

**SHREE H. N. SHUKLA INSTITUTE OF
PHARMACEUTICAL EDUCATION AND
RESEARCH**



B.PHARM

(SEMESTER -I)

SUBJECT NAME: PHARMACEUTICAL ANALYSIS -I

SUBJECT CODE: BP102TP

UNIT 3(b): COMPLEXOMETRIC TITRATION

Content

Complexometric titration: Classification, metal ion indicators, masking and demasking reagents, estimation of Magnesium sulphate, and calcium gluconate.

INTRODUCTION

Complexometric titration is important for **metals and their salts**, certain anions and indirectly some drugs.

Though many substances are used as titrant in complexation phenomenon, **ethylene diamine tetra acetic acid disodium salt**, commonly known as EDTA, is most widely used.

Complexometric titrations are those reactions in which, simple metal ion is transformed into complex ion by addition of reagent which is known as **ligand**.

Complexometric titration is a form of volumetric analysis in which the formation of a coloured complex is used to indicate the end point of a titration.

The complex formed is stable and water soluble.

THEORY OF COMPLEXOMETRIC TITRATION

Complex ion formation:

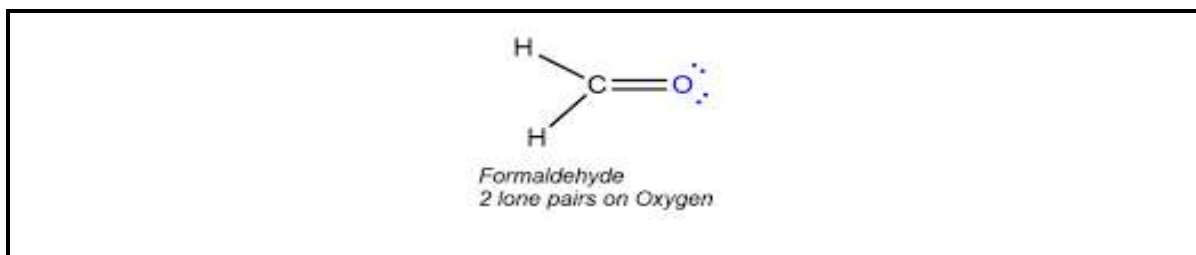
- A complexation reaction with a metal ion involves the replacement of the one or more of the coordinated solvent molecules by other nucleophilic groups. These groups are generally known as a ligand. Number of ligand that can attach to a central ion is known as coordination number (n).
- Ligands are those compounds which have some one or more lone pair of electron in outer shell of the any one atom of that compound.
- Replacement of water molecules by other ligand groups can occur until the complex is formed.
- Lone pair of electrons are useful to form a coordinated bond with the metal ion and thus formation of complex ion occurs. Thus, these types of ligands having lone pair of electrons are also known as complexing agent.

Lone pair of electrons are referred to as valence electrons that are not shared with another atom in a covalent bond and is sometimes called as unshared pair.

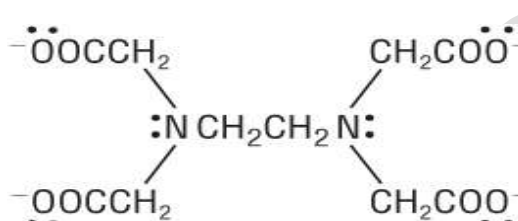
Lone pairs are found in the outermost electron shell of atoms.

e.g. HCHO

Electrons in outermost shell



- Most widely used ligand: **EDTA – multidentate**
- Ethylene diamine tetra acetic acid- Disodium salt.

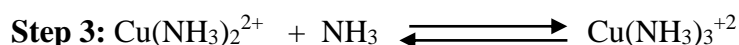
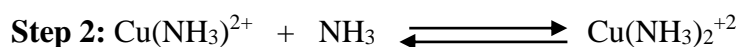


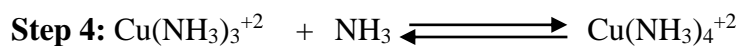
- EDTA is a Hexadentate. It have 6 pairs of electron which can form coordinated bond with metal ion.
- The ligand molecule usually possess oxygen, nitrogen or sulphur ion one or more number in their structure.
- Ligands may be classified on the bases of the number of point of attachment to the metal ion.

1. **Monodentate Ligand**
2. **Bidentate Ligand**
3. **Multidentate Ligand**

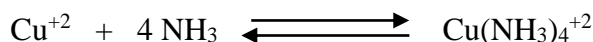
Monodentate ligand: (Unidentate)

- The ligand is bound to the metal ion at only one point by the donation of a lone pair of electrons to the metal.
- Thus, we can say that only one atom of that ligand having a lone pair of electron. These types of ligands are known as monodentate ligand. For e.g. NH_3 , Halide ions or the molecules H_2O .
- NH_3 is a unidentate ligand. It is capable of complexing with cupric ions (Cu^{+2}). The complex $\text{Cu}(\text{NH}_3)_4^{2+}$ proceeds in the following steps.



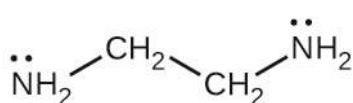


Considering the overall reaction:



Bidentate Ligand:

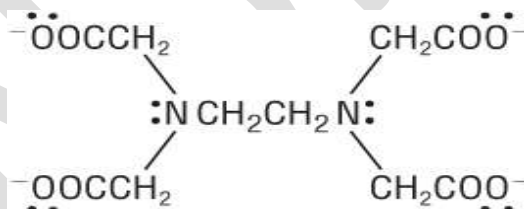
- When ligand molecules or ion has two atoms, each of which has a lone pair of electrons, then the molecule has two donor atoms, and it may be possible to form two coordinate bonds with the same metal ion, this is called a bidentate ligand.
- e.g. Ethylene diamine [Tris (ethylene diamine) cobalt (III) complex] – $[\text{Co}(\text{en})_3]^{3+}$



- Here, two lone pair of electrons by two atom in one molecule

Multidentate ligand:

- Multidentate ligand contains more than two coordinating atoms per molecules.
- For e.g. 1,2- diaminoethane tetra acetic acid (EDTA). It has two donor hydrogen atoms and four donor oxygen atoms in the molecule, so it can be hexadentate.



It has been assumed that the complex species does not contain more than one metal ion, but under appropriate conditions it is possible to form a binuclear complex, i.e. one containing two metal ions, or even a polynuclear complex containing more than two metal ions.

Thus interaction between Zn^{+2} and Cl^- ions may result in the formation of binuclear complexes e.g. $[\text{ZnCl}_6]^{2-}$, in addition to simple species such as ZnCl_3^- and ZnCl_4^{2-} .

Ethylene diamine tetra acetic acid (EDTA) disodium salt is very versatile complexing agent. The disodium salt is used in preparation of solution because of its greater water solubility. The important features of EDTA are:

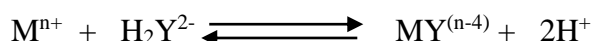
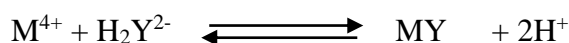
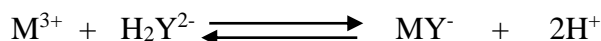
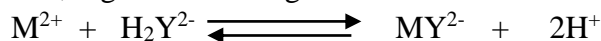
- 1) Complexes formed are stable.
- 2) Complex formation is quantitative and instantaneous.
- 3) Complexes formed are water soluble.
- 4) Complexes formation occurs with most metals of periodic table in 1:1 ratio.

- **Stability of Complexes:**

To simplify the following discussion, EDTA is assigned by H_4Y . Symbolic representation of EDTA disodium salt. $Na_2H_2Y \cdot H_2O$.

By ionization in water, it gives reactive species H_2Y^{2-} .

With metal ion, it gives following reaction:



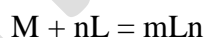
In this reaction acid is liberated. Hence, buffers are added to maintain pH of solution. pH has marked effect on stability of complex. Since reaction of M^{n+} (metal ion) with EDTA involves formation of acid. This reaction is reversible.

Due to liberation of acid alkaline range buffers are employed. If acid is not neutralized or removed, complex will break. Thus, complexes are stable in alkaline media and decompose in neutral or acidic media.

There is some exceptions are there.

- Some metals like aluminium, lead and mercury form complex under mild acidic condition, while other like bismuth, iron and chromium are stable under distinct acidic condition.
- Monovalent ions like sodium, potassium and Silver form weak complexes. These metals have no stability in acidic media.

Stability of complex is governed by law of mass action. Complex formation is equilibrium process. Metal ion react with Ligand (L). Then,



n= number of ligand molecule

Thus, stability constant K_s –

$$K_s = \frac{[ML_n]}{[M][L]^n}$$

As K_s increases, stability of complex is more. Concentration of unbound metal ion $[M]$ and ligand $[L]$ is less.

Formation of complex may be stepwise reaction. e.g. Cu^{+2} and ligand NH_3 .





$$\text{Overall stability constant } K_f = K_s = K_1 + K_2 + K_3 + K_4 = 2.1 \times 10^{13}$$

DETECTION OF END POINT

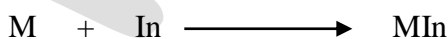
In complexometric titration, end point detection is done by following methods:

- I. By using visual indicator (pM indicator)
- II. Instrumental method detecting end point

I. VISUAL INDICATOR METHOD:

(a) Metallochromic /pM indicator

- These are dyes which show one colour in presence of metal ion. They do not show any colour or show different colour in absence of metal ion.
- Initially, indicator makes complex with metal ion and gives their unique colour. As the titration proceed further and metal ion titrated with EDTA, metal-indicator complex will break and metal-EDTA complex will form.
- Indicator will become free. Free indicator will give its original colour. Change in colour due to free indicator will help to detect end point.



🚦 Properties of metal ion indicator:

- 1) Metal ion indicator should be sufficient stable. It should not dissociate otherwise colour change will not be observed.
- 2) Metal indicator (MIn) complex should be less stable than metal-EDTA complex so that EDTA will take metal ion from MIn complex which will give sharp colour change by liberation of lidicator at the end point.
- 3) The colour reaction should be such that before end point the solution is strongly coloured.
- 4) The colour contrast between the free indicator and metal indicator complex is sufficient so that it can be readily observed.

- 5) The indicator must be sensitive to metal ion concentration.
- 6) The colour reaction is either specific or selective.
- 7) All the above requirements must be fulfilled with in the pH range at which the titration is performed.

✚ The indicator act by following mechanism.

- When metal ion (M) reacts with indicator ion (In). Complex MIn is formed. Stability constant of which is given by:

$$K_{In} = \frac{[MIn]}{[M][In]}$$

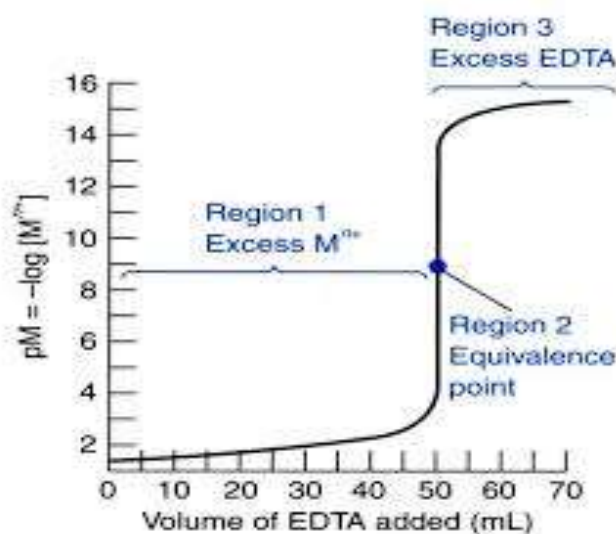
- During titration of metal ion M by titrant EDTA, metal-EDTA complex formation occurs. Stability of this complex is given by:

$$K_s = \frac{[M-EDTA]}{[M][EDTA]}$$

- Here, K_s is greater than K_{In} ($K_s > K_{In}$).
- Thus, before addition of EDTA in to metal ion solution, metal forms complex with indicator and after addition of EDTA, metal-indicator complex starts to dissociate and metal-EDTA complex starts to form due to more stability of that complex.

✚ Graphical Representation:

- Graph of **Concentration of metal ion [M]** Vs **Concentration of sodium edetate** in appropriate buffered solution. It shows sharp break near equivalent point. The rate of change of metal ion concentration is initially slow and it becomes rapid at equivalence point.



- The colour of indicator and those of complexes vary with pH. This fact and the stability of metal indicator complex should be taken into consideration while deciding selection of indicators. e.g. Calcon, Catechol violet, Eriochrome Black T, Mordant Blue 3, Mordant Red 7, Murexide, Pyridylazonaphthol (PAN), Xylenol orange.

(b) pH indicator:

- Metal indicator complex formation results in liberation of acid, if formed.
- Complex is stable in acidic media. Completion reaction goes even in presence of acid then the quantitatively produced acid can be titrated with standard alkali. This reaction then can become acid-base titration and therefore pH indicators like **methyl red** and **methyl orange** can be used to detect end point.

II. INSRUMENTAL METHOD:

- **Potentiometric Titration:** In this method potassium electrode is commonly employed along with standard reference electrode.

Platinum electrode measures redox potential associated with metal-EDTA complex. Potential of electrode is a function of ratio of two states (oxidation/reduction) of metal.

$$E = E_o \log e \frac{[Oxi]}{[Red]}$$

E = The potential of the electrode

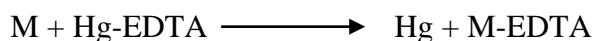
E_o = The standard electrode potential (Reference)

[Oxi] = Concentration of ions in oxidation state

[Red] = Concentration of ions in reduced state

Another electrode used is a mercury electrode which measures the potential changes with replacement reaction. It measures potential changes associated with the replacement reaction between metal ion M⁺ and Hg present in Hg-EDTA complex in titration.

Mercury (Hg) is displaced from Hg-EDTA by metal ion and equilibrium is reset.



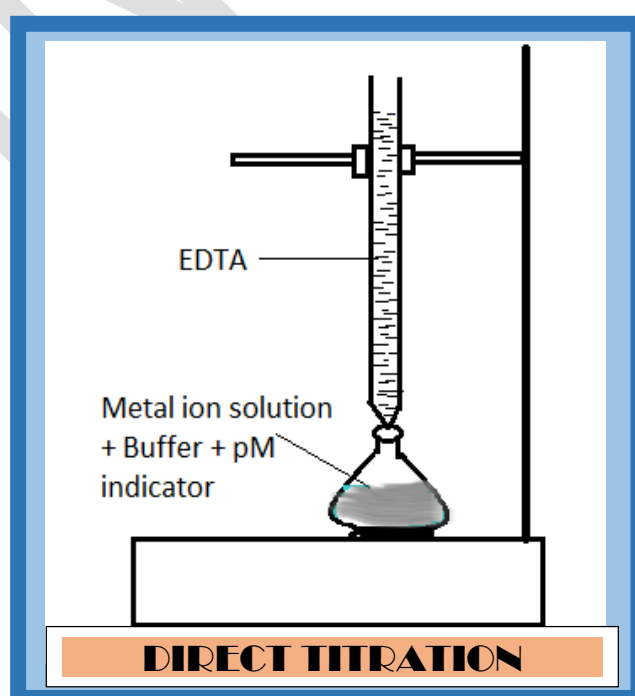
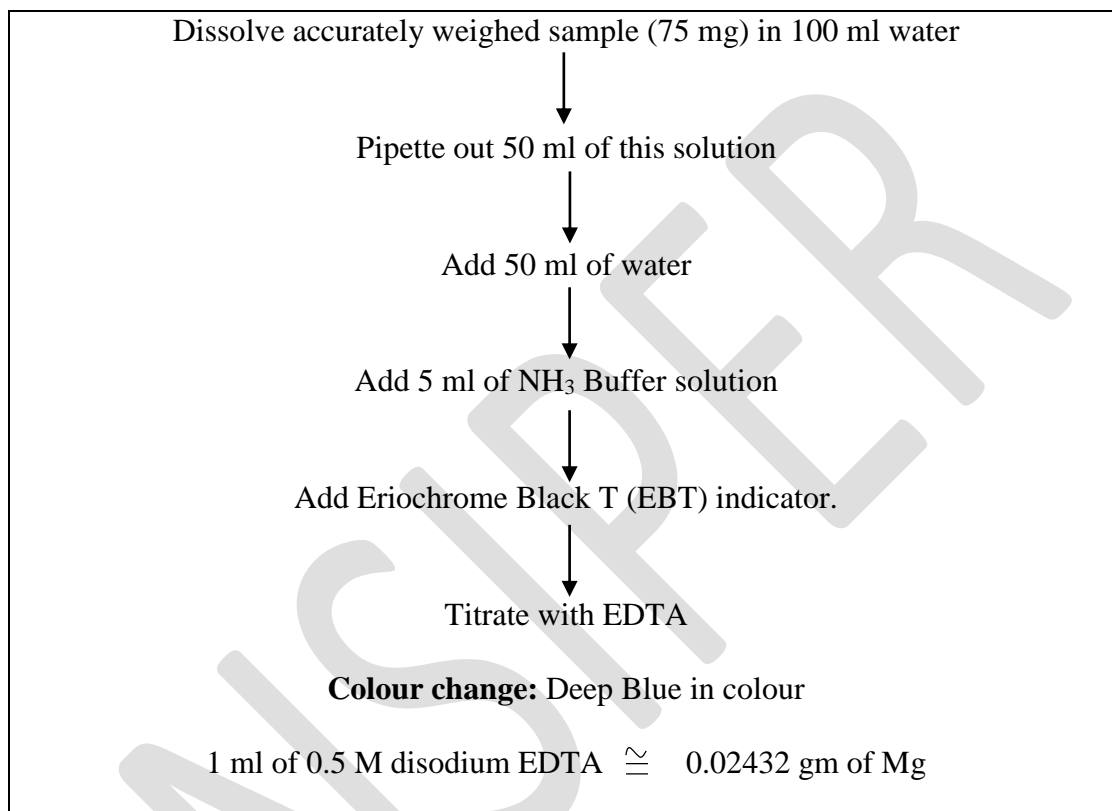
The potential of mercury electrode depends upon the ratio of M/[M-EDTA] and it changes rapidly at the end point.

TYPES OF COMPLEXOMETRIC TITRATION

1) Direct Titration:

- In this method metal ion solution in a suitable buffer is titrated with EDTA using pM indicator. At the equivalent point colour change is observed.
- Important elements which could be detected by direct titration are: Cu, Mn, Ca, Ba, Al, Fe, Co etc.

Principle & Procedure: Example: Determination of Mg

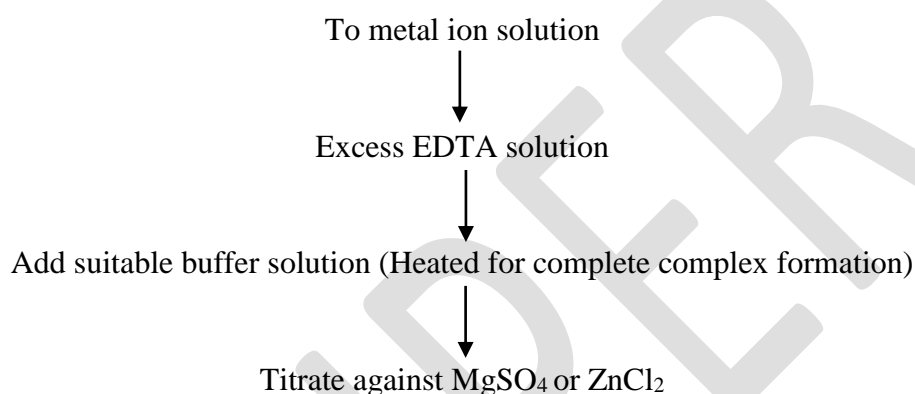


2) Back Titration:

- When direct titration is not possible because of-
 - ☞ Insolubility of substance
 - ☞ Instability of complex
 - ☞ Precipitation of metal hydroxide
- In above situation, Back titration method is adopted.

Procedure:

General Procedure:

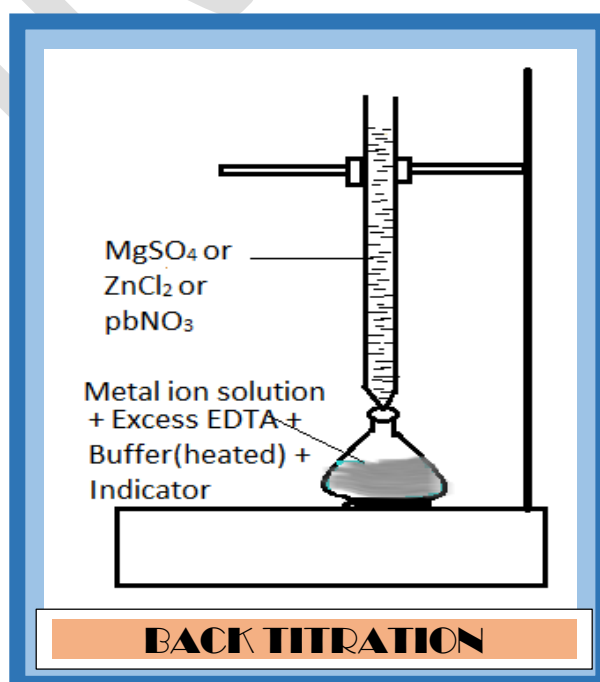


Colour change: Deep Blue in colour

1 ml of 0.5 M disodium EDTA \cong 0.02432 gm of Mg

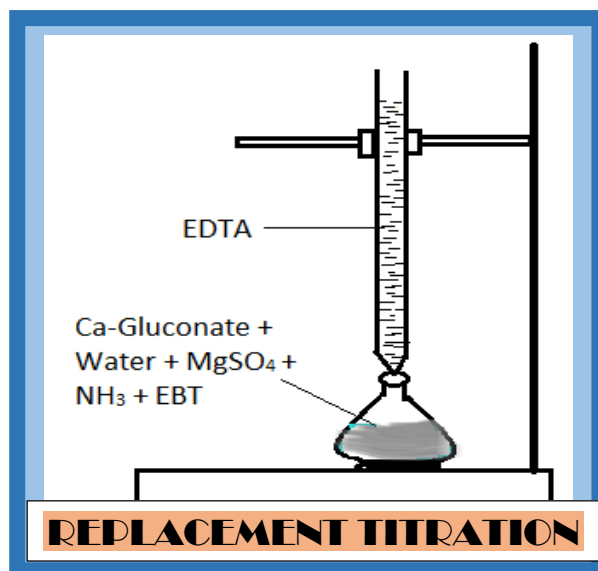
Example: Manganese (Mn) or Aluminium (Al) Salt is back titrated.

- To aluminium salt, 6 pH buffer is added followed by excess of EDTA solution. Excess of EDTA is back titrated with pbNO_3 .

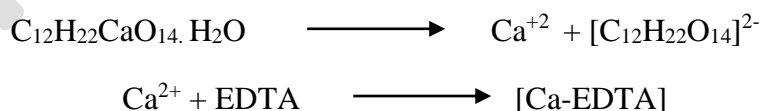


3) Replacement Titration:

- When direct or back titration is not possible, metal ions estimated by replacement technique.
- **Example:** Analysis of calcium salt (Ca^{+2}) is carried out by replacement method.



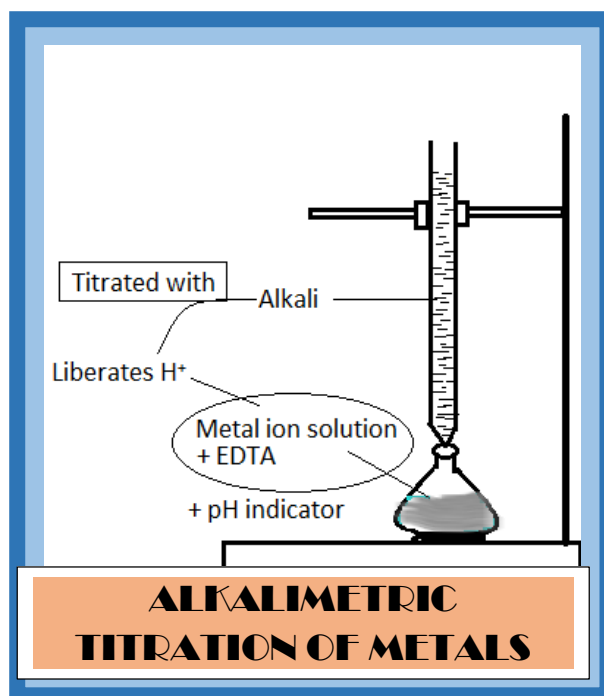
- In this method additional metal ion is added with analyte. This additional metal ion initially forms complex with indicator which will later break by analyte. Thus analyte replaces the metal ion from initially formed complex.
- Displaced metal ion is titrated with EDTA.
- In estimation of calcium gluconate, MgSO₄ is added with analyte solution. Initially Mg-In and Ca-In complex are formed. Here, Stability of Ca-In complex is less than Mg-In complex. Therefore, Mg-In complex is not easily break by EDTA and EDTA break Ca-In complex first and forms Ca-EDTA complex.
- Once all Ca^{+2} ions are consumed by EDTA, next drop of EDTA will react with Mg^{+2} from Mg-In complex and thus Mg-EDTA complex is formed. As this complex forms, Indicator will become free and gives the different colour.



4) Alkalimetric titration of metals:

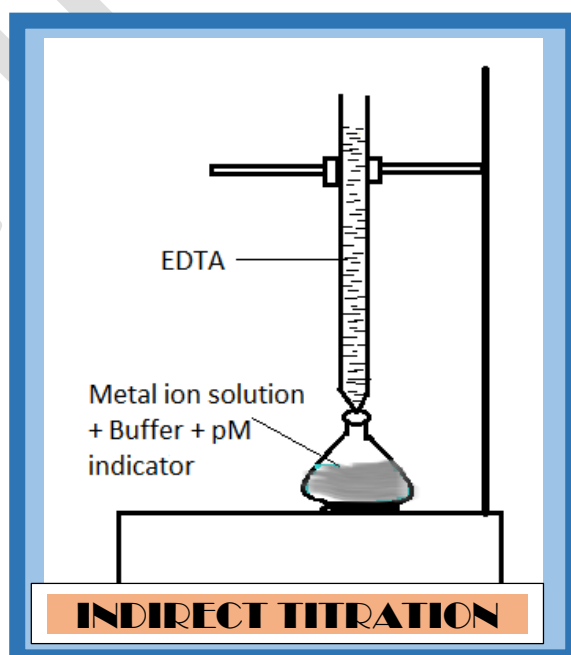
- Metal-EDTA complex formation undergoes ionization and liberates proton (H^+). Proton from disodium EDTA are displaced by heavy metal. Liberated acid is titrated with disodium alkali.

- Here, end point can be detected by visual pH indicator or potentiometric method.
- If metal ion + Iodide – Iodate mixture is added to the solution and EDTA is also added, it will liberate iodine (I_2). This liberated I_2 is then titrated with thiosulphate using starch indicator.



5) Indirect method of titration

- This method is not used for metal ion.
- Organic substances can be analysed by indirect method. For e.g. Codeine, Chlorpromazine.
- In this method, organic substance is precipitated by addition of excess metal ion solution. Excess of metal ion solution is back titrated with EDTA.



6) Complexometric titration by masking and demasking agent

- This method is used when two or more metals are present in the same solution.
- There are two ways for detection of single metal ion from mixture
 1. This can be done either **by selection of suitable pH** at which one metal forms complex without involvement of other metal ion.
 2. Another way is **by using suitable masking agent**.
- EDTA is a very unselective reagent because it complexes with numerous cations so, it is not selective for solution containing mixture of metals. The following procedure will help to increase the selectivity.
 1. Use of masking and demasking agent
 2. pH control
 3. Use of selective metal indicator.

✚ Masking Agent:

- It is auxiliary chelating agent or complexing agent that will form complex more strongly with the metal than the titrant under the condition of titration.

e.g. Triethanolamine is a masking agent for aluminium and iron.
 Triglycerol for copper
 Potassium cyanide for heavy metals
 Ammonium fluoride for iron and aluminium.

- Masking agent act by masking one of the metal ion from the mixture, thus estimation of another metal become easy because masked metal cannot interfere in estimation of another metal present in mixture.
- Masking is done by one of the following two mechanisms.
 1. Masked by precipitation
 2. Masked by complexation
- Masked metal by precipitation are filtered, decomposed and then titrated with disodium EDTA.

Masking Agent act by Precipitation

Sr. No.	Masking agent	Metal masked
1	Sodium sulphide	Co, Cu, Pb
2	Sulphate	Pb, Ba
3	Oxalate	Ca, Pb

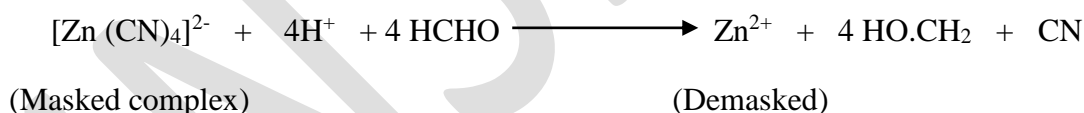
4	Fluoride	Ca, Mg, Pb
5	Ferrocyanide	Zn, Cu
6	Thioglycerol	Cu
7	Dimercaprol	Hg, Cd, Zn, Ar, Pb, Bi

Masking Agent act by Complex formation

Sr. No.	Masking agent	Metal masked
1	Ammonium Fluoride	Al, Fe, Ti
2	Ascorbic acid	Fe (III)
3	Dimercaprol	Ni
4	Potassium cyanide	Ag, Co, Hg, Fe, Zn, Cd, Co, Ni
5	Potassium iodide	Hg(II)
6	Tiron	Al, Ti
7	Triethanolamine	Al, Fe(III), Mn

Demasking Agent:

- They are defined as the agents which reverse the process of masking.
- It is the substance which release the masked metal ion. Example: The cyanide complex of Zinc and Cadmium can be demasked by formaldehyde (HCHO).
- Demasked agent now able to enter in particular reaction.



- Thus masking and then selective demasking permits successive titration of many metals. E.g. Cu, Cd, and Ca from solution can be determined selectively by use of masking and demasking agent. Cu and Cd masked by cyanide ion, not Ca, which allows to determine separated Ca with disodium EDTA.

Now, Cd demasked from cyanide by formaldehyde, free Cd determine along with Ca by disodium EDTA. Thus, all elements can be determined by masking and demasking.

ESTIMATION OF MAGNESIUM SULPHATE

Principle:

Estimation of magnesium sulphate is done by direct EDTA (complexometric titration). In this method Magnesium Sulphate (analyte) is directly titrated by EDTA by using pM indicator.

Here, first Mg-In complex forms when EDTA is not added, as titration proceed and EDTA is added in reaction mixture, it have tendency to form complex [Mg-EDTA] which is more stable than [Mg-

In] Complex. Thus, [Mg-In] complex breaks and indicator becomes free. This free indicator gives different colour. Thus, end point is detected.

Procedure:

Dissolve accurately weighed sample (75 mg) of Mg in water 100 ml.



Pipette out 50 ml of this solution in titration flask, add 50 ml of water.



5 ml of NH₃ buffer solution and a few drops of Eriochrome black T as indicator.

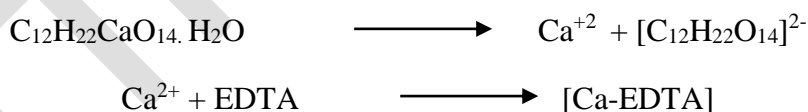


Titrate it with EDTA until the solution is deep blue in colour.

Factor: 1 ml of 0.05 M Disodium EDTA = 0.02432 g of Mg

ESTIMATION OF CALCIUM GLUCONATE**Principle:**

- It is complexometric titration which involves replacement of Mg²⁺ ions from its [Mg-In] complex. Indicator do not give distinct colour change at the end point with ca-gluconate. Therefore a known volume of 0.05 M MgSO₄ solution is added.
- Initially when calcium on and magnesium ions are present in solution and when indicator is added. It forms complex with Mg as [Mg-In] is stronger than [Ca-In] complex and impart pink colour to solution.
- When titration commences added EDTA forms complex with calcium ions as [Ca-EDTA] is stronger than [Mg-EDTA] complex, when all the Ca⁺² ions are complexes then Mg⁺² relieves from [Mg-In] complex and free Mg⁺² forms complex with EDTA and end point reached. Thus [Mg-In] complex breaks liberating free Mg⁺² and In⁻. This free indicator gives blue colour to the solution.

**Procedure:**

Weight accurately about 0.5 gm calcium gluconate



Dissolve it in 50 ml warm water and cool it.



Add 5 ml 0.05 M MgSO₄ (x M) and 10 ml ammonia solution.



Titrate it against 0.05 M EDTA solution using EBT as an indicator.