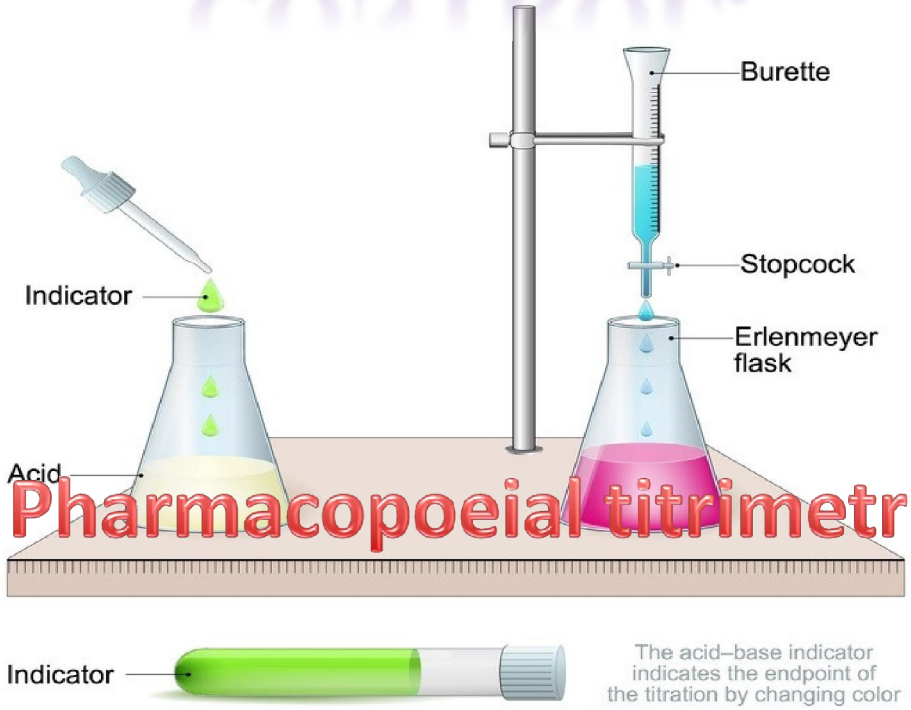
Master 2: Pharmaceutical Chemistry

Module: Drug Analysis and Control

CHAPTER VI. CHEMICAL ANALYSIS FOR MEDICINES QUALITY CONTROL.

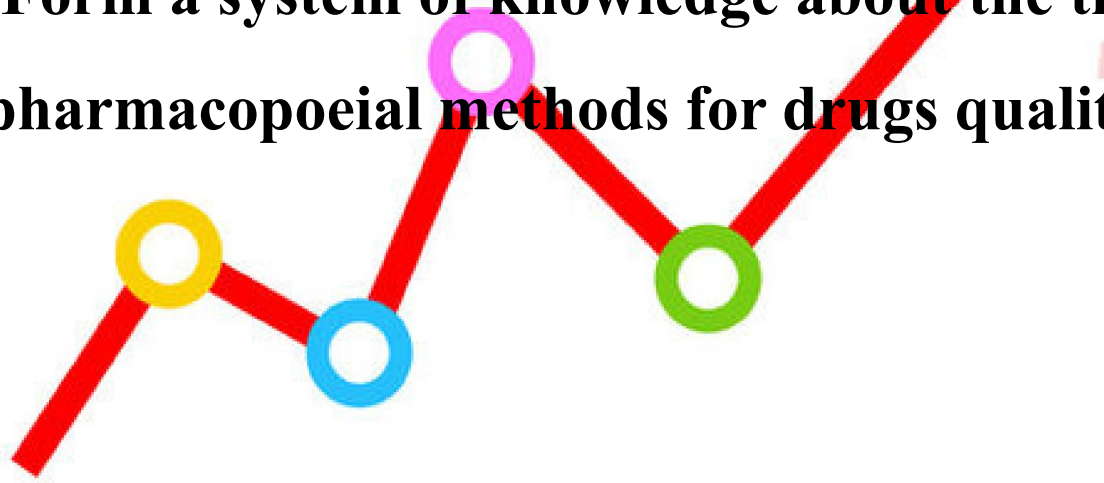


Course.01 Pharmacopoeial titrimetric methods

Pharmacopoeial titrimetric methods

OBJECTIVE

Form a system of knowledge about the titrimetric pharmacopoeial methods for drugs quality control.



Generality

The term titrimetric analysis refers to quantitative chemical analysis carried out by determining the volume of a solution of accurately known concentration which is required to react quantitatively with a measured volume of a solution of a substance to be determined. The solution of accurately known concentration is called standard solution.

The term volumetric analysis was used for this form of quantitative determination but it has now been replaced by titrimetric analysis. In titrimetric analysis the reagent of known concentration is called titrant and the substance being titrated is termed the titrand.

Generality

Chemical reactions used for titration methods should meet following requirements:

– There must be a simple reaction which can be expressed by a chemical equation; the substance to be determined should react completely with the reagent in stoichiometric or equivalent properties.

2- The reaction should be relatively fast. (Most ionic reaction satisfy this condition.) In some cases the addition of a catalyst may be necessary to increase the speed of a reaction.

3- There must be an alteration in some physical or chemical property of the solution at the equivalence point.

4- An indicator should be available which, by a change in physical properties (color or formation of a precipitate), should sharply define the end point of the reaction.

Definition of some terms

Titration

Titration is the process in which the standard reagent is added to a solution of an analyte until the reaction between the analyte and reagent is complete.

Equivalence point and End point

The equivalence point of a titration is a theoretical point that can not be determined experimentally. Instead, we can only estimate its position by observing some physical change associated with the condition of equivalence. This change is called the end point for titration.

Titration error

The difference between the observed end point and the true equivalence point in a titration.

$TE = V_{ep} - V_{eq}$

Definition of some terms

Indicators

Indicators are often added to analyte solution in order to give an observable physical change (end point) at or near the equivalence point. In other wards indicator is a compound having a physical property (usually color) that changes abruptly near the equivalence point of a chemical reaction.

Indicator selection also depends on the type of reaction:

acid-base indicators – phenolphthalein, methyl red, methyl orange, phenol red, and others; starch solution is used in iodometric titrations, tropeolin OO for diazotisation titrations, in argentimetric titrations solutions K_2CrO_4, $FeSO_4$, etc. are used; murexide is applied in complexometric titrations.

Definition of some terms

End Points in Volumetric Analysis

Detection of an end point involves the observation of some property of the solution that change in a characteristic way at or near the equivalent point. The properties that have been used for this purpose are numerous and varied; they include:

1. Color due to the reagent, the substance being determined, or an indicator substance.

2. Turbidity changes resulting from the formation or disappearance of solid phase.

3. Electric conductivity of the solution.

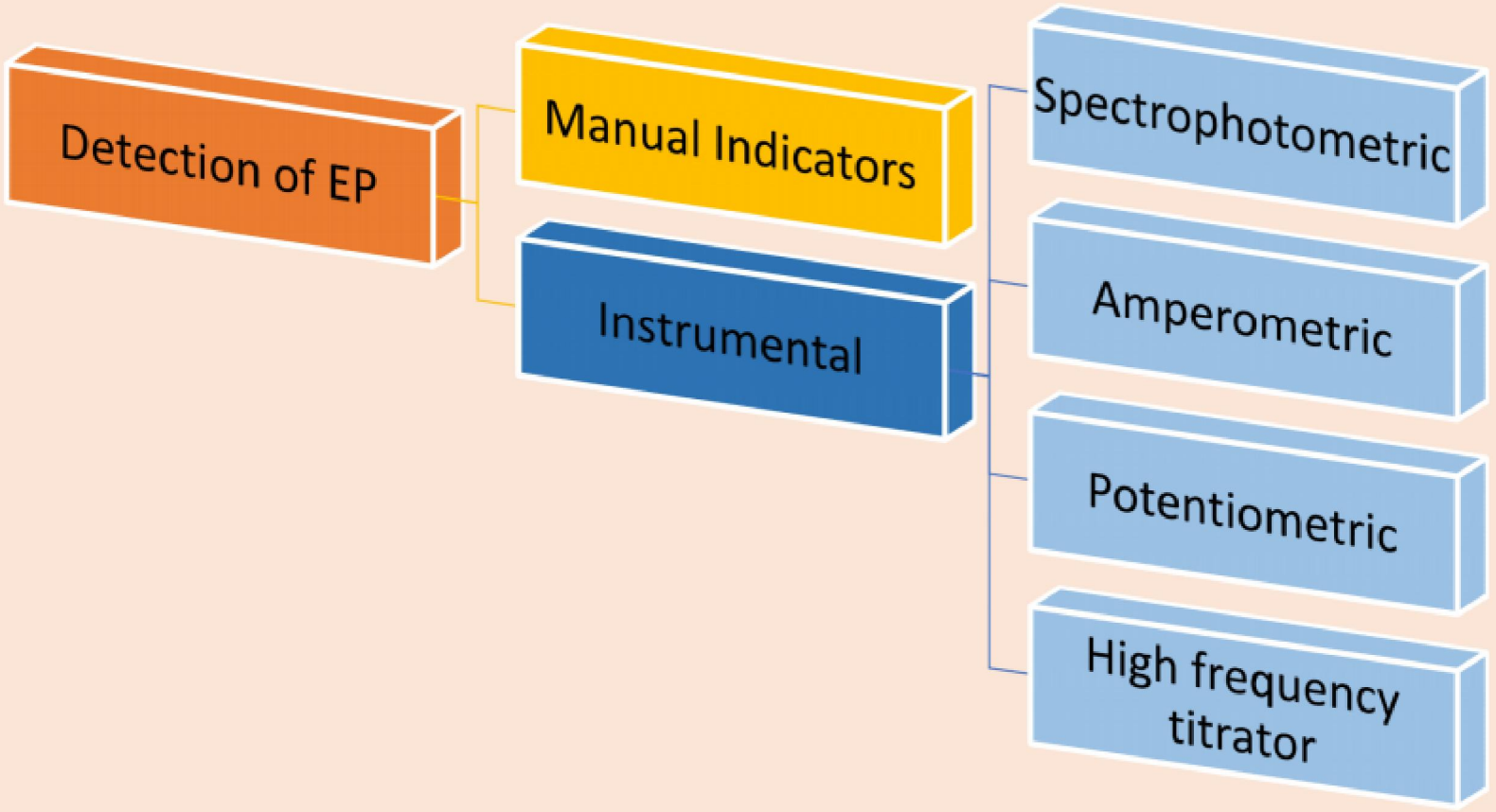
4. Electric potential between a pair of electrodes immersed in the solution.

5. Refractive index of the solution.

6. Temperature of the solution.

7. Electric current passing through the solution

Methods of end point detection



Definition of some terms

Types of titration used in pharmaceutical analysis :

Direct titration and back titration

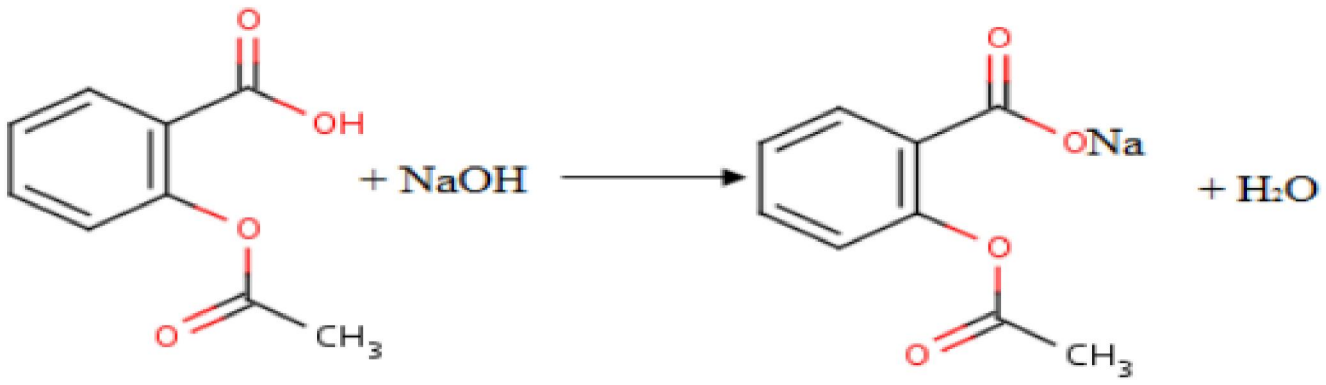
When a titrant reacts directly with an analyte, the procedure is termed a direct titration. It is some times necessary to add an excess of standard titrant and then determine the excess amount by back titration with a second standard titrant. In other wards back titration is a process in which the excess of standard solution used to react with an analyte is determined by titration with a second standard solution.

Back – titration are often required when the rate of reaction between the analyte and reagent is slow or when the standard solution lacks stability. In back – titration, the equivalence point corresponds to the point when the amount of initial titrant is chemically equivalent to the amount af analyte plus the amount of back titrant.

Direct titration

Example: alkalimetric determination of aspirin. Indicator phenolphthalein changes its color (pink color appearance) at the endpoint.

- At the equivalence point products (salt – sodium acetylsalicylate and water) are formed:



Analyte reacts directly with the titrant and in accordance with the equivalents law, equivalence factor 1/z = 1:

$$n(NaOH) = n(aspirin);$$
$$n(aspirin) = C(NaOH) \cdot V(NaOH).$$

Back titration

Example: acidimetric determination of lithium carbonate:

$$Li_2CO_3 + 2HCl_{excess} = 2LiCl + H_2O + CO_2 + HCl_{residue};$$

$$V(HCl) = V_1;$$

$$HCl_{residue} + NaOH = NaCl + H_2O;\ V(NaOH) = V_2.$$

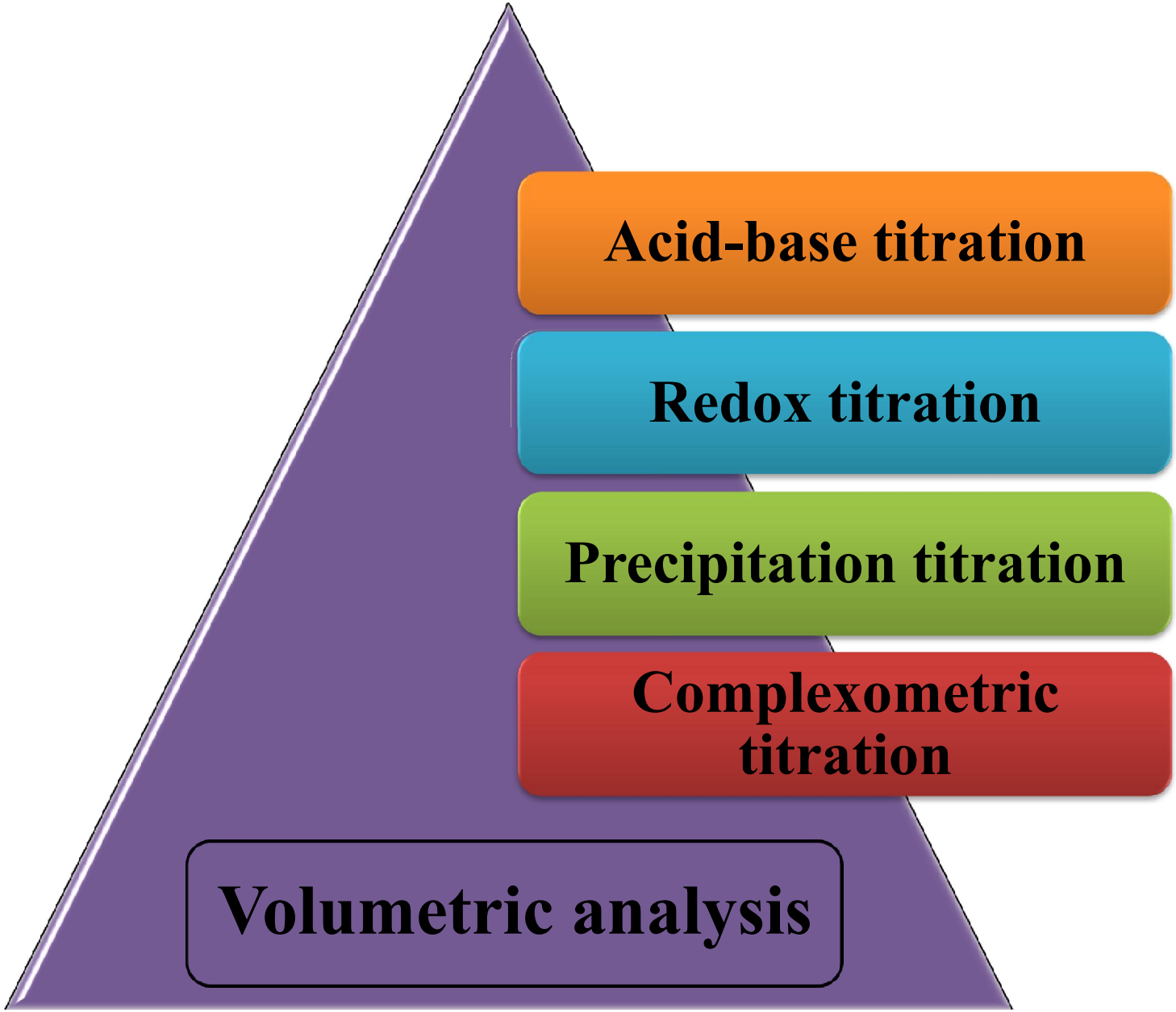
In the back titration in accordance with the equivalents law:

$$n(1/z\ Li_2CO_3) = n(1/z\ HCl) - n(1/z\ NaOH);$$

$$n(1/z\ Li_2CO_3) = C(1/z\ HCl) \cdot V_1 - C\ (1/z\ NaOH) \cdot V_2;$$

or $n(1/z\ Li_2CO_3) = C(1/z\ HCl) \cdot \Delta V$, where: $\Delta V = V_1 - V_2$.

Classification of reaction in titrimetric analysis



Acid-base titration

An acid base titration is the determination of the concentration of an acid or base by exactly neutralizing the acid or base with an acid or base of known concentration. This allows for quantitative analysis of the concentration of an unknown acid or base solution. its also known as Neutralization titration.

Example:

$HCl + NaOH \longrightarrow NaCl + H_2O$

$CH_3COOH + NaOH \longrightarrow CH_3COONa + H_2O$

❖The objective of carry out acid base titration is to determine equivalent quantity of other substance required for neutralization.

Redox titration

Definitions

•**Oxidation:** It can be defined as loss of electrons or increase in oxygen content.

• **Reduction:** It can be defined as gain of electrons or increase of hydrogen content.

• **Oxidizing agent:** substance which get reduced.

• **Reducing agent:** substance which get oxidized.

• Both processes are combined and occur together so we combine them in one word as REDOX reaction.

Redox titration

Reaction of ferrous ion with ceric ion

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

$Fe^{2+} - e \rightleftharpoons Fe^{3+}$ (Loss of electrons: **Oxidation**)

$Ce^{4+} + e \rightleftharpoons Ce^{3+}$ (Gain of electrons: **Reduction**)

- **In every redox reaction, both reduction and oxidation must occur.**
- **Substance that gives electrons is the reducing agent or reductant.**
- **Substance that accepts electrons is the oxidizing agent or oxidant.**

Precipitation titration

Precipitation Reactions

❖**Precipitation is the formation of a solid in a solution**

❖**solid formed is called the precipitate .**

❖**A precipitation reaction occurs when water solutions of two different ionic**

$$KCl + AgNO_3 \longleftrightarrow AgCl + KNO_3$$

Cl^- solution — *Precipitating agent* — *White precipitate*

❖**The precipitate is itself ionic; the cation comes from one solution and the anion from another**

Precipitation titration

Precipitation titration is a titration method based on the formation of precipitate, which is slightly soluble

- The basic requirements are:
- The reaction must be sufficiently rapid and complete, lead to a product of reproducible composition and of low solubility.
- And a method must exist to locate the end point.

Argentometric titration:

- Titrations involving silver are termed argentometric, from the Latin name for silver, argentum.

- The major precipitation reaction used is that of silver with a range of anions. These anions include:
- Halides (Cl- , Br- , I-)
- Pseudohalides (S 2- , HS- , CN- , SCN-)

Complexometric titration

COMPLEX (COORDINATION COMPOUND)

Compound results from the combination of metal ion as (acceptor) with donor molecules (ligand) through coordinated bond (donor→ acceptor)

Metal ion + Ligand→ Coordination compound (complex)

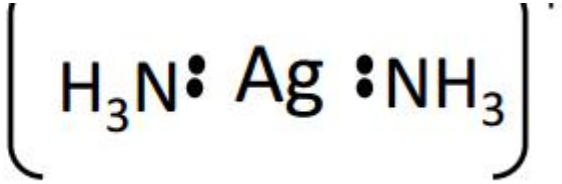
(Lewis acid) (Lewis base)

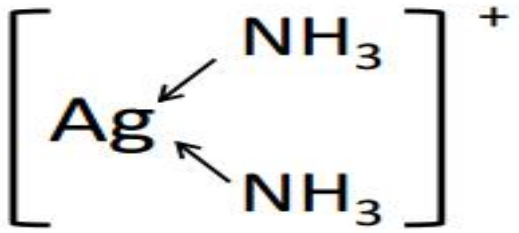
Examples:

$M^{n+} + L = (L \longrightarrow M)$

$[Ag(NH_3)_2]^+$

$[Fe(SCN)_6]^{3-}$





Complexometric titration

COMPLEX (COORDINATION COMPOUND)

Complex Ion = Transition Metal Cation Surrounded by Ligands

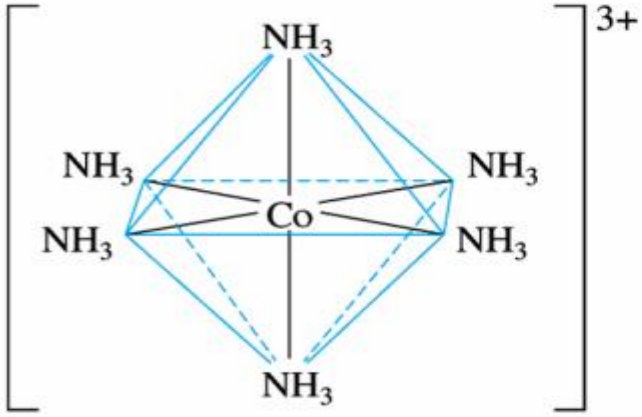
Ligand = Molecule or Ions of Nonbonding Electron Pairs

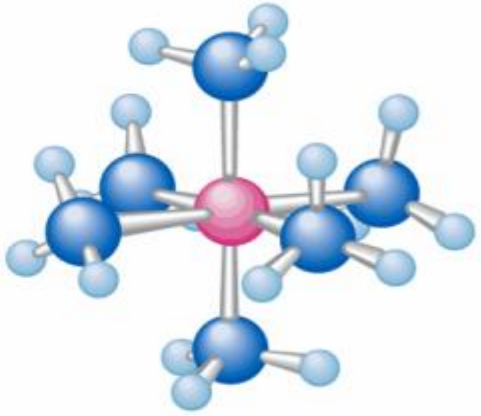
Bonding is Called "Coordination"

Examples:

For the complex [Co(NH3)6]3+

Co3+ is the electron acceptor and shares a pair of electrons with each of N-atom in NH3





Complexometric titration

COMPLEXOMETRY

A volumetric titration involves the formation of soluble complex between metal ion (as acceptor) and ligand (as donor) to form coordination bonds.

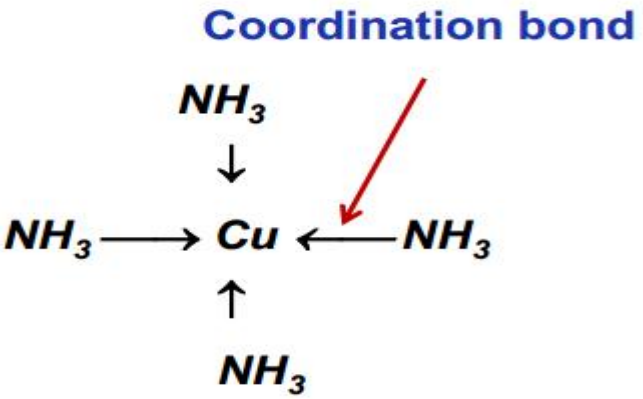
(A titration based on the formation of a coordination complex is known as a complexometric titration). Complexometric titrations are particularly useful for the determination of a mixture of different metal ions in solution

The metal ion is known as Central metal atom.

The anion or neutral molecule is known as Ligand (L)

$$Cu^{2+} + 4NH_3 \leftrightarrow [Cu(NH_3)_4]^{2+}$$

Ligand



Complexometric titration

NATURE OF THE ACCEPTOR ATOM (METAL ION)

The metallic ion (atom) has stable electronic configuration. It forms additional completed shells by accepting electron pairs from donor atoms.

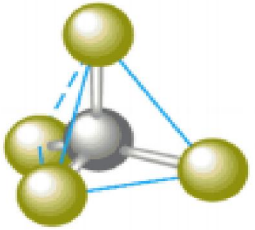
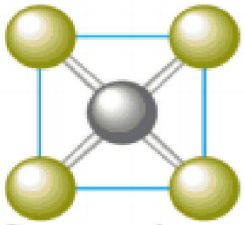
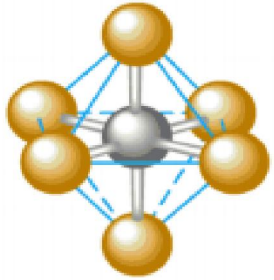
Coordination Number:

1. **The no. of coordinate bonds formed to a metal ion by their ligands (The number of covalent bonds that a cation tends to form with electron donors is called coordination number).**
2. **It could be 2, 4, 6, depending on the metal ion and its oxidation number.**

Complexometric titration

NATURE OF THE ACCEPTOR ATOM (METAL ION)

The geometries of the ligands about the central atom are as shown

Coordination number	Geometry
2	 Linear
4	 Tetrahedral  Square planar
6	 Octahedral

Complexometric titration

NATURE OF THE DONOR ATOM

In aqueous solution, donors are nonmetallic elements N, O, and S.

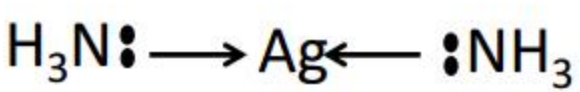
Ion	Coordination number	Typical complex
Ag^{+}	2	$Ag(NH_3)_2^{+}$
Cu^{2+}	4	$Cu(NH_3)_4^{2+}$
Zn^{2+}	4	$Cd(NH_3)_4^{2+}$
Hg^{2+}	4	$Hg(NH_3)_4^{2+}$
Co^{2+}	6	$Co(NH_3)_6^{2+}$
Ni^{2+}	6	$Ni(NH_3)_6^{2+}$
Fe^{3+}	6	$Fe(CN)_6^{3-}$

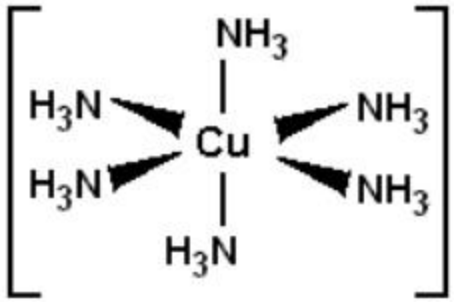
Complexometric titration

TYPE OF COMPLEXING AGENTS (LIGANDS)

This classification is according to the no. of sites attached to the metal ion

1. Unidentate (Monodentate) Ligand or "Simple Ligand“ The ligand attached to metal at one site e.g. H2O, NH3, CN-, Cl-, I-, Br-(i.e. forming one coordinate bond, or capable of donating one unshared pair of electrons)



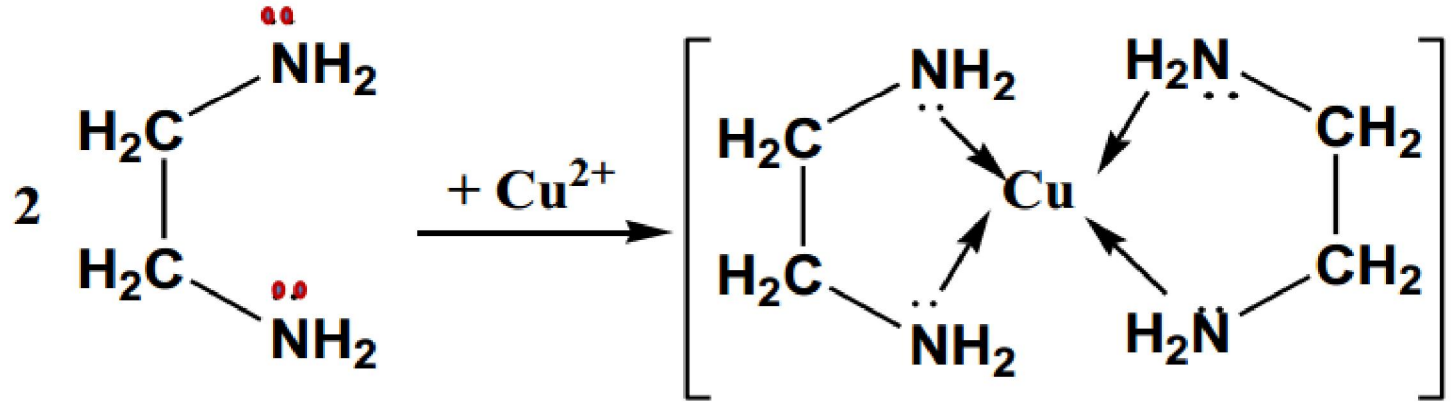


Complexometric titration

TYPE OF COMPLEXING AGENTS (LIGANDS)

2. Bidentate Ligand

The ligand attached to metal at two sites.



Ethylene diamine

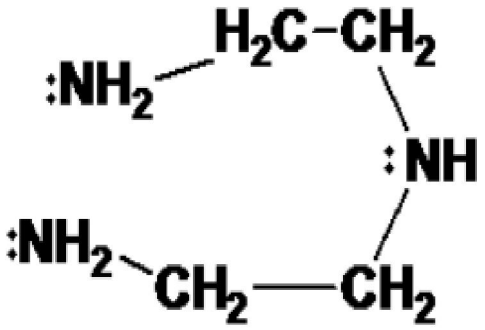
Copper amine complex

Complexometric titration

TYPE OF COMPLEXING AGENTS (LIGANDS)

3. Tridentate Ligands

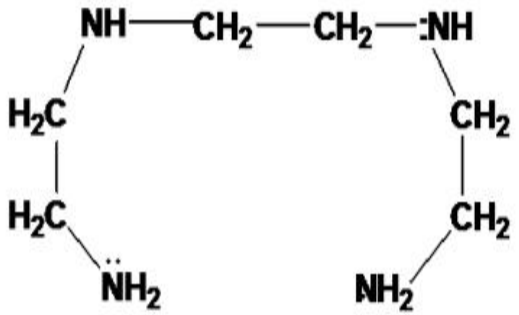
The Ligand attached to metal at 3 sites



Diethylene triamine

4. Tetradentate Ligands

The Ligand attached to metal at 4 sites



Triethylene tetramine

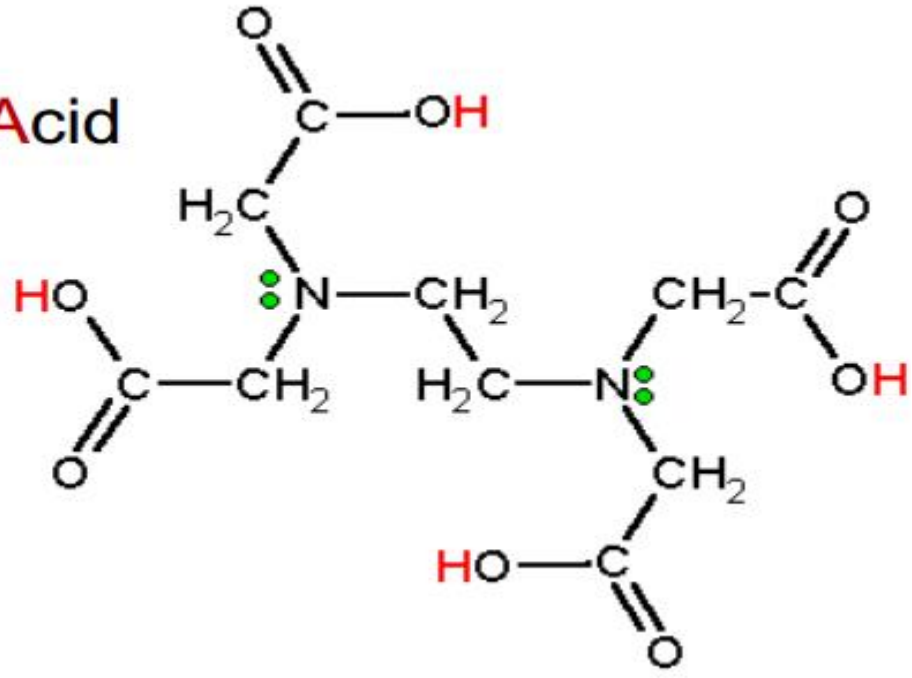
Complexometric titration

TYPE OF COMPLEXING AGENTS (LIGANDS)

5. Multidenate Ligands (Chelating Agent)

Substance with multiple sites available for coordination bonding with metal ions. Such bonding typically results in the formation of five or six membered rings.

Ethylene Diamine Tetra acetic Acid



EDTA has six sites for complex formation.
The electron pairs on the two nitrogen atoms and the four electron-rich carboxyl groups.

Complexometric titration

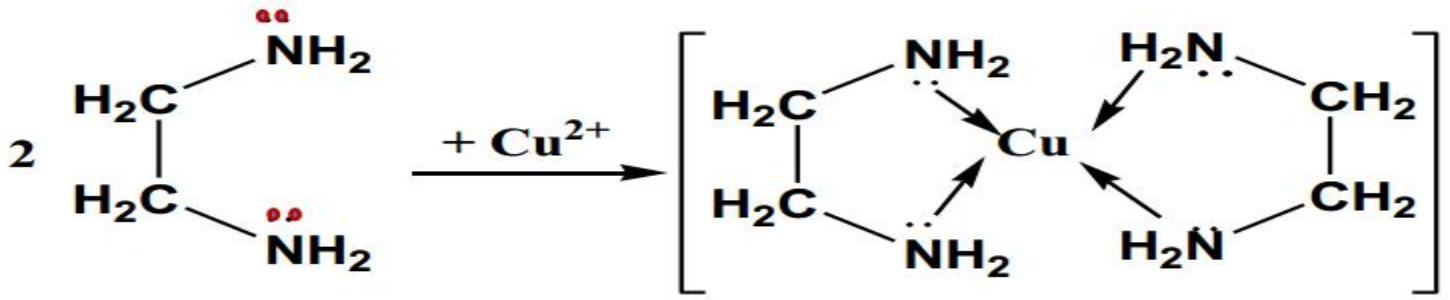
CHELATION

Chelate: A complex formed between the ligand containing two or more donor atoms and a metal, forming ring structure (heterocyclic rings or chelate rings).

Chelating agents: organic molecules containing two or more donor groups that combine with metal to form a complex of ring structure.

Chelate effect;

Enhancing the stability of multidentate complexes than unidentate complexes.

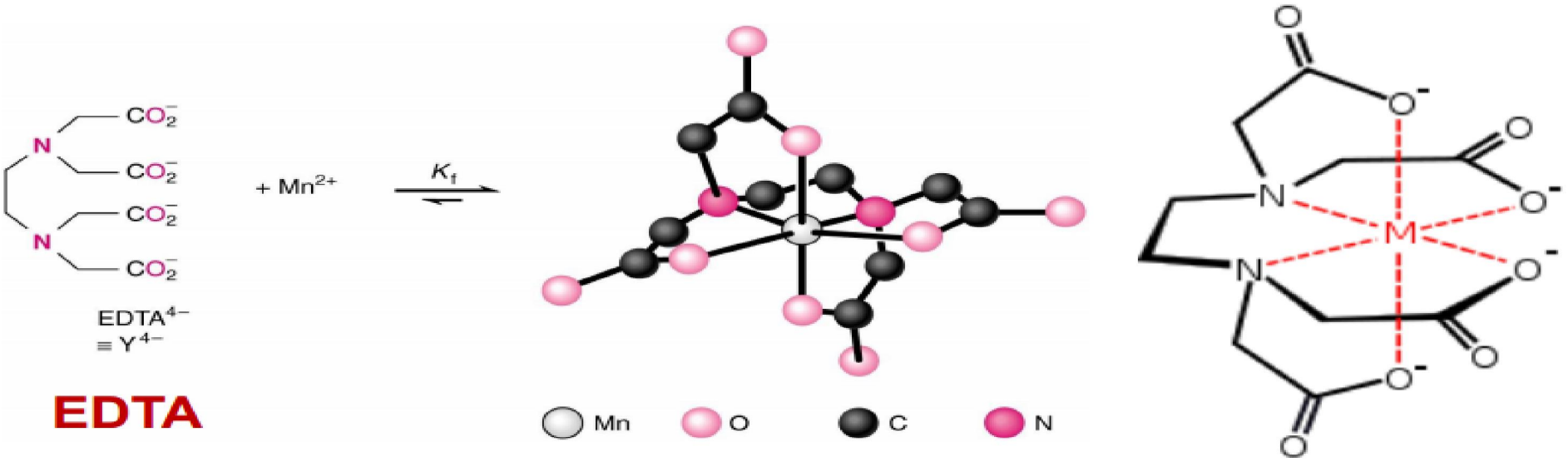


Cu(II) ethylenediamine chelate

Complexometric titration

TITRATION WITH MULTIDENTATE COMPLEXERS (CHELATING AGENTS)

Chelating agent: **Ethylene diamine tetra acetic acid (EDTA) possess enough donor atoms to fill the whole coordination sphere of metal ions in one step.**



The three-dimensional structure of the 1:1 metal-EDTA chelate with Mn2+.

Complexometric titration

ADVANTAGES OF EDTA OR H4Y

1.It forms very stable and soluble stoichiometric, 1:1 complexes with many metal ions.

3.The disodium salt of EDTA is an acceptable primary standard and commercially available.

4.Since the metal complexes are soluble, co precipitation errors are absent.

5.The end point could be easily achieved using metal ion indicators.

2.It offers some selectivity against specific metal ions by controlling the pH at which titration is performed.

Complexometric titration

DETECTION OF END POINT: USE METAL ION INDICATORS

- **Indicator is a dye which is capable of acting as a chelating agent to give a dye-metal complex.**
- **The latter is different in colour from the dye itself and also has a low stability constant than the chelate-metal complex.**
- **The colour of the solution, therefore, remains that of the dye complex until the end point, when an equivalent amount of sodium EDTA has been added.**
- **As soon as there is the slightest excess of EDTA, the metal-dye complex decomposes to produce free dye; this is accomplished by a change in colour.**

Complexometric titration

DETECTION OF END POINT: USE METAL ION INDICATORS

Metal indicators must comply with the following requirements:

• Metal-indicator complex must be less stable than the metal-EDTA complex.

• Binding between metal and indicator must not be too weak. It has to avoid EDTA replacing at the beginning of the titration.

• In general, the metal-indicator complex should be 10 to 100 times less stable than the metal-titrant complex.

• Colour of the indicator and the metal complexed indicator must be sufficiently different

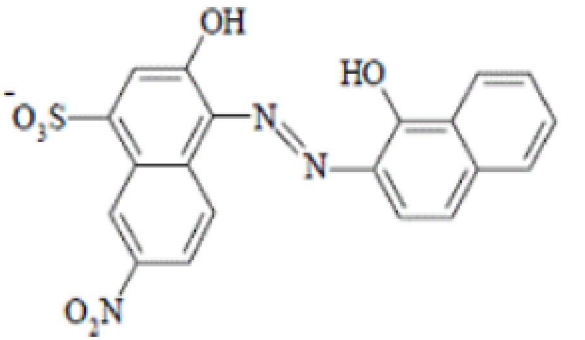
Complexometric titration

EXAMPLES OF METAL ION INDICATORS

1. Eriochrome black T (EBT)

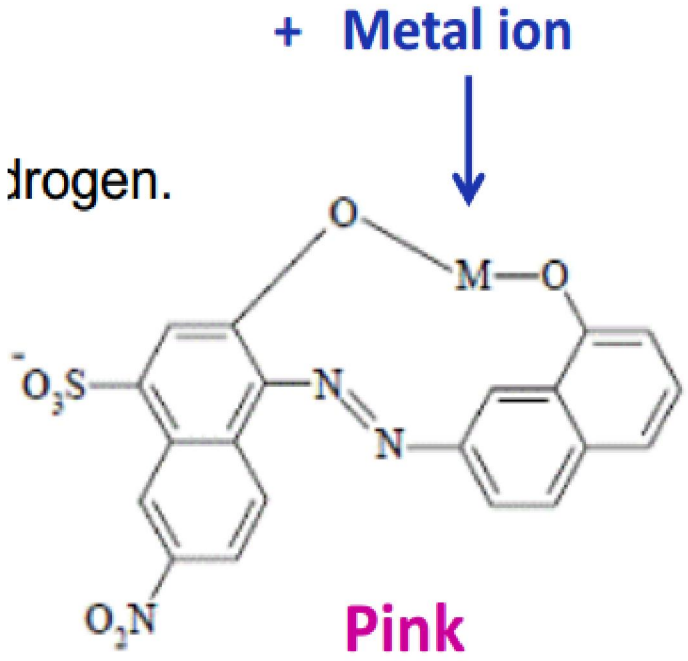
It can be represented by H2In The color of Indicator change with the change of pH

EBT contains 2 replaceable phenolic hydrogen.



(Eriochrome black T, Solochrome black T)

Blue (pH 10)



Before Titration:

- Mg^{2+} + In^- → MgIn
  (colourless) (blue) (red)

During Titration: Before the end point

- Mg^{2+} + EDTA → Mg-EDTA
  (free Mg^{2+} ions) (Solution red due to MgIn complex)

At the end point:

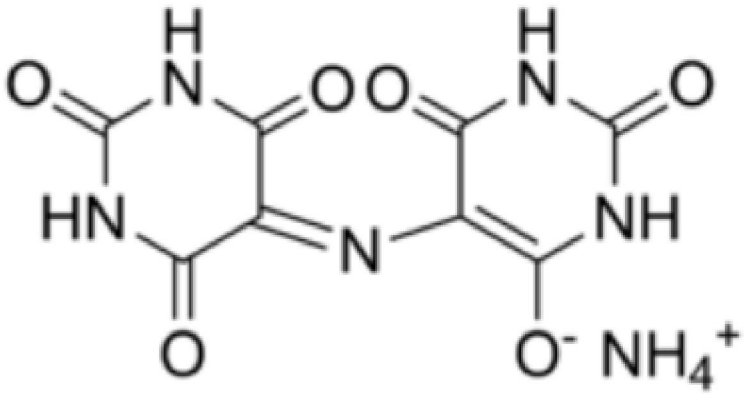
MgIn + EDTA → MgEDTA + In^-
(red) (colourless) (colourless) (Blue)

Complexometric titration

EXAMPLES OF METAL ION INDICATORS

2. Murexide

Ammonium salt of purpuric acid and its anion has the following structure.



•Murexide is used for the direct titration calcium at pH=10, the end point chan from pink to violet.

Metal	Color of complex	Color of indicator
Ca^{2+}	Pink	violet
Cu^{2+}	Orange	Violet
Co^{2+}	Yellow	violet
Ni^{2+}	yellow	violet

Complexometric titration

EXAMPLES : DIRECT DETERMINATION OF WATER HARDNESSOF METAL INDICATORS

- **Water hardness is due to the presence of Ca^{2+} & Mg^{2+}salts.**
- **EDTA forms complex with Ca^{2+}& Mg^{2+}**
- **Ca-EDTA complex is more stable than Mg-EDTA complex.**
- **At pH 12 EDTA forms complex with Ca^{2+} only.**

Complexometric titration

EXAMPLES : DIRECT DETERMINATION OF WATER HARDNESSOF METAL ION INDICATORS

Total Ca2+& Mg2+

•Total Ca2+ and Mg2+ determined by titration with EDTA at pH 10 using ammonia buffer and EBT as indicator

Upon titration with EDTA, Ca2+ will be chelated first, then Mg2+.

For Ca2+ Only

Direct titration with EDTA at pH 12 using 8% NaOH and Murexide.

Mg2+ is precipitated as Mg(OH)2leaving Ca2+to be titrated withEDTA

For Mg 2+

Total – Ca2+= Mg2+

ADVANTAGES OF TITRIMETRIC METHODS

- **High Rate Of Analysis;**
- **Equipment Simplicity;**
- **Ability For Analysis Automation;**
- **High Accuracy And Reproducibility.**