chelation

Answer: A. Mechanical decontamination

10. Which action is generally NOT recommended after ingestion of a poison?

A. Seeking expert medical advice

B. Identifying the substance

C. Routine induction of vomiting

D. Monitoring the patient

Answer: C. Routine induction of vomiting

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