# B. Pharmacy 1st Semester - Pharmaceutical Analysis Notes

## UNIT – 3 📚

### Topics Covered:

- **Precipitation titrations:** Mohr's method, Volhard's, Modified Volhard's, Fajans method, estimation of sodium chloride
- **Complexometric titration:** Classification, metal ion indicators, masking and demasking reagents, estimation of Magnesium sulphate, and calcium gluconate
- **Gravimetry:** Principle and steps involved in gravimetric analysis. Purity of the precipitate: co-precipitation and post precipitation, Estimation of barium sulphate
- **Basic Principles, methods and application of diazotisation titration**

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## Unit 3 (a) PRECIPITATION TITRATIONS ⚗️

### 📌 INTRODUCTION

Precipitates are insoluble ionic solids that are formed in aqueous solution by combination of cations and anions. However, all reactions in aqueous solutions do not necessarily produce precipitates. Factors that determine the formation of precipitates vary. Some reactions depend on temperature, whereas other reactions depend on solution concentration.

In the solid state, the solute molecules are held together by intermolecular forces of attraction and are arranged in a fixed repeating pattern which is called a crystal of solid. These forces of attraction are broken down by solvent-solute attraction, thus the solid gets dissolved in solvent and solubility is achieved.

## Requirements for Titrimetric Analysis:

The requirements for a reaction to be useful in titrimetric analysis are:

- The precipitate must be practically insoluble
- The precipitation reaction should be rapid and quantitative
- The titration result should not be hampered by adsorption (co-precipitation) effects
- It must be possible to detect the equivalence point during titration

## 🧪 SOLUBILITY PRODUCTS

The solvent should compete with crystal forces and overcome them, which often means that the solvent environment must be similar to that provided by the crystal structures. This is the basis for the simple rule "like dissolves like", means solute-solute attraction is overcome by solute-solvent attraction.

During precipitation reaction, the opposite condition is aspired for, where the intermolecular forces between molecules of product are high and solute-solute forces replace the solute-solvent forces. Consider an aqueous solution of a slightly soluble salt "BA" in equilibrium with excess of solid at constant temperature.

$BA(s) \rightleftharpoons B^+ + A^-$

Where; BA(s) represents the solid at constant temperature. In dilute aqueous solution essentially, no un-dissociated BA will be present in the solution. Since activity of solid is constant, the equilibrium constant for this equation may be written as:

**$Ksp = [B^+][A^-]$**

Solubility product is important because it permits the calculation of one of the ion concentrations if the concentration of the other is known. A substance precipitates out when the product of the ionic concentration exceeds the Ksp value. In the equation solid BA will precipitate out, when the product of $[B^+][A^-]$ exceeds Ksp.

## 🌡️ EFFECT OF SOLUBILITY ON PRECIPITATE

### Effect of Acid:

The solubility of a salt will be increased by decrease in pH (or increasing acidity); if the anion of the salt is the conjugate of weak acid.

### Effect of Temperature:

Solubility of most inorganic salts is increased by elevating the temperature of the solution. Solubility of some substances influenced by temperature is small, but with others it is more. It gives advantage if the precipitation process is carried out in hot solution because impurities are dissolved more readily and filtration is faster.

However, in the case of fairly soluble compounds, like magnesium ammonium phosphate, the solution must be cooled in ice water before

filtration to prevent the loss of precipitate in filtrate.

**Effect of Solvent:**

Most of the inorganic salts are more soluble in water as compared to organic solvents. Water shows large dipole movement and attracts both cations and anions to form hydrated ions. The solubility of most inorganic compounds is reduced by the addition of organic solvents such as methyl, ethyl and n-propyl alcohols.

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## 🔬 MOHR'S METHOD

This method falls under the category of determining the end point by formation of coloured precipitate, and is used for the determination of $Cl^-$ and $Br^-$ in a neutral solution. Silver nitrate ($AgNO_3$) is used as titrant and it is a secondary standard solution; so $AgNO_3$ is standardized by primary standard solution of NaCl (measured volume).

### Indicator:

5% Potassium chromate ($K_2CrO_4$) is used as indicator and forms reddish brown precipitate. Chlorides and bromides are used as analyte in this method. pH range of the titration is 6.5–10.3. Method is used for quantitative determination of NaCl, KCl, NaBr, KBr etc.

### Principle:

Consider the titration of 0.1 M NaCl with 0.1 M $AgNO_3$ in the presence of few ml of dilute $K_2CrO_4$ solution as indicator. When $AgNO_3$ is added, AgCl will precipitate out first. But analyst usually expect the salt with smaller

solubility product to precipitate first. But this is true only if both salts dissociate to yield the same number of ions.

Chloride ions in this case are in great excess of that of chromate ions. As the equivalence point is reached, no $Ag^+$ or $Cl^-$ is in excess. But, now additional drop of $AgNO_3$ will react with $CrO_4^{2-}$ to precipitate as $Ag_2CrO_4$ (reddish brown).

### RESTRICTIONS OF USAGE OF MOHR'S METHOD:

- It is not possible to use titration in basic solution otherwise it will produce AgOH
- It is not possible to use titration in the presence of ammonia ions (Due to ligand formation)
- It is not possible to use titration in the presence of reducers which reduce $CrO_4^{2-}$ (chromate) ions to $Cr^{3+}$ ions
- It is not possible to use titration in the presence of many anions ($PO_4^{3-}$, $S^{2-}$ etc.) which gives the coloured precipitate of silver ions

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## ⚖️ VOLHARD'S METHOD

Volhard's method is based on the formation of a color compound at the end point. Silver ion is titrated with thiocyanate in an acidic solution using ferric ion as an indicator.

Silver Nitrate ($AgNO_3$), ammonium thiocyanide ($NH_4SCN$) and potassium thiocyanide (KSCN) are used as titrants. $AgNO_3$ is standardized by NaCl (Primary standard solution); $NH_4SCN$ and KSCN are used as titrant

(standard) in Volhard's method. Iron alum is used as indicator and this method is carried out in four steps:

## Steps:

1. **Step 1:** Standardization of $AgNO_3$ by NaCl
2. **Step 2:** Addition of standardized $AgNO_3$ (in excess) to the sample for back titration
3. **Step 3:** Titration of remaining amount of $AgNO_3$
4. **Step 4:** Reaction with indicator at the end point

## Indicator:

Iron (III) salt is used as indicator in presence of nitric acid to form the reddish colored complex $[Fe(SCN)]^{2+}$ i.e. $NH_4Fe(SO_4)_2 \cdot 12H_2O$ (Ammonium iron (III) sulphate or ferric ammonium sulphate or iron alum).

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

The titration is carried out in presence of nitric acid. Halogenides, thiocyanide, cyanides, sulphides, carbonates, chromate, oxalates and arsenates can be determined by this method. The titration is done in acidic pH medium to prevent precipitation of iron hydroxides, $Fe(OH)_3$.

## Modified Volhard's Method:

Chloroform or other wetting agents are added after addition of excess amount of silver nitrate; because precipitate of AgCl may be solubilized in the solution during estimation. So, addition of chloroform will prevent the solubility of AgCl.

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## 🎨 FAJAN'S METHOD

K. Fajan proposed this method, through his studies on nature of adsorption. He introduced a useful type of indicator for precipitation titration. Such indicators are adsorbed on the surface of the precipitation at the equivalence point and this adsorption is accompanied by a color change. These indicators are acidic or basic dyes.

### Examples of Indicators:

- **Acid dyes:** Fluorescein, Eosin etc.
- **Basic dyes:** Rhodamine series

Silver nitrate ($AgNO_3$) is a secondary standard solution, so standardized on primary standard solution of NaCl (by a measured volume). Range of the pH is 6.5 - 10.3 for chlorides and 2.0 - 10.3 for Bromides and iodides.

### Indicators:

- **Dichlorofluorescein** (for Chlorides)
- **Eosine** (For Bromides and Iodides)

### MECHANISM OF INDICATOR ACTION:

The property of a colloidal precipitate to adsorb its own ions which are in excess, is used in this case. When NaCl solution is titrated with $AgNO_3$, the AgCl precipitate will adsorb chloride ions which are initially in excess.

Thus, the primary adsorbed layer will be formed by chloride ions, which will hold the secondary adsorbed layer of oppositely charged $Na^+$. At the

equivalence point, $Ag^+$ ions are in excess and hence AgCl ions adsorb $Ag^+$ ions as primary adsorb layer and $NO_3^-$ as secondary adsorb layer.

If the $Na^+$ salt of fluorescein is also present in the solution then the negatively charged fluorescein ions would be adsorbed instead of $NO_3^-$ as secondary adsorbed layers and this adsorption occur along with a change to pink colored complex of $Ag^+$ and fluorescein ions.

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## 🧂 ESTIMATION OF SODIUM CHLORIDE

### Aim:

To carry out the assay of the given sample of sodium chloride.

### Requirements:

Silver nitrate, sodium chloride, potassium chromate solution, distilled water, burette, pipette, volumetric flask, beaker and funnel.

### Principle:

Assay of the sodium chloride solution is carried out by standard silver nitrate solution and method is based on the principle of precipitation.

**Indicator:** 5% potassium chromate $K_2CrO_4$ (For formation of precipitate of reddish-brown $Ag_2CrO_4$).

### PREPARATION OF REAGENTS:

#### Preparation of 0.1 N $AgNO_3$:

Weigh accurately 16.989 g of $AgNO_3$ on a watch glass and transfer into a 1000 ml volumetric flask. Add freshly prepared distilled water and dissolve

the silver nitrate and makeup the final volume to 1000 ml.

**Preparation of 0.1 N NaCl:**

Weigh accurately 5.844 g of NaCl and transfer into a 1000 ml volumetric flask. Add freshly prepared distilled water and dissolve the silver nitrate and make up the final volume to 1000 ml.

**Preparation of 5% $K_2CrO_4$:**

Accurately weigh and dissolve 5.0 g $K_2CrO_4$ in 20 ml of distilled water and make up the final volume upto 100 ml.

**EXPERIMENT:**

Take 10 ml of 0.1 N NaCl solution into a conical flask and add 1 ml of potassium chromate indicator solution. Titrate the above solution against silver nitrate solution until brick red coloured precipitate is formed in the conical flask. Repeat the experiment three or more times until two consecutive results are same or precise and tabulate the results. Take the precise readings for calculation of actual normality of $AgNO_3$. Accurately weigh 0.25 g of silver chloride and dissolve in 50 ml of water, add 1 ml of potassium chromate indicator solution.

**Observation Table:**

| S.N | START POINT | END POINT | VOLUME CONSUMED |
|---|---|---|---|
| 1 | | | |
| 2 | | | |
| 3 | | | |
| 4 | | | |

## Calculation:

**$N_1V_1 = N_2V_2$**

Where:

- $N_1$ (Normality of Sodium Chloride) = 0.1 N
- $V_1$ (Volume of sodium Chloride) = 10 ml
- $N_2$ (Normality of Silver) = x N
- $V_2$ (Volume of Silver nitrate Consumed) = y ml
- 1 ml of 0.1 N $AgNO_3$ = 1 ml of 0.1 N NaCl
- Molecular wt of NaCl = 58.45
- 0.1 N NaCl = 5.845 g per 100 ml
- So, 1 ml 0.1 N NaCl = 0.005845 g of NaCl
- Each ml of 0.1 N $AgNO_3$ = 0.05845 g of NaCl

## % Purity of NaCl:

**% Purity = (Weight found/Weight taken) × 100**

## Result:

Percentage purity of the given sample of sodium chloride was found to be x %.

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## Unit 3 (b) COMPLEXOMETRIC TITRATION 🔗

### 📌 PRINCIPLE OF COMPLEXOMETRIC TITRATION

**EDTA (Ethylene Diamine Tetra Acetic Acid)**

Complexometric titration is a type of volumetric analysis and also known as chelatometric titration. End point is detected by the change in colour of the solution due to complexometric reactions.

Sometimes other methods are used to determine end point in this type of titrations i.e. Spectrophotometry, Amperometry, Potentiometry, high frequency titrator etc. Complexometric methods are employed for determination of metal ion mixtures in solution(s). Presence of indicator shows distinguished colour change at the end point of the titration.

### 🧪 COMPLEXING AGENTS

**EDTA (Ethylene diamine tetra acetic acid)**

EDTA contains four carboxylic groups and two amine groups which act as donors of electron pairs. EDTA donates six lone pairs of electrons for the formation of co-ordinate covalent bonds with cationic metals and known as hexa-dentate ligand. In practical aspects, EDTA is generally partially ionized and produces less than six co-ordinate covalent bonds with cationic metals. Disodium salt of EDTA is commonly used to determine the cationic metals in the solutions.

### DTPA (Diethylene tri-amine penta acetic acid)

Pentetic acid or Diethylene triamine penta acetic acid (DTPA) is an amino-polycarboxylic acid which contains diethylene-triamine skeleton with five carboxylic groups. DTPA is extended version of EDTA with extra carboxylic and amino group. Affinity of DTPA is high for cationic metals. So, penta-anion DTPA is potentially an Octa-dentate ligand considering each nitrogen centre and $COO^-$ groups.

### Ammonia ($NH_3$)

Ammonia is also used as a complexing agent with molecular weight 17. It is mono-dentate in nature and forms complex with copper ions. One lone pair of electrons present in nitrogen of the ammonia can be donated to metal ions like copper, and forms complex and acts as a complexing agent.

### EGTA (Ethylene glycol-bis [amino ethyl ether] tetra acetic acid)

EGTA or ethylene glycol tetra-acetic acid is an amino poly carboxylic acid, which act as a complexing agent. It shows lower affinity of complexation with magnesium as compared to EDTA, and more selective for calcium ions.

### Ethylene Diamine

Ethylene diamine is also a chelating agent and forms chelate with copper ions.

## 🎭 MASKING AND DEMASKING REAGENTS

### Masking Agent:

One of the important aspect of Complexometric titration is its adoptability in estimation of two or more metals in the same solution. This can be done either by selection of suitable pH at which one metal forms a complex without the involvement of other metal ion or by using a suitable masking agent.

A masking agent is called as auxiliary chelating agent or complexing agent. It a substance that will form complex more strongly with the metal than the titrant under the conditions of titration.

**Examples of masking agents:**

- Triethanolamine for aluminium and iron
- Thioglycerol for copper
- Potassium cyanide for heavy metals
- Ammonium fluoride for iron and aluminium

Cyanide ion is one of the effective masking agent to form stable complexes with Cd, Zn, Hg (II), Cu, Co, Ni, Ag, Pt. But it does not mask the alkaline earths, manganese and lead. Masking is an equilibrium process and it is possible to reverse it by using Demasking agents.

**Demasking agents:**

Demasking agents are used to break the metal ion-complexing agent stable complex; so determination of the metal ion(s) can be carried out.

**Types of Demasking agents:**

1. **Methanol-acetic acid complex:** This complex is used to demask the cyanide complexes of zinc and cadmium. Ratio between the methanol

and acetic acid should be 3:1.

2. **Solvent extraction method:** It can be used for separation of zinc from mixture of lead and copper. Add ammonium thiocyanate solution in the mixture solution and zinc form complex zinc thiocyanate.
3. **Formaldehyde:** Formaldehyde is used to demask the cyanide complexes of cadmium and zinc, after Demasking, metal ions can be determined by titrating with EDTA.
4. **Chloral hydrate:** It is also used to demask the cyanide complexes of cadmium and zinc; after Demasking metal ions can be determined by titrating with EDTA.

## 🌈 INDICATORS

Indicators used in Complexometric titrations are known as metal ion indicators or metallochromic indicators or pM indicators. In acid base titration, indicators are responsive to hydrogen ion concentration; but in Complexometric titration indicators are responsive to the metal ions like $Mg^{2+}$, $Ca^{2+}$, $Cu^{2+}$ etc.

### Eriochrome Black T

Eriochrome black T is also known as Solochrome Black T or mordant black II or EDT. Chemically it is sodium 1(1-hydroxy-2naphthylazo)-6-nitro-naphthol-4-sulphonate. It is a triprotic acid and represented by $H_3In$. The proton of sulphonic acid group is ionized in aqueous solution.

**Color changes:**

- **Acidic pH (pH < 5.5):** $H_2In^-$ (Red color)
- **Neutral to basic pH (7–11):** $In^{2-}$ (Blue color)

- **Highly basic pH (pH > 11):** $In^{2-}$ (Yellowish-orange color)

**CALMAGITE**

Calmagite is stable in aqueous solution and can be used as a replacement of Eriochrome black T indicator.

**Color changes:**

- **Acidic pH (pH < 7):** $H_2In^-$ (Red color)
- **Neutral to basic pH (7.1–9.1):** $HIn^{2-}$ (Blue color)
- **Highly basic pH (11.4–13.3):** $In^{3-}$ (Reddish-orange color)

**MUREXIDE**

Murexide is ammonium salt of purpuric acid. Four protons present in the amido group of murexide are responsible for complexation at different pH range.

**Color changes:**

- **Acidic pH (pH < 7):** $H_4In$ (Red violet colour)
- **Neutral to basic pH (7 – 10):** $H_3In^-$ (Violet colour)
- **Highly basic pH (< 10):** $H_2In^{2-}$ (Blue colour)

**CALCON**

Calcon is also known as Solochrome dark blue or Eriochrome black blue indicator. This indicator has limited use because it can be used only at pH 12.3 to avoid interference of magnesium ions.

**Catechol violet**

It is also known as pyrocatechol violet; chemically it is catechol-sulfonphthalein and a tetra protic acid ($H_4In$).

### Xylenol orange

It can be used as an indicator for Complexometric titrations.

### Pyridylazo naphthol (PAN)

This indicator gives red colour in presence of copper ions and yellow colour in absence of copper ions.

## 📊 TYPES OF COMPLEXOMETRIC TITRATIONS

| Type | Method | Application |
|---|---|---|
| **Direct titration** | Standard chelating solution added directly to metal ion | Simple, convenient for fast reactions |
| **Back titration** | Excess EDTA added, then back titrated | For slow reactions or precipitation issues |
| **Replacement titration** | Metal displaces another from less stable complex | For metals giving poor end points |
| **Indirect titration** | For anions that don't react with EDTA directly | Alkalimetric titrations |

### Direct titration

It is the simplest and the most convenient method used in chelatometry. In this method, the standard chelating solution is added to the metal ion solution until the end point is detected. This method is analogous to simple acid-base titrations. Direct titration method cannot be applicable

for slow complexation reaction; because of interference due to the presence of other ions.

**Back titration**

In this method, excess of a standard EDTA solution is added to the metal solution, which is to be analyzed, & the excess is back titrated with a standard solution of another metal ion.

**Application:** Determination of $Mn^{2+}$: This metal cannot be directly titrated with EDTA because of precipitation of $Mn(OH)_2$. An excess of known volume of EDTA is added to an acidic solution of Mn salt and then ammonia buffer is used to adjust the pH to 10 and the excess EDTA remaining after chelation is back titrated with standard Zn solution kept in burette using Eriochrome black T as indicator.

**Replacement Titration**

In this method, the metal which is to be analyzed, displaces quantitatively the metal from the complex. When direct or back titrations do not give sharp end points, the metal may be determined by the displacement of an equivalent amount of Mg or Zn from a less stable EDTA complex.

**Application:** $Mn^{2+}$ displaces $Mg^{2+}$ from Mg-EDTA solution. The freed Mg metal is then directly titrated with a standard EDTA solution. In this method, excess quantity of Mg-EDTA complex is added to $Mn^{2+}$ solution. $Mn^{2+}$ quantitatively displaces $Mg^{2+}$ from Mg-EDTA complex. This displacement takes place because $Mn^{2+}$ forms a more stable complex with EDTA. Using this method $Ca^{2+}$, $Pb^{2+}$, $Hg^{2+}$ can also be determined using Eriochrome black T indicator.

### Indirect Titration

This method is also known as Alkalimetric titrations. It is used for the determination of ions such as anions, which do not react with EDTA chelate. Protons from disodium EDTA are displaced by a heavy metal.

**Application:** Barbiturate will not react directly with EDTA and barbiturate forms complex with $Hg^{2+}$ ions quantitatively. Titration of Hg-barbiturate with EDTA gives the concentration of equivalent amount of barbiturate.

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## Unit 3 (C) GRAVIMETRIC ANALYSIS & DIAZOTIZATION TITRATION

### 📌 INTRODUCTION OF GRAVIMETRIC ANALYSIS

Gravimetric analysis involves measurement of weight of the substance to be analysed from a solution after isolating by precipitating the component as an insoluble compound of known chemical composition. The method is a quantitative analysis method by weight. From the weight of the compound, the calculation is done to determine the content.

For this process, the separation of the specific element from the sample compound should be achieved effectively. There are different ways through which the separation can be achieved:

1. **Precipitation method**
2. **Volatilization or evolution method**
3. **Electro-analytical method**
4. **Miscellaneous physical methods**

## Advantages of Gravimetric Method:

- Analysis can be done accurately and precise by using modern and sensitive analytical balance in gravimetric method
- Filtrate can be examined for completion of the precipitation reaction and errors can be reduced at high extent
- Direct measurement of the compound(s) is done in gravimetric method; so calibration is not required in gravimetric method. It is an absolute method of analysis
- Gravimetric method is inexpensive as compared to other analytical methods
- The weight of the element or radical can be calculated in a single step
- Gravimetric factor is used to convert gram of a compound to gram of an element or radical. It varies for different compounds

## 🧪 PRECIPITATION TECHNIQUES

Precipitation method is a process of weighing an element or radical in the form of precipitates which is separated by filtration from solution. Precipitation method is affected by some factors:

✓ Precipitated compound must be convertible into a pure compound by ignition or by simple evaporation
✓ Precipitated compound must be free from soluble impurities
✓ Precipitated compound must be insoluble in solution
✓ Precipitated compound must be readily separated the solution by filtration process

### Colloidal Precipitates

Gravimetric analysis encounters colloidal precipitates sometimes at initial stages of reaction. The hydroxide precipitates of most of the metals are colloidal in nature and require necessary treatment before filtration. Colloid shows non-settling nature under gravity and high surface area which is responsible for showing adsorption of other impurities. Electrovalent colloids have a tendency to absorb common ions.

**Properties of Colloids**

- **Brownian motion:** Colloidal particles shows zig-zag movement in a colloidal solution
- **Tyndall Effect (Reflection and light scattering):** Tyndall effect is the ability of a colloid to scatter light. The beam of light can be seen through the colloid

## 🌊 SUPERSATURATION

Supersaturation is a thermodynamically unstable state; it can be achieved by addition of excess substance (to a solution) as compared to normal condition. The supersaturation point is divided into three zones:

**Zone 1 – Nucleation zone:**

The solution may not nucleate for a long time but this zone will sustain growth. It is frequently necessary to add a seed crystal.

**Zone 2 – Nucleation zone:**

Crystals nucleate and grow in nucleation zone.

**Zone 3 – Precipitation zone:**

Substance(s) are precipitated out in the solution in this zone.

## ⚠️ CO-PRECIPITATION

Co-precipitation is the contamination of a precipitate by a normally soluble substance that coprecipitates with the desired precipitate. Several mechanisms can cause co-precipitation:

### Inclusion

An inclusion occurs when the impurity occupies a lattice site in the crystal structure of the carrier, resulting in a crystallographic defect; this defect occurs when the ionic radius and charge of the impurity are similar to those of the carrier. An adsorbate is an impurity that is weakly bound to the surface of the precipitate.

### Occlusion

An occlusion occurs when an adsorbed impurity (foreign ions) gets physically entrapped inside the rapidly growing crystals. Occlusion can be minimized by slowing down the precipitation process.

### Adsorption

Adsorption is a common source of co-precipitation that is likely to cause significant contamination of precipitates with large specific surface areas.

### Mechanical entrapment

Mechanical entrapment occurs when crystals lie close together during growth. Several crystals grow together and trap a portion of the solution in a tiny pocket under this condition. Mechanical entrapment is lowest when

the rate of precipitate formation is slow under conditions of low supersaturation.

## 🔬 EXPERIMENTAL METHODOLOGY

In this technique, the analyte is converted to an insoluble form which can be washed, dried and weighed in order to determine the concentration of the analyte in the original solution. Gravimetric method is applied to the samples where a good precipitating agent is available. The precipitated product should be quantitative, easily washed, filtered and dried in suitable quantity for accurate weighing. Therefore, gravimetry is regarded as a macro analytical technique.

**Steps in Gravimetric Analysis:**

1. **Preparation of the Solution:** Sample solution is prepared for the analysis; precipitation should be carried out in dilute solution(s). Adjustment of the volume, appropriate pH and getting the desired properties of the solution for the precipitate is taken care in this step.
2. **Precipitation:** This step requires addition of the precipitating agent in the form of solution to the sample solution. After addition of the first drop of the precipitating agent, supersaturation occurs, and nucleation starts to occur, where molecules of precipitate aggregate together and forms a nucleus.
3. **Digestion of the Precipitate:** The precipitate is left hot for 30 min to 1 hour in order for the particles to be digested. Digestion involves dissolution of small particles and re-precipitation on larger ones resulting in particle growth and better precipitate characteristics. This process is called Ostwald ripening. An important advantage of

digestion is observed for colloidal precipitates where large amounts of adsorbed ions cover the huge area of the precipitate.

4. **Washing and Filtering the Precipitate:** It is crucial to wash the precipitate very well in order to remove all adsorbed species which will increase the weight of the precipitate. Large amount of water should not be used for washing since some part of the precipitate may be lost.
5. **Drying and Ignition:** The purpose of drying (heating at about 120-150°C in an oven) or ignition in a muffle furnace at temperature ranging from 600-1200°C is to get a material with exactly known chemical structure so that the amount of the analyte can be accurately determined.

## 📈 POST-PRECIPITATION

Other ions form precipitates with the precipitating agent. But rate of the reaction is slower and the precipitate of the analyte is left for a long time without filtration or during digestion process; these foreign ions precipitate out in the same solution and the process is known as post precipitation. Post precipitation is responsible for positive error in the gravimetric analysis.

## 🧮 GRAVIMETRIC CALCULATIONS

Weight of analyte is calculated from the weight of precipitate. Stoichiometric calculations method is used for gravimetric determination.

**Weight of substance sought = Weight of precipitate × Gravimetric factor**

The gravimetric factor is calculated as: **Gravimetric factor = (Molecular weight of substance sought)/(Molecular weight of precipitate) × (Number of moles of precipitate)/(Number of moles of substance sought)**

## 📄 FILTER PAPERS

Filter paper is a semi-permeable paper barrier placed perpendicular to a liquid or air flow. It is used to separate fine solids from liquids or air. Ashless filter paper is mainly used for gravimetric methods in quantitative chemical analysis. It has a base weight of 80 $g/m^2$.

## ⚖️ ESTIMATION OF BARIUM SULPHATE

**Principle:**

When dilute Sulphuric acid ($H_2SO_4$) is added to the dilute solution of barium chloride ($BaCl_2$), a white precipitate of barium sulphate ($BaSO_4$) is formed. A white gelatinous precipitate is obtained which is filtered, washed, dried, ignited and weighed as barium sulphate ($BaSO_4$).

**$BaCl_2 + H_2SO_4 \rightarrow BaSO_4 \downarrow + 2HCl$**

**Requirements:**

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), volumetric flask, conical flask, burette, pipette etc.

**Experiment:**

Pipette out 25 ml of given solution of barium chloride ($BaCl_2$) in 500 ml beaker. Add 0.5 ml of concentrated Sulphuric acid ($H_2SO_4$) and 100 ml of distilled water. Heat the resulting solution to boiling. To this hot solution, add dilute Sulphuric acid ($H_2SO_4$) solution drop wise with constant stirring until the precipitation is complete.

Allow the precipitate to settle down and test the supernatant liquid for complete precipitation. Now, filter the precipitate by decanting method through Whatman filter paper. Wash the precipitate 3-4 times with hot water and dry it by placing the funnel in an oven. After drying, transfer the filter paper containing precipitate to the pre-constantly weighed crucible and ignite it till all the carbonaceous matter is burnt off.

Now, cool the crucible and add one drop of each of concentrated hydrochloric acid (HCl) and concentrated Sulphuric acid ($H_2SO_4$). Cool the crucible by placing in a desiccator and weigh it. Precipitation should be carried out in a dilute hot solution and in the presence of 0.05N HCl, which helps to increase the size of the precipitate particles.

**Calculation:**

**% of $BaSO_4$ = (Weight of $BaSO_4$ obtained/Weight of sample taken) × 100**

**% of Ba = (Weight of $BaSO_4$ obtained × Atomic weight of Ba)/(Molecular weight of $BaSO_4$ × Weight of sample taken) × 100**

Where:

- Atomic weight of Ba = 137.33
- Molecular weight of $BaSO_4$ = 233.39

# 💊 DIAZOTIZATION TITRATION 🧪

## 📌 INTRODUCTION

This titration involves the conversion of the primary aromatic amine to a Diazonium compound by the reaction with sodium nitrite. Initially, this method was applied to the synthetic dye industry. In this method, the primary aromatic amine is reacted with the sodium nitrite in acidic medium 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 involved in this method is to treat the amino group containing drug with the acid solution. The resulting solution is immersed in the cold water bath or ice water bath by maintaining the temperature at 0–5°C. Then this solution is titrated with the sodium nitrite solution. The end point is determined by starch iodine paper.

**Indirect method:**

The principle involved in this method is that, the excess nitrous acid is added to the titration sample solution and it is back titrated with the other appropriate titrant. This method is mainly used for the titration of insoluble Diazonium salts.

**Other method:**

The main principle involved in this method is, the formation of the diazo oxide which is more stable than the diazo compounds. The aminophenol is readily oxidized by the nitrous acid and converted to the quinones in the presence of copper sulphate solution and forms the diazo oxide compounds. This readily undergoes the coupling reaction with the nitrous acid.

## ⚗️ PRINCIPLE

Primary aromatic amines in the presence of HCl acid react with Sodium nitrite ($NaNO_2$) to form diazotization. When sodium nitrite is reacted with the hydrochloric acid, sodium chloride and nitrous acid are formed. The obtained nitrous acid is reacted with the primary aromatic amine to form the Diazonium salt.

**Chemical Reactions:**

1. $\mathbf{NaNO_2 + HCl \rightarrow NaCl + HNO_2}$
2. $\mathbf{R\text{-}NH_2 + HNO_2 + HCl \rightarrow R\text{-}N_2^+Cl^- + 2H_2O}$

This method is also known as nitrite titration. Starch iodine paper is used to detect end point. After completion of the reaction, starch iodine paper reacts to give the colour change at the end point.

The reaction is carried out in ice bath to maintain the temperature between 0-5°C; if temperature rises then nitrogen of Diazonium salt will be evaporated as nitrogen gas. Diazotization titration method is used to determine Sulphanilamide, Sulphonamides and other sulpha drugs.

## 🧪 PROCEDURE

**Standard Solution:**

2.5 gm of the sample is accurately weighed and transferred into a 250 ml standard flask. To this, 50 ml of concentrated hydrochloric acid and 5 gm potassium bromide are added. Final volume is made up with distilled water.

From this standard solution appropriate volume (50 ml) is pipetted out into a stoppered conical flask and the temperature is maintained at 0-5°C. Then the solution is titrated with the N/10 $NaNO_2$ solution until the starch iodine paper turns into blue colour.

**Potentiometric Titration:**

Alternatively, the titration can be performed using Potentiometry also. About 0.5 gm of sample is weighed accurately and transferred into a 250 ml beaker. The contents are dissolved using 10 ml HCl and 75 ml of water.

A pair of bright platinum electrodes are inserted into the solution and connected through a sensitive galvanometer. A potential drop between 30-50 mμ across the electrodes is produced using a suitable potentiometer.

Titration is slowly carried out with N/10 $NaNO_2$ with continuous stirring until a permanent deflection of the galvanometer is observed at the end point. Liberation of excess of nitrous acid at the end point depolarizes the electrode, current flows and full deflection in galvanometer needle is observed.

This is known as the dead stop end point. The electrode must be clean otherwise the end point is sluggish. Cleaning the electrodes in boiling nitric

acid containing a little ferric chloride for about 30 sec and then washing with water will solve the problem of sluggish endpoint.

The blank determination is carried out and the volume is subtracted from the sample titration volume to give the exact volume required to react with the amine.

## 🌡️ CONDITIONS FOR THE DIAZOTIZATION TITRATION

**Rate of Titration:**

Addition of sodium nitrite to the sample solution takes time to react with the amino group present in the sample solution. Different amino compounds react with the nitrous acid at different rates. Based on this, the amino compounds are classified into two main groups:

- **Slow diazotizable compounds:** Sulphanilic acid and anthranilic acid
- **Fast diazotizable compounds:** Aniline, aminophenol and toluidine

The reaction rate is increased by the addition of the potassium bromide solution.

**Temperature:**

Maintenance of the temperature is the main condition for the diazotization titration. The Diazonium salts formed are not stable at elevated temperatures. They are readily decomposable at elevated temperatures; therefore, the temperature should be maintained at 0-5°C.

## ✅❌ ADVANTAGES AND DISADVANTAGES

**Advantages:**

- Selective for all types of sulphonamides
- High sensitivity and reproducibility
- Accurate results for pharmaceutical analysis
- Suitable for quality control of drugs

**Disadvantages:**

- The method is applicable for a very less variety of samples
- Relatively slow when compared to other methods
- Temperature conditions to be properly maintained throughout the reaction
- The end point detection is very difficult
- The colour produced is not stable
- Lack of specificity

## APPLICATIONS OF DIAZOTIZATION TITRATION

| Drug/Compound | Application |
|---|---|
| **Amphetamine** | Determination in pharmaceutical formulations |
| **Benzoic acid (Vitamin $B_1$)** | Quantitative analysis |
| **Dopamine** | Pharmaceutical analysis |
| **Procaine & Sulphonamides** | Quality control testing |
| **Chlorpheniramine** | Drug content determination |
| **Ephedrine** | Pharmaceutical assay |

## Summary Table - Comparison of Analytical Methods

| Method | Principle | Indicator | pH Range | Applications |
|---|---|---|---|---|
| **Mohr's Method** | Precipitation with $AgNO_3$ | $K_2CrO_4$ (5%) | 6.5-10.3 | NaCl, KCl, NaBr, KBr |
| **Volhard's Method** | Back titration with $SCN^-$ | $Fe^{3+}$ (Iron alum) | Acidic | Halides, thiocyanates |
| **Fajan's Method** | Adsorption indicators | Fluorescein, Eosin | 6.5-10.3 ($Cl^-$), 2.0-10.3 ($Br^-$, $I^-$) | Halides |
| **Complexometric** | EDTA chelation | Metal indicators | Varies with metal | Metal ions |
| **Gravimetric** | Weight measurement | Visual (precipitation) | Optimized | Elements/radicals |
| **Diazotization** | Diazonium salt formation | Starch-iodine | Acidic | Primary aromatic amines |

## 🎯 CONCLUSION

This unit covers the fundamental analytical techniques used in pharmaceutical analysis including precipitation titrations, complexometric titrations, gravimetric analysis, and diazotization titrations. Each method has its specific applications, advantages, and limitations. Understanding these techniques is crucial for pharmaceutical quality control and drug analysis.

The methods discussed provide accurate and reliable means for quantitative determination of various pharmaceutical compounds, ensuring drug safety and efficacy through proper analytical testing procedures.