# Pharmaceutical Analysis Unit 3 :
# An Ebook on Titrimetric and Gravimetric Methods

## Unit 3 (a) Precipitation Titrations

### Introduction to Precipitation Titrations

Precipitation titrations are a type of volumetric analysis where the reaction between the analyte and the titrant forms a **practically insoluble ionic solid**, known as a precipitate, in an aqueous solution. This formation occurs through the combination of cations and anions.

While many ionic compounds can be mixed, not all reactions in aqueous solutions will necessarily produce a precipitate. Several factors influence whether a precipitate forms, including **temperature** and **solution concentration**.

In a solid state, solute molecules are held together by **intermolecular forces of attraction** and are arranged in a fixed repeating pattern, forming a crystal. When a solid dissolves, these attractive forces are overcome by the interaction between the solvent and the solute, known as **solvent-solute attraction**.

A classic example of a precipitation reaction used in titrimetric analysis is the reaction between potassium chloride (KCl) and silver nitrate ($AgNO_3$), which produces silver chloride (AgCl) as a precipitate and potassium nitrate ($KNO_3$) in solution: $KCl + AgNO_3 \rightarrow AgCl$ (Precipitate) $+ KNO_3$

For a precipitation reaction to be useful in titrimetric analysis, certain requirements must be met:

- The precipitate formed should be **practically insoluble**, meaning it has a very low solubility in the solvent.
- The precipitation reaction must be **rapid and quantitative**, ensuring that the reaction goes to completion quickly and with a high yield.
- The titration results should **not be negatively affected by adsorption effects**, also known as co-precipitation, where impurities get trapped within or on the surface of the precipitate.
- It must be possible to **accurately detect the equivalence point** during the titration, which is the point where the amount of titrant added is chemically equivalent to the amount of analyte in the sample.

### Solubility Products

The concept of solubility products is fundamental to understanding precipitation reactions. When a solid dissolves in a solvent, the solvent molecules must be able to interact with the solid's crystal forces and

overcome them. This interaction is often strongest when the solvent environment is chemically similar to the crystal structure, leading to the general rule that "**like dissolves like**." This means that solute-solute attraction is overcome by solute-solvent attraction.

Conversely, during a precipitation reaction, the opposite condition is sought: the intermolecular forces between the product molecules become high, and solute-solute forces dominate, replacing the solute-solvent forces.

Consider an aqueous solution of a slightly soluble salt, BA, in equilibrium with its excess solid at a constant temperature: $BA(S) \rightleftharpoons B^+ + A^-$ Here, BA(S) represents the solid at a constant temperature.

In a dilute aqueous solution, essentially no un-dissociated BA molecules will be present. The equilibrium constant for this dissolution process is called the **solubility product (Ksp)**, and it is expressed as the product of the concentrations of the ions in solution: $Ksp = [B^+][A^-]$

The solubility product is crucial because it allows for the calculation of one ion's concentration if the other is known. A substance will precipitate out of solution when the **product of the ionic concentrations exceeds the Ksp value**. If $[B^+][A^-] > Ksp$, precipitation will occur until the ion product equals Ksp.

**Effect of Solubility on Precipitate**

The solubility of a precipitate can be influenced by several factors:

- **Effect of Acid (pH):** For salts whose anion is the conjugate base of a weak acid, such as carbonates or oxalates, the solubility of the salt generally **increases with decreasing pH (or increasing acidity)**. This is because the hydrogen ions from the acid react with the anion, shifting the dissolution equilibrium towards more dissolution and thus increasing solubility.
- **Effect of Temperature:** The solubility of most inorganic salts **increases as the temperature of the solution is elevated**. This is because increased temperature provides more kinetic energy to the molecules, helping to overcome the lattice energy of the solid. This property is often used in precipitation processes to dissolve impurities more readily and speed up filtration. However, for some substances, the influence of temperature on solubility is minimal. In some cases, like with fairly soluble compounds such as magnesium ammonium phosphate, the solution might need to be **cooled in ice water before filtration** to prevent the loss of precipitate into the filtrate due to increased solubility at higher temperatures.
- **Effect of Solvent:** Water, being a highly polar solvent with a large dipole moment, effectively attracts both cations and anions to form hydrated ions, making most inorganic salts more soluble in water. However, the solubility of many inorganic compounds can be **reduced by adding organic solvents** like methyl, ethyl, and n-propyl alcohols. These organic solvents often reduce

the dielectric constant of the solution, which weakens the electrostatic interactions between the ions and the solvent, promoting precipitation.

**Mohr's Method**

Mohr's method is a **direct precipitation titration** used for the quantitative determination of chloride ($Cl^-$) and bromide ($Br^-$) ions. It is distinctive because the end point is detected by the formation of a **colored precipitate**.

In this method, **silver nitrate ($AgNO_3$)** is used as the titrant. Since silver nitrate is a secondary standard, it must be **standardized against a primary standard solution of sodium chloride (NaCl)** beforehand.

The primary reaction involves silver ions ($Ag^+$) reacting with chloride ions ($Cl^-$) to form a white precipitate of silver chloride (AgCl): $AgNO_3 + NaCl \rightarrow AgCl$ (white precipitate) + $NaNO_3$

**Indicator:** A **5% potassium chromate ($K_2CrO_4$)** solution is used as the indicator. At the end point, after all chloride ions have reacted with silver ions, the first excess drop of silver ions reacts with the chromate indicator to form a **reddish-brown precipitate of silver chromate ($Ag_2CrO_4$)**. This color change signals the end of the titration. $2AgNO_3 + K_2CrO_4 \rightarrow Ag_2CrO_4$ (reddish-brown precipitate) + $2KNO_3$

Mohr's method is widely used for the quantitative determination of salts like NaCl, KCl, KBr, etc. The titration is typically carried out in a **neutral pH range, specifically between 6.5 and 10.3**.

During the titration of, for example, 0.1 N NaCl with 0.1 N $AgNO_3$ using potassium chromate as an indicator, silver chloride (AgCl) precipitates first because it has a smaller solubility product ($K_{sp}(AgCl) = 1.8 \times 10^{-10}$) compared to silver chromate ($K_{sp}(Ag_2CrO_4) = 1.2 \times 10^{-12}$). This means AgCl is less soluble and precipitates before $Ag_2CrO_4$. At the equivalence point, nearly all chloride ions have reacted. Any additional drop of $AgNO_3$ then reacts with the chromate ions to form the reddish-brown $Ag_2CrO_4$, indicating the end point.

**Restrictions on Usage of Mohr's Method:** Mohr's method has certain limitations:

- It **cannot be used in basic solutions** because silver hydroxide (AgOH) would precipitate, interfering with the titration.
- It is **not suitable in the presence of ammonia ions** due to the formation of soluble silver-ammonia complexes (ligand formation), which would prevent AgCl precipitation.
- It **cannot be used in the presence of reducers**, as these would reduce chromate ($CrO_4^{2-}$) ions to chromic ($Cr^{3+}$) ions, destroying the indicator's effectiveness.
- It is **not applicable in the presence of many other anions** such as phosphate ($PO_4^{3-}$), sulfide ($S^{2-}$), or arsenate ($AsO_4^{3-}$), which can form painted precipitates of silver ions, masking the end point.

**Volhard's Method**

Volhard's method is a **back titration method** based on the formation of a colored complex at the end point. It is particularly useful for the determination of silver ions, or for halides (chlorides, bromides, iodides), cyanides, thiocyanates, and arsenates, among others, when a direct method is not feasible. The titration is carried out in an **acidic solution** to prevent the precipitation of iron hydroxides, especially when using a ferric ion indicator.

In this method, **silver ion is titrated with thiocyanate** using a ferric ion ($Fe^{3+}$) as an indicator. The end point is marked by the formation of a **brick-red or reddish-brown colored complex**.

The reagents commonly used include **silver nitrate ($AgNO_3$)** as a titrant (standardized against primary standard sodium chloride, NaCl) and **ammonium thiocyanate ($NH_4SCN$) or potassium thiocyanate (KSCN)** as the back-titrant. Iron alum (ammonium ferric sulfate or ferric ammonium sulphate, $NH_4Fe(SO_4)_2 \cdot 12H_2O$) is typically used as the indicator.

The method is typically carried out in four main steps:

**Step 1: Standardization of Silver Nitrate ($AgNO_3$)** First, the silver nitrate solution is standardized, often against potassium chloride (KCl) or sodium chloride (NaCl). $AgNO_3 + KCl \rightarrow AgCl + KNO_3$

**Step 2: Addition of Standardized $AgNO_3$ (in excess) to the Sample for Back Titration** An accurately known excess amount of standardized silver nitrate solution is added to the sample containing the analyte (e.g., chloride ions). The analyte reacts completely with the silver ions to form a precipitate. $AgNO_3$ (excess) + $NaCl \rightarrow AgCl$ (precipitate) + $NaNO_3$ + $AgNO_3$ (remaining excess)

**Step 3: Titration of Remaining Amount of $AgNO_3$** The unreacted, excess silver nitrate is then back-titrated with a standard solution of thiocyanate (KSCN or $NH_4SCN$). $AgNO_3 + NH_4SCN \rightarrow AgSCN$ (precipitate) + $NH_4NO_3$ $AgNO_3 + KSCN \rightarrow AgSCN$ (precipitate) + $KNO_3$

**Step 4: Reaction with Indicator at the End Point** Once all the excess silver ions have reacted with thiocyanate, the next drop of thiocyanate solution reacts with the **ferric ion indicator** ($Fe^{3+}$) to form a distinctive **reddish-colored complex, ferric thiocyanate ($Fe(SCN)^{2+}$)**. This color change signals the end point. $Fe^{3+} + SCN^- \rightarrow Fe(SCN)^{2+}$ (reddish colored complex)

**Indicator:** Iron (III) salt, such as ferric ammonium sulphate, is used as an indicator. The titration is performed in the presence of **nitric acid** to prevent the precipitation of iron hydroxides, $Fe(OH)_3$, which would interfere with the indicator.

Volhard's method can determine halides, thiocyanides, cyanides, sulphides, carbonates, chromates, oxalates, and arsenates.

**Modified Volhard's Method:** When determining chloride ions using Volhard's method, the silver chloride precipitate formed can be slightly soluble in the solution, especially in the presence of excess thiocyanate, potentially leading to errors. To prevent the solubility of AgCl, **chloroform or other wetting agents** are added after the addition of excess silver nitrate. This creates a protective layer around the AgCl precipitate, preventing it from dissolving and ensuring a sharper end point.

**Fajan's Method**

Fajan's method is another type of precipitation titration that utilizes **adsorption indicators**. Professor K. Fajan proposed this method based on his studies of the nature of adsorption.

**Adsorption indicators** are organic dyes that adsorb onto the surface of the precipitate at the equivalence point, and this adsorption is accompanied by a distinct **color change**. These indicators are typically **acidic or basic organic dyes**. Examples of acid dyes include Fluorescein and Eosin. Examples of basic dyes include Rhodamine series.

In Fajan's method, **silver nitrate ($AgNO_3$)** is used as a secondary standard solution and is standardized against a primary standard solution of **sodium chloride (NaCl)**. The optimal **pH range** for the titration varies depending on the analyte and indicator: it is typically **6.5-10.3 for chlorides** and **2.0-10.3 for bromides and iodides**.

**Indicators for Fajan's Method:**

- **Dichlorofluorescein** is commonly used for chloride titrations.
- **Eosine** is used for bromide and iodide titrations.

**Mechanism of Indicator Action:** The principle relies on the property of a **colloidal precipitate** to adsorb its own ions which are in excess. Consider the titration of an NaCl solution with $AgNO_3$:

1. **Before the equivalence point:** Chloride ions ($Cl^-$) are in excess. The silver chloride (AgCl) precipitate preferentially adsorbs $Cl^-$ ions, forming a **primary adsorbed layer of negatively charged chloride ions**. This layer then attracts and holds a secondary adsorbed layer of oppositely charged sodium ions ($Na^+$) from the solution.
2. **At the equivalence point:** As $Ag^+$ ions become in excess (just after the equivalence point), the AgCl precipitate now adsorbs $Ag^+$ ions as its **primary adsorbed layer**. This primary layer attracts and holds a secondary adsorbed layer of negatively charged ions. If an adsorption indicator like fluorescein (which is present as the negatively charged fluorescein ion, $Na^+F^-$) is in the solution, it will be adsorbed onto the positively charged surface of the precipitate instead of nitrate ions ($NO_3^-$). This adsorption of fluorescein ions onto the $Ag^+$-coated precipitate leads to a change in the electron cloud of the dye molecule, resulting in the formation of a **pink-colored complex with $Ag^+$**, signaling the end point.

**Estimation of Sodium Chloride**

The estimation of sodium chloride (NaCl) is a practical application of precipitation titrations, often performed using Mohr's method.

**Aim:** To carry out the assay (quantitative determination) of a given sample of sodium chloride.

**Requirements:**

- **Reagents:** Silver nitrate ($AgNO_3$), sodium chloride (NaCl), potassium chromate ($K_2CrO_4$) solution, distilled water, concentrated hydrochloric acid, concentrated sulfuric acid.
- **Apparatus:** Burette, pipette, volumetric flask, conical flask, beaker, funnels, watch glass, analytical balance, muffle furnace, desiccator.

**Principle:** The assay of sodium chloride solution is carried out by **standard silver nitrate solution**, and the method is based on the principle of precipitation. Specifically, it involves the formation of a silver chloride precipitate. $AgNO_3 + NaCl \rightarrow AgCl$ (precipitate) $+ NaNO_3$

**Indicator: 5% potassium chromate ($K_2CrO_4$)** solution is used as the indicator. It forms a reddish-brown precipitate of silver chromate ($Ag_2CrO_4$) at the end point. $2AgNO_3 + K_2CrO_4 \rightarrow Ag_2CrO_4$ (reddish-brown precipitate) $+ 2KNO_3$

**Preparation of Reagents:**

- **0.1 N Silver Nitrate ($AgNO_3$):** Accurately weigh **16.989 g of $AgNO_3$** on a watch glass and transfer it to a 1000 ml volumetric flask. Add freshly prepared distilled water and dissolve the silver nitrate, then make up the final volume to 1000 ml.
- **0.1 N Sodium Chloride (NaCl):** Accurately weigh **5.844 g of NaCl** and transfer it to a 1000 ml volumetric flask. Add freshly prepared distilled water and dissolve the sodium chloride, then make up the final volume to 1000 ml.
- **5% Potassium Chromate ($K_2CrO_4$):** Accurately weigh and dissolve **5.0 g of $K_2CrO_4$** in 20 ml of distilled water and make up the final volume to 100 ml.

**Experiment (Standardization of $AgNO_3$ or Direct Estimation):**

1. Take **10 ml of 0.1 N NaCl solution** into a conical flask.
2. Add **1 ml of potassium chromate indicator solution** to the flask.
3. Titrate the above solution against the **silver nitrate solution** from the burette.
4. Continuously swirl the flask until a **brick-red colored precipitate** is formed, which persists upon swirling. This is the end point.
5. **Repeat the experiment** three or more times until two consecutive results are precise and agree closely. Record the volume of silver nitrate consumed.

For actual purity determination, weigh a precise amount of the sodium chloride sample (e.g., 0.25 g of silver chloride, although this appears to be a typo and should refer to the sodium chloride sample) and dissolve it in 50 ml of water, add 1 ml of potassium chromate indicator solution, and titrate against standardized silver nitrate solution.

**Observation Table:** Record the start point, end point, and volume consumed for each trial.

| SN | Start Point (ml) | End Point (ml) | Volume Consumed (ml) |
|---|---|---|---|
| 1 | | | |
| 2 | | | |
| 3 | | | |
| 4 | | | |

**Calculation:** The normality of the silver nitrate solution ($N_2$) or the percentage purity of the NaCl sample can be calculated using the formula: $N_1V_1 = N_2V_2$ Where:

- $N_1$ = Normality of Sodium Chloride (e.g., 0.1 N)
- $V_1$ = Volume of Sodium Chloride (e.g., 10 ml)
- $N_2$ = Normality of Silver (or $AgNO_3$), which is 'x' N
- $V_2$ = Volume of Silver Nitrate Consumed, which is 'y' ml

To calculate the percentage purity of NaCl: Molecular weight of NaCl = 58.45 0.1 N NaCl = 5.845 g per 100 ml So, 1 ml of 0.1 N NaCl = 0.005845 g of NaCl Each ml of 0.1 N $AgNO_3$ is equivalent to 0.005845 g of NaCl.

**% Purity of NaCl = (Volume of $AgNO_3$ x Actual Normality of $AgNO_3$ x 0.05845 x 100) / (Weight of NaCl x 0.1 (Expected normality of $AgNO_3$))**

**Result:** The percentage purity of the given sample of sodium chloride will be calculated and reported as x%.

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## Unit 3(b) Complexometric Titration

### Principle of Complexometric Titration

Complexometric titration is a type of **volumetric analysis** that involves the formation of a **soluble, colored complex** between a metal ion (analyte) and a complexing agent (titrant). It is also widely known as **chelatometric titration** because the complexing agents often form chelate complexes.

The **end point** in complexometric titrations is typically detected by a **change in the color of the solution** due to the complexometric reactions. This color change is usually sharp and distinct.

Beyond visual color change indicators, other instrumental methods can also be used to determine the end point in these titrations, such as:

- **Spectrophotometry:** Measuring changes in light absorption.
- **Amperometry:** Measuring changes in current.
- **Potentiometry:** Measuring changes in electrode potential.
- **High-frequency titrators:** Detecting changes in the electrical conductivity of the solution.

Complexometric methods are particularly useful for the **determination of metal ions** in solutions, especially in mixtures of metal ions. The presence of a suitable indicator is crucial, as it shows a distinguished color change at the equivalence point of the titration.

**Complexing Agents**

Complexing agents are molecules or ions that can form stable complexes with metal ions. The most common and important complexing agent in complexometric titrations is EDTA.

- **EDTA (Ethylene Diamine Tetra Acetic Acid):** EDTA is a highly versatile complexing agent. Its structure contains **four carboxylic acid groups** and **two amine groups**. These groups act as **donors of electron pairs**, which means they have lone pairs of electrons that can be donated to metal ions to form coordinate covalent bonds. EDTA is a **hexadentate ligand**, meaning it can donate six lone pairs of electrons to a single metal ion, forming a very stable, cage-like structure called a chelate. In practical applications, EDTA is generally used as its disodium salt (Disodium salt of EDTA) because it is more soluble in water than the free acid. It is commonly used to determine cationic metals in solutions.

- **DTPA (Diethylene tri-amine penta acetic acid):** Also known as Pentetic acid, DTPA is an **amino-polycarboxylic acid** with a diethylene-triamine backbone and **five carboxylic groups**. DTPA is considered an extended version of EDTA, possessing an extra carboxylic group and an additional amino group. Its affinity for cationic metals is notably high. DTPA is a potentially **octadentate ligand**, meaning it can form up to eight coordinate bonds by utilizing its three nitrogen centers and five $COO^-$ groups.

- **Ammonia ($NH_3$):** Ammonia, with a molecular weight of 17, is also used as a complexing agent. It is a **monodentate ligand**, meaning it donates one lone pair of electrons (from the nitrogen atom) to a metal ion. For example, ammonia forms complexes with copper ions.

- **EGTA (Ethylene glycol-bis [amino ethyl ether] tetra acetic acid):** EGTA is another amino polycarboxylic acid that acts as a complexing agent. It exhibits a **lower affinity for complexation with magnesium** compared to EDTA, but it is **more selective for calcium ions**. This selectivity makes it useful in specific analyses where calcium needs to be determined in the presence of magnesium.

- **Ethylene Diamine:** Ethylene diamine is a chelating agent that also forms chelate complexes, for example, with copper ions. It is a bidentate ligand, meaning it can form two coordinate bonds with a metal ion.

**Masking and Demasking Reagents**

In complexometric titrations, especially when dealing with mixtures of metal ions, it is often necessary to prevent certain ions from reacting with the complexing agent or interfering with the indicator. This is where masking and demasking reagents come into play.

**Masking Agents:** A masking agent is an auxiliary chelating or complexing agent that forms a **stable, non-reactive complex** with an interfering metal ion, effectively "masking" it. This prevents the interfering ion from reacting with the titrant (e.g., EDTA) or the indicator, allowing for the selective determination of other metal ions in the same solution. Masking can be achieved in several ways:

- By selecting a **suitable pH** at which only the target metal forms a complex, while others do not.
- By using a **specific masking agent** that selectively complexes with the interfering ion.

The complex formed between the masking agent and the metal should be **more stable than the complex that would form with the titrant** under the given conditions. Examples of masking agents and the metals they react with:

- **Triethanolamine:** Masks aluminium and iron.
- **Thioglycerol:** Masks copper.
- **Potassium cyanide:** Masks heavy metals like cadmium (Cd), zinc (Zn), mercury (Hg(II)), copper (Cu), cobalt (Co), nickel (Ni), silver (Ag), and platinum (Pt). However, it does not mask alkaline earth metals (like Mg, Ca) or manganese and lead. Masking is an equilibrium process and can often be reversed.
- **Ammonium fluoride:** Masks iron and aluminium.

**Demasking Agents:** Demasking agents are used to **break the stable complex** formed between a metal ion and a masking agent, thereby releasing the masked metal ion. This allows the metal ion to then be determined by titration. Examples of demasking agents:

1. **Methanol-acetic acid complex:** This complex is used to **demask the cyanide complexes of zinc and cadmium**. A ratio of 3:1 methanol to acetic acid is recommended.
2. **Solvent extraction method:** This can be used for the separation of zinc from a mixture of lead and copper. Adding **ammonium thiocyanate solution** to the mixture solution forms zinc thiocyanate, which can then be extracted into an organic solvent, effectively demasking and separating zinc.
3. **Formaldehyde:** Formaldehyde is used to **demask the cyanide complexes of cadmium and zinc**. After demasking, the released metal ions can be determined by titrating with EDTA.
4. **Chloral hydrate:** Similar to formaldehyde, chloral hydrate is also used to **demask the cyanide complexes of cadmium and zinc**, allowing subsequent determination of these metal ions with EDTA.

**Indicators for Complexometric Titrations**

Indicators used in complexometric titrations are known as **metal ion indicators** or **metallochromic indicators**, or sometimes **pM indicators**. Unlike acid-base titration indicators which are responsive to hydrogen ion concentration (pH), complexometric indicators are responsive to **metal ion concentrations (pM)**, changing color when they bind or release a metal ion.

Here are some common complexometric indicators:

- **Eriochrome Black T (EBT):** Also known as Solochrome Black T or mordant black II, EBT is chemically sodium 1-(1-hydroxy-2-naphthylazo)-6-nitro-naphthol-4-sulphonate. It is a **triprotic acid** (represented as $H_3In$) and its color changes with pH:
    - **Acidic pH (< 5.5):** Red ($H_2In^-$)
    - **Neutral to basic pH (7-11):** Blue ($HIn^{2-}$)
    - **Highly basic pH (> 11):** Yellowish-orange ($In^{3-}$) In complexometric titrations, it forms a wine-red complex with certain metal ions (e.g., $Mg^{2+}$, $Ca^{2+}$) at the working pH, which then changes to blue when EDTA removes the metal ions from the indicator.
- **Calmagite:** Calmagite is stable in aqueous solution and can be used as a replacement for Eriochrome Black T, offering similar color changes. Its color also depends on pH:
    - **Acidic pH (< 7):** Red
    - **Neutral to basic pH (7.1-9.1):** Blue
    - **Highly basic pH (11.4-13.3):** Reddish-orange

- **Murexide:** Murexide is the ammonium salt of purpuric acid. It is an indicator where four protons present in the amido group are responsible for complexation at different pH ranges. Its color changes with pH and complexation:

    - **Acidic pH (< 7):** Red violet color
    - **Neutral to basic pH (7-10):** Violet color
    - **Highly basic pH (< 10):** Blue color Murexide is often used for titrations of calcium, nickel, and copper.
- **Calcon:** Also known as Solochrome dark blue or Eriochrome black blue indicator. Calcon has limited use as an indicator because it can only be used at **pH 12.3** to avoid interference from magnesium ions, making it specific for calcium in highly alkaline solutions.

- **Catechol Violet:** Also known as pyrocatechol violet, it is chemically catecholsulfonphthalein and is a tetraprotic acid ($H_4In$). It can be used as an indicator for various complexometric titrations.

- **Xylenol Orange:** This indicator is widely used for titrations of metal ions, particularly those that form stable complexes with EDTA in acidic solutions.

- **Pyridylazo Naphthol (PAN):** PAN gives a **red color in the presence of copper ions** and a **yellow color in the absence of copper ions**. This distinct color change makes it useful for copper titrations.

**Types of Complexometric Titrations**

Complexometric titrations can be broadly classified into several types based on their procedure:

- **Direct Titration:** This is the **simplest and most convenient method** in chelatometry. In direct titration, the **standard chelating solution (e.g., EDTA) is added directly to the metal ion solution** (analyte) until the end point is detected, usually by a color change of the indicator. This method is analogous to simple acid-base titrations. However, the direct titration method is **not suitable for slow complexation reactions** or when there is **interference due to the presence of other ions** that react with EDTA or the indicator. **Example:** Determination of calcium ($Ca^{2+}$) in calcium gluconate injections or calcium lactate tablets. $Ca^{2+}$ + EDTA → Ca-EDTA

- **Back Titration:** In this method, an **accurately known excess of a standard EDTA solution is added to the metal solution** to be analyzed. The excess EDTA that has not reacted with the metal ion is then **back-titrated with a standard solution of another metal ion**. This method is

useful when:

- The metal ion reacts too slowly with EDTA.
- The metal ion precipitates in the pH range required for the direct titration.
- A suitable indicator for direct titration is not available.
- The metal ion blocks the indicator. **Example:** Determination of $Mn^{2+}$. Manganese(II) precipitates as $Mn(OH)_2$ in the basic pH range (around 10) required for titration with Eriochrome Black T. Therefore, a known excess volume of EDTA is added to an acidic solution of Mn salt. An ammonia buffer is then used to adjust the pH to 10. The excess EDTA remaining after chelation with $Mn^{2+}$ is then back-titrated with a standard zinc ($Zn^{2+}$) solution, using Eriochrome Black T as the indicator. $Mn^{2+}$ + EDTA (in excess) → Mn-EDTA + EDTA (remaining) EDTA (remaining) + $Zn^{2+}$ → Zn-EDTA (color change)

- **Replacement Titration:** In this method, the metal ion to be analyzed **displaces quantitatively a metal from a less stable EDTA complex**.

  This is used when direct or back titrations do not give sharp end points. The released metal (often magnesium or zinc) is then titrated with a standard EDTA solution.

  This displacement occurs because the analyte metal forms a more stable complex with EDTA than the metal already in the complex.

  **Example:** Determination of $Mn^{2+}$. Manganese(II) quantitatively displaces $Mg^{2+}$ from a pre-formed Mg-EDTA solution because $Mn^{2+}$ forms a more stable complex with EDTA. The freed $Mg^{2+}$ metal is then directly titrated with a standard EDTA solution. This method can also be used to determine $Ca^{2+}$, $Pb^{2+}$, and $Hg^{2+}$ using Eriochrome Black T indicator. $Mn^{2+}$ + Mg-$EDTA^{2-}$ → Mn-$EDTA^{2-}$ + $Mg^{2+}$ $Mg^{2+}$ + $EDTA^{4-}$ → Mg-$EDTA^{2-}$

- **Indirect Titration:** This method is also known as **Alkalimetric titrations** in some contexts. It is used for the determination of **ions such as anions** (e.g., sulphate, phosphate) that do not react directly with EDTA.
  In this method, protons from disodium EDTA are displaced by a heavy metal. **Example:** Barbiturate will not react directly with EDTA. However, barbiturate forms a complex with $Hg^{2+}$ ions quantitatively. The titration of this Hg-barbiturate complex with EDTA then gives the equivalent amount of barbiturate indirectly. Barbiturate + $EDTA^{4-}$ → No reaction But, Barbiturate + $Hg^{2+}$ → Barbiturate-Hg (Complex) Barbiturate-Hg (Complex) + $EDTA^{4-}$ → Hg-$EDTA^{2-}$ + Barbiturate (freed)

## Unit 3(c) Gravimetric Analysis & Diazotization Titration

### Introduction to Gravimetric Analysis

Gravimetric analysis is a **quantitative analysis method by weight** that involves measuring the weight of a substance to be analyzed from a solution after isolating it by precipitating the component as an insoluble compound of known chemical composition. The core principle is that the amount of a substance can be determined by carefully weighing a solid that contains the substance.

The process aims to effectively **separate a specific element or radical** from the sample compound. There are several ways through which this separation can be achieved:

- **Precipitation method:** The most common method, where the analyte is converted into an insoluble precipitate.
- **Volatilization or evolution method:** Involves heating the sample to drive off a volatile component, and the weight loss is measured.
- **Electro-analytical method:** Uses electrolysis to deposit the analyte onto an electrode, which is then weighed.
- **Miscellaneous physical methods:** Other physical separation techniques.

Gravimetric methods are generally considered **accurate and precise**, especially when using modern and sensitive analytical balances. Errors can be significantly reduced by examining the filtrate for complete precipitation, ensuring no analyte remains in solution.

A key advantage of gravimetric analysis is that it is an **absolute method of analysis**, meaning it does not require calibration against standards. The direct measurement of the compound(s) is performed. Furthermore, it can be relatively **inexpensive** compared to other analytical methods.

The weight of the element or radical being determined can be calculated in a single step using a **gravimetric factor**. **% Analyte (element/radical) = (Weight of precipitate x Gravimetric factor x 100) / Weight of Sample**

The **gravimetric factor** is a ratio used to convert the weight of the precipitate to the weight of the analyte. It is the ratio of the formula weight of the analyte to the formula weight of the precipitate, often considering stoichiometry. For instance, if 1 mole of $Cl_2$ gives 2 moles of AgCl: **Gravimetric Factor for $Cl_2$ = Formula weight of $Cl_2$ / (2 x Formula weight of AgCl)** Or, more generally, if 'x' g of analyte produces 'y' g of precipitate: **Weight of substance sought = Weight of precipitate x Gravimetric factor**

### Precipitation Techniques in Gravimetric Analysis

The precipitation method is a central technique in gravimetric analysis. It involves weighing an element or radical in the form of a precipitate, which is then separated from the solution by filtration. Several factors influence the quality of the precipitate, including:

- The precipitated compound must be convertible into a pure compound through **ignition or simple evaporation**.
- The precipitated compound must be **free from soluble impurities**.
- The precipitated compound must be **insoluble in the solution**, minimizing losses.
- The precipitated compound must be **readily separable from the solution by filtration**.

**Colloidal Precipitates:** Gravimetric analysis sometimes encounters **colloidal precipitates**, especially in the initial stages of the reaction. Hydroxide precipitates of most metals, for instance, are often colloidal in nature and require specific treatment before filtration. Colloids are characterized by their **non-settling nature under gravity** and a **high surface area**, which makes them prone to adsorbing other impurities. Electrovalent colloids, in particular, tend to adsorb common ions.

**Properties of Colloids:**

- **Brownian motion:** Colloidal particles exhibit a random, zig-zag movement in a colloidal solution due to collisions with solvent molecules.
- **Tyndall Effect (Reflection and light scattering):** Colloids have the ability to scatter light. When a beam of light passes through a colloidal solution, the light path becomes visible, unlike in true solutions or suspensions.

**Supersaturation**

Supersaturation describes a **thermodynamically unstable state** where a solution contains more dissolved solute than it normally would at equilibrium at a given temperature. This state can be achieved by adding an excess amount of a substance to a solution compared to its normal solubility limit.

The supersaturation point can be divided into three zones:

- **Zone 1 - Nucleation zone:** In this zone, the solution may remain supersaturated for a long time without forming a precipitate. It might be necessary to **add a seed crystal** to initiate nucleation (the formation of the first tiny solid particles).
- **Zone 2 - Nucleation zone:** Here, spontaneous **nucleation and crystal growth** occur. The rate of new particle formation is high.
- **Zone 3 - Precipitation zone:** In this zone, the substance(s) rapidly precipitate out of the solution, as the concentration far exceeds solubility and conditions are favorable for rapid crystal growth.

**Co-precipitation**

Co-precipitation is a common problem in gravimetric analysis where **impurities are precipitated along with the desired analyte**, leading to errors. It involves the contamination of a precipitate by substances that are normally soluble under the conditions of the precipitation. Several mechanisms contribute to co-precipitation:

- **Inclusion:** An inclusion occurs when an impurity occupies a **lattice site within the crystal structure** of the precipitate, resulting in a crystallographic defect. This typically happens when the ionic radius and charge of the impurity are similar to those of the carrier ion (the ion of the precipitate). The adsorbate (impurity) is weakly bound to the surface of the precipitate before being incorporated. **Example:** The precipitation of barium (Ba) as barium sulfate ($BaSO_4$) in the presence of lead ions (Pb) can lead to inclusion of lead in the $BaSO_4$ crystal. This problem can be overcome by **separating the analyte from contaminating ions before the precipitation process**.

- **Occlusion:** An occlusion occurs when an **adsorbed impurity (foreign ions)** gets physically trapped inside the rapidly growing crystals. This usually happens when the crystal growth is too fast. Some constituents of the precipitation medium may be trapped within the crystal structure, leading to either positive or negative errors. Trapped materials can include water, analyte ions, precipitating agents, or other solution components. Occlusion can be minimized by **slowing down the precipitation process**, which allows impurities to escape before being trapped. Dissolution and re-precipitation of the precipitate may be necessary to remove occluded impurities.

- **Adsorption:** This is a common source of co-precipitation, especially with precipitates having **large specific surface areas** (like colloidal precipitates). Adsorption involves impurities adhering to the surface of the precipitate.

- **Mechanical entrapment:** Mechanical entrapment occurs when **crystals lie close together during growth**, trapping a portion of the solution (and its dissolved impurities) in tiny pockets within the crystal aggregate. This is most common when the rate of precipitate formation is slow under conditions of low supersaturation, allowing large crystals to form and entrain solvent.

**Experimental Methodology for Gravimetric Analysis**

In gravimetric analysis, the analyte is typically converted into an **insoluble form that can be washed, dried, and weighed** to determine its concentration in the original solution. This method is applied when a **good precipitating agent** is available. Gravimetry is considered a **macro analytical technique** because it usually requires larger sample sizes.

The precipitated product should ideally be **quantitative** (complete precipitation), **easily washed** (to remove impurities), **filtered**, and obtained in a **suitable quantity for accurate weighing**.

The general experimental steps are:

1. **Preparation of the Solution:**
    - The sample solution is prepared for analysis, often requiring **dilution** to ensure proper precipitation conditions.
    - The **volume and pH of the solution are adjusted** to achieve the desired properties for the precipitate (e.g., to ensure complete precipitation and avoid side reactions).
2. **Precipitation:**
    - The **precipitating agent is added** to the sample solution, usually slowly and with stirring.
    - Upon addition, **supersaturation and nucleation** begin, where molecules of the precipitate aggregate together and form a nucleus, which then grows into larger particles.
3. **Digestion of the Precipitate:**
    - After precipitation, the precipitate is often left **hot for 30 minutes to 1 hour** in contact with the mother liquor. This process is called **digestion** (or Ostwald ripening).
    - Digestion involves the **dissolution of smaller particles and re-precipitation on larger ones**, which leads to an increase in particle size, improved crystal structure, and better filterability. It also helps to reduce co-precipitation by allowing trapped impurities to diffuse out.
    - This process is particularly important for **colloidal precipitates**, where a large surface area is covered by adsorbed ions; digestion helps in producing a more compact and purer precipitate.
4. **Washing and Filtering the Precipitate:**
    - It is **crucial to wash the precipitate very well** to remove all adsorbed soluble species that would otherwise increase the weight of the precipitate and lead to errors.
    - Care must be taken **not to use large amounts of water for washing**, as some part of the precipitate may be lost due to slight solubility, especially if the wash solution is not saturated with the precipitate. A suitable wash solution (e.g., dilute electrolyte) is often used to minimize losses and prevent peptization (dispersion of the precipitate back into a colloid).
5. **Drying and Ignition:**

- The precipitate, after filtration and washing, is typically **dried in an oven at temperatures ranging from 120-150°C**.
- For some precipitates, **ignition in a muffle furnace at temperatures between 600-1200°C** is required. This process converts the precipitate into a material with an exactly known chemical structure, ensuring that the final weighed product is pure and stable, allowing for accurate determination of the analyte's amount.

**Gravimetric Calculations:** The weight of the analyte is calculated from the weight of the precipitate using **stoichiometric calculations** and the gravimetric factor. For example, if $Cl_2$ is to be precipitated as AgCl: 1 mole of $Cl_2$ gives 2 moles of AgCl. Gravimetric Factor for $Cl_2$ = (Formula weight of $Cl_2$) / (2 x Formula weight of AgCl) This factor allows the analyst to convert the moles or milligrams of the precipitate to the equivalent amount of the analyte.

**Filter Papers: Ashless filter paper** is primarily used for gravimetric methods in quantitative chemical analysis. It is a semi-permeable paper barrier that allows liquid or air flow while retaining fine solids. Ashless filter papers are designed to leave a negligible ash residue after ignition (typically a base weight of 80 g/m²), ensuring the weight of the filter paper does not interfere with the precipitate's weight.

**Post-precipitation**

Post-precipitation is a phenomenon where a **second substance slowly precipitates onto the surface of a previously formed precipitate** if the solution is left for a prolonged period without filtration or during the digestion process. The rate of reaction for this second substance is slower compared to the primary precipitation.

These foreign ions precipitate out in the same solution, often contaminating the desired precipitate. Post-precipitation is a common source of **positive error in gravimetric analysis** because it increases the measured weight of the precipitate beyond what is solely due to the analyte. It can be minimized by prompt filtration after digestion or by carefully controlling the conditions.

**Estimation of Barium Sulphate**

The estimation of barium sulfate ($BaSO_4$) is a classic example of gravimetric analysis.

**Principle:** When dilute sulfuric acid ($H_2SO_4$) is added to a dilute solution of barium chloride ($BaCl_2$), a **white precipitate of barium sulfate ($BaSO_4$)** is formed. This precipitate is then filtered, washed, dried, ignited, and weighed to determine the amount of barium. $BaCl_2 + H_2SO_4 \rightarrow BaSO_4$ (white gelatinous precipitate) + 2HCl

**Requirements:**

- **Reagents:** Barium chloride ($BaCl_2$) solution (12.57 g in 1000 ml of distilled water), precipitating agent (3 ml of concentrated $H_2SO_4$ in 100 ml of distilled water), wash solution (hot distilled water), concentrated hydrochloric acid (HCl), 0.05N HCl.
- **Apparatus:** Volumetric flask, beaker, conical flask, burette, pipette, watch glass, sintered glass filter, vacuum pump, crucible, desiccator.

**Experiment:**

1. Pipette **25 ml of the given solution of barium chloride ($BaCl_2$)** into a 500 ml beaker.
2. Add **0.5 ml of concentrated sulfuric acid ($H_2SO_4$)** and **100 ml of distilled water**.
3. **Heat the resulting solution to boiling**.
4. To this hot solution, **add dilute sulfuric acid ($H_2SO_4$) solution dropwise with constant stirring** until the precipitation is complete.
5. Allow the precipitate to **settle down** and then **test the supernatant liquid for complete precipitation**.
6. **Filter the precipitate by decanting through Whatman filter paper** (or a sintered glass filter).
7. **Wash the precipitate 3-4 times with hot water**.
8. **Dry the filter paper containing the precipitate** by placing the funnel in an oven.
9. After drying, **transfer the filter paper and precipitate to a pre-constantly weighed crucible**.
10. **Ignite the crucible** until all the carbonaceous matter from the filter paper is burnt off and the precipitate is converted to pure $BaSO_4$.
11. **Cool the crucible** in a desiccator and weigh it. Add one drop of each of concentrated hydrochloric acid (HCl) and concentrated sulfuric acid ($H_2SO_4$) and ignite again, then cool and re-weigh to ensure constant weight.
12. **Precipitation should ideally be carried out in a dilute hot solution and in the presence of 0.05N HCl**, as this helps to increase the size of the precipitate particles, leading to better filterability and reduced co-precipitation.

**Calculation:** Let the constant weight of barium sulfate ($BaSO_4$) precipitate be 'x' g. Formula weight of $BaSO_4$ = 233.42 Atomic weight of Ba = 137.36 233.42 g of $BaSO_4$ contains 137.36 g of $Ba^{2+}$ ions. Therefore, 'x' g of $BaSO_4$ contains **(137.36 x x) / 233.42 g of $Ba^{2+}$ ions**.

**Diazotization Titration**

**Introduction:** Diazotization titration is an analytical method primarily used for the **determination of primary aromatic amines**. This titration involves the **conversion of a primary aromatic amine to a diazonium compound** through a reaction with **sodium nitrite ($NaNO_2$) in an acidic medium**. This method was initially developed and widely applied in the synthetic dye industry, where diazonium

compounds are important intermediates. The reaction involves the primary aromatic amine reacting with sodium nitrite in an acidic environment (usually with HCl) to form a diazonium salt.

**Types of Diazotization Titrations:** There are mainly three types of methods based on the titration procedure:

- **Direct Method:** The main principle of the direct method is to treat the **amino group-containing drug (primary aromatic amine) with an acid solution**. The resulting solution is then immersed in a **cold water bath or ice water bath**, maintaining the temperature between **0-5°C**. This cold solution is then **titrated with a sodium nitrite solution** until the end point is determined.

- **Indirect Method:** The principle here is that an **excess of nitrous acid** (formed from sodium nitrite and acid) is added to the titration sample solution. The unreacted excess nitrous acid is then **back-titrated with another appropriate titrant**. This method is mainly used for the titration of **insoluble Diazonium salts** or for samples where the direct titration is not suitable.

- **Other Method:** Another approach involves the **formation of a diazo oxide**, which is more stable than the diazo compounds. For example, aminophenol is readily oxidized by nitrous acid and converted to quinones in the presence of copper sulfate solution. This then undergoes a **coupling reaction with nitrous acid**, which can be measured.

**Principle:** The core principle is the reaction of primary aromatic amines with sodium nitrite in the presence of hydrochloric acid (HCl) to form diazonium salts. First, sodium nitrite reacts with hydrochloric acid to form nitrous acid (HONO) and sodium chloride: $NaNO_2 + HCl \rightarrow HONO + NaCl$

The obtained nitrous acid then reacts with the primary aromatic amine to form the diazonium salt. This reaction needs to be carefully controlled, especially regarding temperature. Aromatic amine ($Ar\text{-}NH_2$) + $HONO + HCl \rightarrow$ Diazonium salt ($Ar\text{-}N_2^+Cl^-$) + $2H_2O$

This method is also known as **nitrite titration**.

**End Point Detection:** The end point is typically detected using **starch-iodide paper**. After the completion of the reaction (when all primary aromatic amine has reacted), the first excess drop of nitrous acid reacts with potassium iodide in the starch-iodide paper to liberate iodine. The iodine then forms a **blue-colored complex with starch**, signaling the end point. $KI + HCl \rightarrow KCl + HI$ $2HI + 2NaNO_2 + 2HCl \rightarrow I_2 + 2NO + 2NaCl + 2H_2O$ $I_2$ + Starch → Starch-$I_2$ complex (Blue color at the end point)

**Temperature Control:** The reaction must be carried out in an **ice bath to maintain the temperature between 0-5°C**. This is critical because diazonium salts are highly unstable and readily decompose at elevated temperatures, leading to the evolution of nitrogen gas and inaccurate results.

**Applications:** Diazotization titration is used to determine **Sulphanilamide, Sulphonamides, and other sulpha drugs**.

**Procedure (Example for a primary aromatic amine):**

**Standard Solution Preparation:**

1. Accurately weigh **2.5 gm of the sample** (e.g., a primary aromatic amine).
2. Transfer it to a **250 ml standard flask**.
3. Add **50 ml of concentrated hydrochloric acid** and **5 gm of potassium bromide** (which acts as a catalyst to increase the reaction rate).
4. Make up the final volume to 250 ml with distilled water.
5. From this standard solution, pipette out an appropriate volume (e.g., 50 ml) into a stoppered conical flask.

**Titration:**

1. Immerse the conical flask in an **ice bath** to maintain the temperature at **0-5°C**.
2. Titrate the solution with a **N/10 $NaNO_2$ solution** from a burette.
3. Continuously swirl the flask.
4. At intervals, test a drop of the solution with **starch-iodide paper**.
5. The end point is reached when the starch-iodide paper turns **blue**, indicating the presence of excess nitrous acid.

**Potentiometric Titration (Alternative End Point Detection):** Alternatively, the titration can be performed using **Potentiometry** for a more precise end point.

1. Accurately weigh about **0.5 gm of the sample** and transfer it into a 250 ml beaker.
2. Dissolve the contents in **10 ml HCl and 75 ml of water**.
3. Insert a pair of **bright platinum electrodes** into the solution and connect them through a sensitive galvanometer.
4. A **potential drop of between 30-50 µV across the electrodes** is produced using a suitable potentiometer.
5. Titration is carried out slowly with N/10 $NaNO_2$ solution, with **continuous stirring**.
6. The end point is observed as a **permanent deflection of the galvanometer**, indicating the liberation of excess nitrous acid.

7. The **liberation of excess nitrous acid at the end point depolarizes the electrode**, causing current flow and a full deflection in the galvanometer needle. This is known as the "dead stop end point."
8. To ensure proper electrode function, the electrodes must be clean. **Cleaning the electrodes in boiling nitric acid containing a little ferric chloride for about 30 seconds**, followed by washing with water, helps to solve problems of a sluggish end point.
9. A **blank determination** is carried out, and its volume is subtracted from the sample titration volume to get the exact volume required to react with the amine.

**Conditions for the Diazotization Titration**

Maintaining specific conditions is vital for accurate and reliable results in diazotization titrations.

- **Rate of Titration:** The addition of sodium nitrite to the sample solution takes time to react completely with the amino group. Different amino compounds react with nitrous acid at different rates. Based on their reaction rates, amino compounds are classified into two main groups:
    - **Slow diazotizable compounds:** Examples include Sulphanilic acid and Anthranilic acid. These require slower addition of titrant and longer waiting times for the reaction to complete.
    - **Fast diazotizable compounds:** Examples include Aniline, Aminophenol, and Toluidine. These react more quickly with the titrant. The reaction rate can be increased by the **addition of potassium bromide solution**, which acts as a catalyst.
- **Temperature: Maintenance of the temperature between 0-5°C is the most important condition** for diazotization titration. Diazonium salts are highly unstable and readily decompose at elevated temperatures. Therefore, the reaction vessel must be kept in an ice bath throughout the titration. If the temperature rises, the diazonium salt will decompose, releasing nitrogen gas and leading to inaccurate results.

**Advantages and Disadvantages of Diazotization Titration**

**Advantages:**

- **Selectivity:** The method is selective for **all types of sulphonamides**, as well as primary aromatic amines.
- **Sensitivity and Reproducibility:** It offers good sensitivity and reproducibility when performed under carefully controlled conditions.
- **Versatility:** The method is applicable for a **very wide variety of samples** containing primary aromatic amino groups.

**Disadvantages:**

- **Slow Reaction:** Compared to other titration methods, diazotization reactions are relatively slow, requiring careful and often prolonged addition of titrant.
- **Strict Temperature Control:** The temperature conditions must be properly maintained throughout the reaction (0-5°C), which can be difficult to achieve and maintain precisely, especially in routine analysis.
- **Difficult End Point Detection:** The end point detection, especially with starch-iodide paper, can be very difficult to observe sharply due to the transient nature of the color change and the inherent challenges in visually confirming the precise moment of excess nitrous acid.
- **Color Instability:** The color produced at the end point may not be stable or distinct, leading to a lack of specificity and potential over-titration.

**Applications of Diazotization Titration**

Diazotization titrations have several important applications in pharmaceutical analysis for the determination of various compounds containing primary aromatic amine groups:

- Used in the determination of **amphetamine**.
- Used in the determination of **benzoic acid (Vitamin $B_3$)** – *Note: Benzoic acid is not a primary aromatic amine. This might be a mistake in the source, or it refers to a derivative of benzoic acid.*
- Used in the determination of **dopamine**.
- Used in the determination of **procaine and Sulphonamides**.
- Used in the determination of **Chlorpheniramine**.
- Used in the determination of **ephedrine**.
- Used in the determination of **procaine**.

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# 📘 Pharmaceutical Analysis – FAQs for Students

## 1. What are Precipitation Titrations and their key requirements?

**Precipitation titrations** are volumetric analysis methods where insoluble solids (precipitates) are formed when cations and anions combine in solution.

✅ **Requirements for a good precipitation titration:**

- The precipitate must be **practically insoluble**.
- Reaction should be **rapid and complete**.
- Results must not be affected by **adsorption/co-precipitation**.
- The **equivalence point** must be accurately detected.

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## 2. Factors affecting solubility of precipitates

- **Acid (pH):** Solubility increases in acidic medium if the salt's anion is from a weak acid.
- **Temperature:** Higher temperature → higher solubility → faster precipitation and easier filtration.
- **Solvent:**
    - Water (polar) → increases solubility of salts.
    - Organic solvents (alcohols) → decrease solubility of salts.

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## 3. What are Mohr's, Volhard's & Fajan's methods?

🔹 **Mohr's Method**

- Titrant: **$AgNO_3$**

- Indicator: **$K_2CrO_4$** (forms red-brown $Ag_2CrO_4$ at endpoint)
- pH: **6.5 – 10.3**
- Limitation: Not suitable in ammonia, reducing agents, or strong alkaline media.

🔹 **Volhard's Method (Back titration)**

- Excess **$AgNO_3$** added → back-titrated with **thiocyanate ($SCN^-$)**.
- Indicator: **$Fe^{3+}$** → forms reddish-brown **$Fe(SCN)^{2+}$** complex.
- Can be used in acidic solution (with $HNO_3$).

🔹 **Fajan's Method**

- Uses **adsorption indicators** (dyes like dichlorofluorescein, eosin).
- Mechanism: Indicator ions adsorb onto precipitate surface at equivalence → colour change.

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## 4. What is Complexometric Titration? Role of EDTA

**Complexometric titration (Chelatometry):** Used to determine **metal ions** in solution.

- **EDTA** is the most common titrant:
    - Hexadentate ligand (6 donor sites).
    - Forms **stable complexes** with metal ions.
- Other chelators: DTPA, EGTA, Ammonia, Ethylenediamine.

👉 End point usually detected by colour change or instrumental methods (spectrophotometry, potentiometry, etc.).

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## 5. What are Masking and Demasking Agents?

- **Masking Agents** → Prevent certain metal ions from reacting with EDTA by forming stable complexes.
    - Examples:
        - **Triethanolamine** → masks $Al^{3+}$, $Fe^{3+}$
        - **Cyanide ion** → masks Zn, Cd, Cu, Ni, Ag, Pt
- **Demasking Agents** → Break the complex between masking agent and metal → free metal ion for titration.
    - Examples: **Formaldehyde, Chloral hydrate, Methanol-acetic acid**

👉 Both processes improve **selectivity & accuracy** in complexometric titration.

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## 6. What is Gravimetric Analysis? Steps Involved

**Gravimetric analysis** = Quantitative analysis by weighing a precipitate.

### 📌 Steps:

1. **Preparation of solution** – adjust pH, dilute sample.
2. **Precipitation** – add precipitating agent → supersaturation → precipitate forms.
3. **Digestion (Ostwald ripening):** Heat for 30–60 min → small crystals dissolve, big ones grow → purer & filterable precipitate.
4. **Filtration & Washing** – separate solid, wash to remove impurities.

5. **Drying/Ignition** – dry at 120–150°C or ignite at 600–1200°C → stable product for weighing.

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## 7. What are Co-precipitation and Post-precipitation?

🔹 **Co-precipitation (impurities carried down with precipitate)**

- **Inclusion:** Impurity fits in lattice.
- **Occlusion:** Impurity trapped inside crystals.
- **Adsorption:** Impurity sticks to surface.
- **Mechanical entrapment:** Solution pockets trapped between crystals.

👉 Causes **positive/negative errors** in results.

🔹 **Post-precipitation**

- Other ions precipitate **later**, if analyte is left too long in mother liquor.
- Leads to **positive errors** in gravimetric analysis.

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## 8. What is Diazotization Titration?

**Diazotization titration** → Converts a **primary aromatic amine** into a **diazonium salt** using $NaNO_2$ in acidic medium (0–5°C).

📌 **Methods:**

1. **Direct Method** – titrate drug with $NaNO_2$ directly.
2. **Indirect Method** – add excess nitrous acid, back-titrate.

3. **Modified Method** – form stable diazo-oxide.

## 📌 Applications:

- Estimation of **Amphetamine, Dopamine, Sulphonamides, Ephedrine, Procaine, Chlorpheniramine**.

## ✅ Advantages:

- High selectivity & reproducibility
- Applicable to a wide range of drugs

## ❌ Limitations:

- Requires **low temp (0–5°C)**
- Slow reaction
- Endpoint detection is difficult
- Colour produced may be unstable

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