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Diploma in Pharmacy 1st Year
Pharmaceutical Chemistry
Chapter 2 : Volumetric and Gravimetric Analysis

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PHARMACEUTICAL CHEMISTRY

Chapter 2

Volumetric and Gravimetric Analysis

- The quantitative analytical method is widely used is volumetric analysis
- It is defined as the method involved in measurement of the volume of a solution whose concentration is known
- This method is also applied to determine the concentration of analyte
- Volumetric analysis or titration is defined as the measurement of volume of second substance which combines with the first known concentration

Fundamentals of volumetric analysis

- Titration measures the volume which completes the reaction between the solution and reagent
- The amount of reagent and solution is determined by the volume and concentration of reagent which are used in the titration
- Mole fraction of the equation determines the amount of unknown chemicals in the specific volume of the solution

Procedure for volumetric analysis

- ◆ The solution that needs to be analysed should have a specific weight in the sample of +/- 0.0001g of the material
- ◆ It is important to choose right kind of material which is to be analysed to obtain accurate results
- ◆ Preference should be given to a substance that reacts rapidly and completely to produce a complete solution
- ◆ The titration should be continued until the reaction is completed and the amount of reactant added should be exactly the amount required to complete the reaction
- ◆ A weighed amount of reagent should be taken and dissolve into a solution if the reagent or reactant is to be made into a standard solution so that it is in a definitive volume within a volumetric flask

Acid Base Titration

- ◆ In chemistry, acid – base titration is used for analysis the unknown organic compound concentration of an acid and base
- ◆ The principle of acid-base titration is based on the neutralisation reaction occurring between acid & base
- ◆ Phenolphthalein is the most commonly used indicator for acid-base titration
- ◆ Acid-Base reaction involve transfer of proton,
Example :- Base accept proton from Acid
$$\text{H}^+ + \text{OH}^- \rightarrow \text{H}_2\text{O}$$
- ◆ It is most common Neutralisation reaction
- ◆ At equivalent point, moles of H^+ are equal to the moles of OH^-

- ◆ During titration one reactant (mostly an acid) is added from the burette to the known volume of the other reactant (mostly base) in a conical flask to make the equivalence point (end point) of the titration and indicator is used

Theories

There are 3 theories , explaining the concept of acids and bases

- Arrhenius theory
- Bronsted Lowry theory
- Lewis theory

Theory	Acid	Base
Arrhenius	H ⁺ Producer	OH ⁻ Producer
Bronsted lowry	H ⁺ donar	H ⁺ acceptor
Lewis	Electron pair acceptor	Electron pair donar

Arrhenius Theory

- The most commonly used concept of acids and bases was developed by Savante Arrhenius in 1884 termed as Arrhenius theory
- According to this theory an acid is a substance which dissociates in Aqu. Solution produce hydrogen ion on other hand a base is a substance which dissolve in aqueous solution to produce hydroxyl ion (OH⁻)
- For example
 - HCl is an Arrhenius acid $\text{HCL} \rightarrow \text{H}^+ + \text{Cl}^-$
 - NaOH is an Arrhenius base $\text{NaOH} \rightarrow \text{OH}^- + \text{Na}^+$
- Arrhenius theory was the first scientific theory that had given definition for acid and base as well as classified them It is the simplest theory and is useful in case of aqueous solution

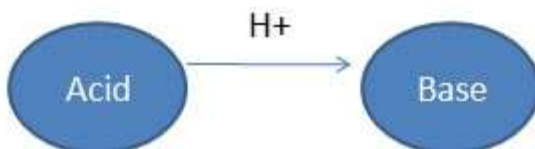
Limitations

- ❖ Acid and base have been defined only in terms of solution and not as a solid substance
- ❖ This theory also failed to explain the neutralisation of acid & base in the absence of solvent
- ❖ There are many basic substance (few organic substance) which do not have oh ions but are basic in nature this fact could not be explained by Arrhenius theory
- ❖ Acidic properties of many salts could not be explained by this theory

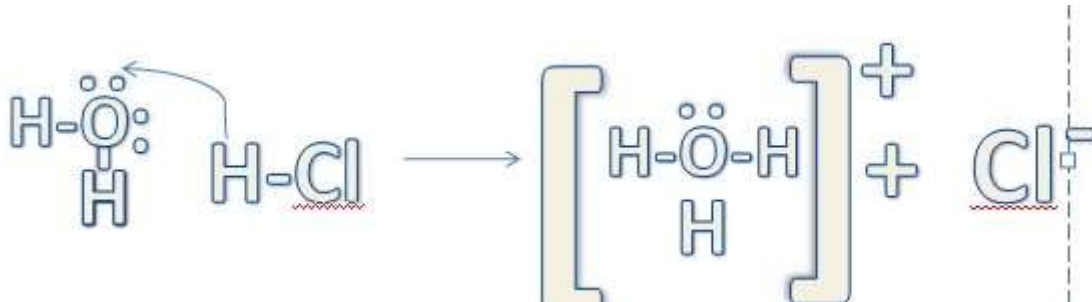
Bronsted Lowry theory

- In 1923 J.N Bronsted and J.M Lowry was introduced a new concept of acid and base
- According to the theory an acid is any mol or ion that can donate a proton (h⁺) and base is any mol or ion that can accept a proton H⁺

An acid is a proton dono:



- A base qualifying Bronsted lowry concept is termed as Bronsted lowry base or Bronsted base
- Where an acid qualifying Bronsted lowry concept is termed as Bronsted lowry acid or Bronsted acid
- **For example :-** On dissolving dry HCl gas in water , each molecule of HCl produces hydronium ion (H₃O⁺) by donating a proton to a water molecule



There fore it can be concluded that water which accept a proton is a bronsted base where HCl gas which donate a proton is a Bronsted.

Advantages

- Much wider scope Bronsted lowry concept of acid and base cover wider range of molecules and ions accepting proton (base) or donating proton (acid)
- Where arrhenius concept of acid & base involve only those substance which release H⁺ or OH⁻ ions in aqueous solution
- Not limited to aqueous solution Arrhenius concept is limited only to aqueous solution Bronsted lowry theory not only covers aqueous sol but also gas phases
- Release of OH⁻ not necessary to qualify as a base Bronsted base is a substance which accept a proton, where Arrhenius base is a substance which release OH⁻ ions in aqueous solution

Limitations

- Bronsted lowry theory of acid & base is based on transfer on proton commonly most of the acids as protonic in nature but some are not
- There are many acid base chemical reaction in which proton transfer not occurs

Lewis Theory of Acids & Bases

- ❑ This method of Acid & Base was given by G.N Lewis in the early 1930
- ❑ He defined Acid is an electron pair acceptor
 - Base is an electron pair donar
- ❑ In this theory the Lewis acid & Lewis base share an electron pair given by base result in the formation of a covalent or coordinate bond between them
- ❑ This resultant compaired bounded with a covalent bond is known as a complex
 - $A + B = A-B$
 - LA LB Complex

According to this concept

- Lewis base are anion or molecule having a lone pair of electron
- Lewis Acid are cation or molecule lacking of electron pair

Advantages

- ★ It included the definition given by both Arrhenius and Bronsted Lowry.
- ★ The Lewis concept explains the acidic & basic nature on the basis of transfer or gain of electron accompanied by loss/donation of electron pair.

Limitations

- ❖ Lewis acid and base can not be arranged in their order of strength as their strength depends on the reaction type
- ❖ Lewis acid and base reactions are explained as expected to be very fast but due to the involvement of electron pair some of these reactions are slow

Neutralisation Curves

- A reaction in which an acid reacts with a base to produce a salt and a neutralised base is known as a neutralisation reaction.

➤ Example

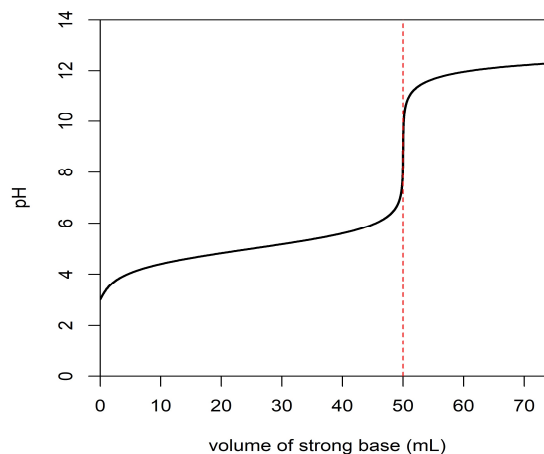
Hydrochloric acid reacts with sodium hydroxide to form sodium chloride & water



- Neutralisation Curve is obtained when pH is plotted against the percentage of acid neutralisation or the no. of millilitres of alkali added
- Neutralisation curve can be plotted between the following variables
 - Weak acid & Strong base
 - Strong acid & Strong base
 - Strong acid & Weak base
 - Weak acid & Weak base

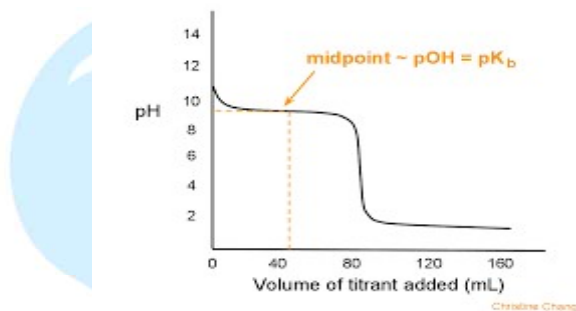
Strong acid & strong base

- ◆ In this titration Strong acid & Strong base are reacted with each other by using a suitable indicator
- ◆ Acid & Base compounds are rapidly broken down into their ions (Cation & Anion) and react with each other and form the salt & Water
- ◆ Initially slow rise in pH
- ◆ Sharp rise in pH due to presence of excess alkali
- ◆ Attain the neutral point $\text{pH}=7$



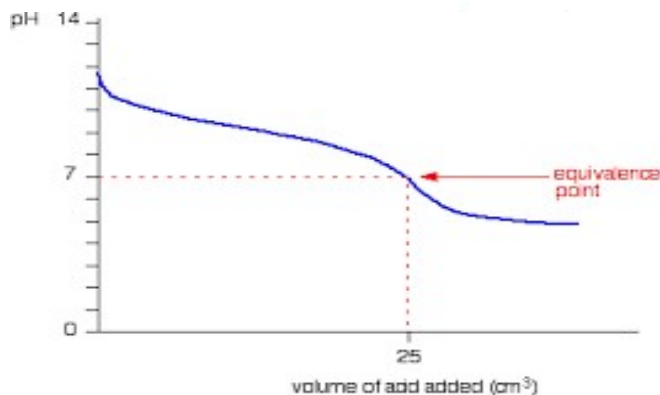
Weak Acid & Strong Base

- ★ In this Titration Method weak acid is treated with the strong base by using the suitable indicator to detect the end point
- ★ During the procedure weak acid are dissociated slowly in its compounds & strong base are dissociates rapidly in its compounds
- ★ Initially the PH normally & where reaction processes the curve will not raise much This point is said to be half neutralisation point
- ★ Sharp rise in PH due to present of excess strong alkali



Weak Acid & Weak base

- In this titration method weak acid * weak base treated with each other by using the suitable indicator
- The chief feature of the curve is that change of PH near equivalence point and during whole neutralisation is very gradual
- Hence the end point cannot be detected by ordinary indicator
- For detection of this titration mixed indicator are used .



Strong acid and Weak base

- In this Titration Method weak base is treated with the strong acid by using the suitable indicator to detect the end point
- During the procedure weak base are dissociated slowly in its compounds & strong acid are dissociates rapidly in its compounds
- Initially the PH normally & where reaction processes the curve will not raise much This point is said to be half neutralisation point
- Sharp rise in PH due to present of excess strong alkali

Acid Base Indicators

- Acid Base indicator (weak organic acid or base) having different colours depending up on the concentration of H^+ ions in the solution are available
- These indicator exhibit a colour change from an acidic colour to an alkaline colour although this colour change does not occurs suddenly or rapidly but take place with in a small PH range usually 2 PH unit which is indicator range
- The position of the colour change on the PH scale is different for different indicators
- The acid base indicators are also known as visual indicator
- Example p-nitrophenol is a weak acid that undergoes dissociation
- Phenolphthaline :- (most popular indicator) is a colourless & diprotic acid when it loses the first proton it gives a colourless solution but when loses another proton it produces a red colour by foeming an anion with the conjugated system

Application

- **Determiration of Aspirin** :- Sample is dissolved in ethanol acid 2-3 drops of phenolphthalein is added as an indicator
- The resulting solution is treated with standard NaOH solution until pink colour is obtained
- **Determiration of Amino Acids** :- Sample is added into 25ml of distilled water & small amount of HCl are added to maintain the PH up to 1.5
- The solution is titrated with standard NaOH solution using phenolphthalein as an indicator
- The procedure is continued until the PH reaches to 12

Non – Aqueous titration

- Titration involving very weak acid or base with the help of non-aqueous solvents to obtain sharp end point are non-aqueous titration.

Principle

- ★ Organic acids & bases are water insoluable very weak & cannot be analysed via conventional titration method thus non-aqueous titration is used which relies on the principle that non-aqueous solvents are used to dissolve the sample.

Non-Aqueous Solvents

- The nature of solvent is a deciding factor for the behaviour of acid & base. Any solute when dissolved in any given solvent with exhibit acidic or alkaline behaviour
- The Non-aqueous solvents have a characteristic role in non-aqueous titration
 1. The solvent should be non-toxic for its wide use in analysis
 2. It should is liquid at he time of analysis
- These organic solvent are used but it is mainly depents on their properties such as capability of self dissociation dielectric constant & acid base character of solvent

The non-aqueous solvents are classified into

➤ Aprotic solvent :

- These solvents are considered chemical neutral or inert under specific condition

- Eg toluene & carbon tetrachloride
- These solvents have low dielectric constant which restrict the ionisation of solute and there is no reaction between their solvent & acids and bases
- The Aprotic solvents are widely used as diluting agent for the reaction mixture

Protophilic solvents :- Solvents which have greater tendency to accept proton
Eg : Water, Alcohol

Protogenic solvents :- These solvents possess acidic character & have high affinity for donating protons
Eg : Alcohol , Organic acid

Amphiprotic solvents :- In these solvents have the ability to donate as well as accept proton because they contain both protogenic & protophilic properties.
Eg : Water , Alcohol , & Organic acid (weak)

Frequently used non-aqueous solvents

- ★ For the determination of non-aqueous titration there are several solvents available (either organic or inorganic) but only few of them are employed for the purpose
- ★ The solvent used must be pure, Dry, & best analytical qualities to ensure precise and sharp end point
- ★ Alcohols : The organic salts of fatty acid can be determined with the help of glycol & alcohol mixture or glycol & hydrocarbon mixture
- ★ Dimethylformamide : DMF is an excellent example of protophilic solvent & is used for the titration of benzoic acid & amide
- ★ Glacial Acetic Acid : Acetonitrile , Rioxane etc

Advantages of non-aqueous solvents

- ✓ The acids & bases of organic origin are easily soluble in non-aqueous solvent
- ✓ Non-aqueous solvent can dissolve two or more acids present in a mixture
- ✓ With the help of a suitable solvent or indicator the selective titration of biological ingredients present in a substance can be done whether it is acidic or basic
- ✓ Titration involving non-aqueous are comparatively simple & more accurate than aqueous titration

Indicators in Non-Aqueous Solvents

- A very narrow range of indicators are present which are employed in non-aqueous titration
- Methyl Red : A 0.2 % W/V solution of Methyl Red is prepared using dioxane. The end point is marked by a change in colour from yellow to red
- Naphthol Benzene :- Naphthol Benzene is used as a solution of 0.2 % W/V in acetic acid. It gives a sharp end point by changing its colour from yellow to green
- Thymol Blue : It is a widely used indicator especially for the substance behaves as acids in solution of DMF
- 0.2 % W/V solution is prepared using methyl alcohol & the end point detected by change in colour from yellow to blue

Application

The application of Non-Aqueous titration are

- Percentage of purity is determined by the assays
- Determination of Hydrophobic compounds
- Determination of the steroids
- Determination of Anti Tubercular drugs
- Determination of phenobarbitone

Precipitation titration

- Precipitation titration is a type of titration which involves the formation of precipitate during the titration techniques
- In precipitation titration the titrant reacts with analytic and forms an insoluble substance called precipitate
- For example AgNO_3 is used as a precipitating agent for the determination of Cl^-

Principle

- Formation of an insoluble product by the combination of two ionic species is known as precipitation.
- Precipitation reaction are not frequently used in titration because of the precipitation reaction do not comply with desired specification.

Indicators used in precipitation

- The end point in precipitation titration can be marked using a reagent known as indicator
- **Adsorption indicators**
- Adsorption indicators are substance that indicates an excess of a reactant in argentometric titration
 - Precipitation becomes coloured when adsorption indicators is adsorbed
 - Eg sodium salt of fluorescein
 - Sodium fluor can be used as an indicator in the titration of chloride with AgNO_3 solution in a neutral or slightly basic medium

Precipitation titration method

- ◆ The precipitation titration silver nitrate with chloride, bromide, iodide, and thiocyanate are most widely used
- ◆ These precipitation titration are also known as Argentometric titration
- ◆ Since silver is always involved during the reaction there fore concluding that there titration have limited use

There procedure are follow in precipitation titration

- I. Mohr s method
- II. Volhard s method
- III. Modified volhard s method
- IV. Farjan s method

Mohr' s method

- This method is named after Karl friedrich Mohr.
- In this method potassium chromate is used as an indicator which produces Red coloured silver chromate at the end point when all the chloride ions have reached.
- In mohrs method the end point is detected when a coloured precipitate of chloride or bromide is formed.
- A neutral sol of chloride ions is titrated with silver nitrate solution using a small quantity of potassium chromate solution as an indicator.
- The chromate ions combine with silver ions at the end point, forming a red coloured and sparingly soluble silver chromate.

Volhard s method

- This method is named after Jacob Volhard
- In this method a soluble coloured compound forms at the end point
- Thiocyanate is used to titrate silver ions in an acidic solution using ferric ions as an indicator
- In which an excess of a standard solution of silver nitrate is added to a chloride containing sample solution. The excess silver is then back titrated using a standardized Sol of potato or ammonium thiocyanate with ferric ions as an indicator

Modified volhard s method I.P 1985

- ❑ The principle of assay by volhard s method is based on indirect volumetric precipitation titration
- ❑ In this method nitric acid solution is used to acidify NaCl solution and then in the presence of nitrobenzene, this solution is treated with measured excess amount of standard solution of silver nitrate
- ❑ Some moles of silver nitrate are consumed in the reaction with NaCl and the remaining unreacted silver nitrate is determined by titration with a standard solution of ammonium thiocyanate. In this titration solution of ferric ammonium sulphate ferric alum is used as an indicator

Farjan s method

- This method named after kazimierz fajan
- Dichlorofluorescein uses as an indicator and the end point is observed when the green colour suspension turns pink
- Fajan s method involves the titration of chloride ions with silver ions using adsorption indicators
- These indicator are basically dyes that adsorb or desorb on the surface of the precipitate at the equivalence point and produces the colour change
- The indicator are acid dyes, fluorescein, etc
- Basic dyes rhodamine service

Application of precipitation titration

- Precipitation reaction are applicable in removal of salts from water during water treatment in qualitative inorganic analysis and also in manufacturing of pigments
- Products of any reaction can also be isolated during work up by the precipitation reaction
- Precipitation reaction are also used in metallurgy

Complexometric titration

- Complexometric titration chelatometry is a form of volumetric analysis in which the formation of a coloured complex is used to indicate the end point of a titration
- Cl- are particularly useful for the determination of a mixture of different metal ions in solution

Principle

- In complexometric titration the metal ions are titrated with a complexing or a chelating agent
- This method is an analytical application of a complexation reaction
- This method involves transforming simple ion into a complex ions and determining the equivalence point using metal indicator electrometrically
- This method is also termed as chelometric titration, chelometry titration, chelometric titration and EDTA titration Ethylene Diamine Tetra Acetic Acid

Theory

- Complexometric titration involves the disappearance of the free metal ions as they are changed into complexa
- In any complexation reaction can be used as a volumetric techniques provided
- The reaction reaches equilibrium rapidly after each portion of titrant is added
- A complete titration indicator capable of locating equivalence point with fair accuracy is available

Classification

Complexometric titration following the four types

- **Direct titration** : This method is similar to acid base titration and involve adding the standard solution and chelon solution to the metal ion solution till the end point is attrived
- **Back titration** : In this method excess of standard EDTA solution is added to the metal solution and the excess is back titration with a standard solution of a second metal ion
- **Replacement titration** : In this method the metal to be analysed quantitatively displaces the metal from the Complex.
- **Indirect titration** : This is also known as alkalimetric titration. It is used for determination of anion which do not react with EDTA chelate protons from disodium EDTA are displaced by a heavy metal and titrated with sodium alkali

Application of complexometric titration

- Determination of permanent and temporary hardness of water separately
- Determination of total hardness of water
- Determination of magnesium and silicon dioxide in magnesium trisilicate
- Determination of calcium and lead in a mixture
- Determination of chromium III and Iron III in mixture kinetic masking
- Determination of manganese in the presence of Ironferromanganese
- Determination of lead and tin in a mixture
- Determination of phosphates

Redox Titration

- In titration the redox/ oxidation- reduction reaction are more extensively used for analysis as compared to the precipitation reaction and acid base reaction
- Reduction is defined as the gain of one or more electron by atomic species or molecules
- Oxidation is loss of one or more electron by the atomic species or molecules oxidation is also known as de electronation
- A titration which deals with a reaction involving oxidation and reduction of certain chemicals species are known as redox Titration

Agents

- ★ **Reducing agent** : Sodium thiosulphate, ferrous sulphate, titanous sulphate, oxalic acid are some of the reducing agents.
- ★ **Oxidising agents**: Potassium dichromate, potassium bromate etc are some of the oxidising agents.

Types of Redox Titration

Based on the method

- **Direct titration** : In this method initially coloured substance are used Thus end point detection does not require an indicator
- **Back titration** : In this method the sample solution is titrated with excess volume of titrant solution

Redox indicator

- Compounds used in the redox titration and having different colours in the reduced and oxidised conditions are called redox indicator.

Types

Based on the Addition of the indicator

- **Self indicator** : These indicator are the titrant itself which develops an intense colour on reaching the end Point.
- **Internal indicator** : These indicator are incorporated into the reaction mixture during the titration.

- **External indicator** : These indicator are introduced externally through a grooved title and mixed with the solution of the indicator.

Selection of indicator

- In an ideal indicator the colour change is observed near or at the equivalence point.
- For reversible and fast colour change the oxidation- reduction equilibrium for an indicator redox system needs to be established very fast.
- If the titration is feasible These could be a large change in potential at the end point that should be sufficient to bring about a change in colour of the indicator.
- Example Diphenylamine , ferroin etc

Application of Redox Titration

- Determination of phenol
- Determination of the presence of Iron in limonite
- Determination of calcium in lime stone
- Analysis of Isoniazid
- Analysis of tocophenol

Gravimetric Analysis

- A quantitative analysis involving weight is known as gravimetric Analysis
- In which the substance to be analysed is covered into an insoluble precipitate
- This precipitate is collected, weighted using suitable method
- Precipitation is the most suitable technique which employs formulation of a precipitate not soluble in the solution

Examples

Analyte	Precipitant
Piperazine adopted tablets BP	picric acid
Piperazine phosphate BP	picric acid

Principle

- Law of mass action and reversible reaction
- Principle of solubility product
- Common ion effect

Law of mass action and reversible reaction

- ⇒ According to the law of mass action the rate of reaction is directly proportional to the product molecular concentration of the reacting substance

Principle of solubility product

- The solubility product expression for a compound is the product of the concentration of its constituent ions each raised to the power that corresponds to the number of ions in one formula unit of the compound
- The quantity is constant at constant temperature for a saturated solution of the compound
- The statement is the solubility product principle
- A slightly soluble Salt is decreased if excess of either of its ions are added

Common ion effect

→ The electron to the decrease in solubility of an ionic precipitation by the addition to the solution of a soluble compound with an ion in common with the precipitate

Types of Gravimetric Analysis

Physical Gravimetric : It is the commonest of all the types and is used in environment engineering. Environmental sample carry matter that is physically seperated and categorised on the basis of volatility and particle size.

Thermogravimetric : In this technique a substance is kept at a controlled temperature system and its mass is measured with respect to temperature This Techniques is used extensively in many discipline like pharmacy, food, polymer science, glasses, volatile solids.

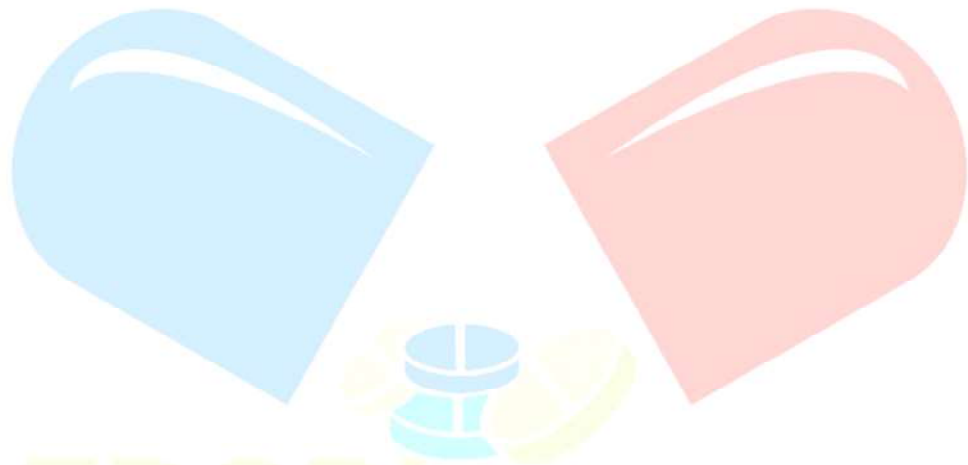
Electro deposition : In this technique the electrochemical reduction and simultaneous deposition of metal ions occur at cathod before starting the electrolysis and after the process ends the cathod is weighted

Difference in the weight corresponds to the mass of analyte that was initially present in the sample This technique is applicable to environmental engineering analysis

Precipitative Gravimetry : This Techniques causes chemical precipitation of an analyte Precipitation method attract the concern of analyst working with gravimetric Analysis . In a gravimetric method precipitative is the major chemical reaction as it could be a highly selective means for separating the desired component from the metrix

Application

- Analysis of standard This is required during testing or instrument calibra ion.
- Analysis Requiring Accuracy This analysis can be conduct using gravimetry Which being time consuming allows only a few determination Pharmacopoeial analysis.
- Lead as chromate This method has less application due to insolubility of chromates.
- However This method helps in gaining experience in gravimetric Analysis.
- The best result are obtained by precipitating from homogeneous solution using the homogeneous generation of chromate ions produced by slow oxidation of chromium III by bromate at 90- 950 in the presence of an ethanoate buffer.



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