

Pharmaceutical معالي المعالي المعالي

Faculty of Pharmacy









Aluminium Hydroxide Tablets Action and use : Antacid

Assay Weigh and powder 20 tablets, avoiding frictional heating. Dissolve a quantity of the powder/containing 0.4 g of Dried Aluminium Hydroxide as completely as possible in a mixture of 3 ml of hydrochloric acid and 3 ml of water by warming on a water bath, cool to below 20° and dilute to 100 ml with water. To 20 ml of this solution add 40 ml of 0.05M disodium edetate VS, 80 ml of water and 0.15 ml of *methyl red solution* and neutralise by the dropwise addition of 1M sodium hydroxide VS. Heat on a water bath for 30 minutes, add 3 g of *hexamine* and titrate with 0.05M yead nitrate VS using 0.5 ml of xylenol orange solution as indicator. Each ml of 0.05M disodium edetate **VS** is equivalent to 2.549 mg of Al_2O_3 .



Complexometric reactions and titration

- Many metal ions form slightly dissociated complexes with various ligands(complexing agents)
- The formation of complexes can also serve as the basis of accurate and convenient titrations for metal ions.
- Complexometric ditration are useful for the determination of large number of metals.
- The analytical chemist makes judicious use of complexes to mask undesired reactions.



 Selectivity can be achieved by appropriate use of masking agents (addition of other complexing agents that react with interfering metal ions) and by pH control, since most complexing agents are weak acids or weak bases whose equilibria are influenced b





Complex Formation Titrations

A review of complexes and ligands is provided. EDTA, the most common complexer used in complex formation titrations is covered extensively. pH dependent equilibrium calculations are introduced along with titration calculations. Several common indicators used with EDTA titrations are also given.









Many analytical methods rely on the formation of complexes.

GravimetryNi / DMGTitrimetric methodsMetal - EDTASpectrophotometryMetal - dithiocarbamate

They can be used to form a measurable species, as indicators or to mask the presence of interfering species.



Complexes

- The metal ion is a Lewis acid (electron pair acceptor)
- And the complexer is a Lewis base (electron pair donor)
- The number of molecules of the complexing agent, called the **ligand**
- Most ligands contain O,S, or N as the complexing atoms.







General structure









Central species

Must have the ability to accept one or more pairs of electrons in available d orbitals - typically a metal ion.

Ligand

Anion, cation or neutral species with ability to donate electron pair to form a coordinate covalent bond.

Counter ion

Required if complex is charged.







Some common ligand groups

halides thiocarbonyl hydroxides carbonyls mercaptans oximes nitroso acids amines

Ligands are typically anionic or polar neutral species when working with aqueous systems.







Ligands can be classified by dentate number - number of bonds/ligand

Monodentate

Dentate (Latin) means having toothlike projection.

1 bond/ligand - ammonia

Bidentate

2 bonds/ligand - ethylene diamine

Multidentate

variable number based on need - EDTA



Monodentate Ligand

Possess only accessible donor group (e.g. NH₃)

$$Cu^{2+} + 4:NH_3 \rightleftharpoons \begin{bmatrix} NH_3 \\ H_3N:Cu:NH_3 \\ NH_3 \end{bmatrix}^{2+}$$

Prof .J .AI-Zehouri

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Form two binds / central species.

A good example is ethylene diamine. NH₂CH₂CH₂NH₂ - (en)

пн2-сн2-сн2- NH2

The amino groups are far enough apart to permit both to interact.









Other common bidentate ligands.

8 - hydroxyquinoline





















V

Polydentate ligands

Disodium Edetate



C10H14N2Na2 O8.2H2O 372.2

Action and use Chelating agent.



NOUL BEER



Polydentate ligands (six)











Ethylenediamine tetraacetic acid One of the most commonly used complexers. Forms 1:1 complexes with most metals (not group 1A) Forms stable, water soluble complexes High formation constants.

not primary standard material.







EDTA is typically used as the disodium salt to increase solubility.











Consider the formation of the EDTA chelate of Ca2+. This can be represented by

$$Ca^{2+} + Y^{4-} \rightleftharpoons CaY^{2-}$$

The formation constant for this is

$$K_f = \frac{[CaY^{2-}]}{[Ca^{2+}][Y^{4-}]}$$

The values of some representative EDTA formation constants are given in the followig table :







Formation constants for some metal - EDTA complexes.

lon	logK _{MY}	lon	logK _{MY}	lon	logK _{MY}
Fe ³⁺	25.1	Pb2+	18.0	La ³⁺	15.4
Th4+	23.2	Cd2+	16.5	Mn2+	14.0
Cr3+	23.0	Zn2*	16.5	Ca2+	10.7
Bi ³⁺	22.8	Co2+	16.3	Mg ²⁺	8.7
Cu2+	18.8	Al3.	16.1	Sr2+	8.6
Ni ²⁺	18.6	Ce3+	16.0	Ba2*	7.8







Effect of pH On EDTA Equilibria The strength and stability of EDTA complexes is pH dependent.

M²* + H₂Y²· → MY²· + H*

The reaction shifted to the left as the hydrogen ion concentration is increased, due to competition for the chelating anion by hydrogen ion

Since it is the Y⁴⁺ for which complexes with the metal, anything that alters its availability will affect our titration

pH is the major concern.





EDTA can be represented as having four K_a values corresponding to the stepwise dissociation of the four protons¹:

$$\begin{aligned} H_{4}Y &\rightleftharpoons H^{+} + H_{3}Y^{-} \quad K_{a1} = 1.0 \times 10^{-2} = \frac{[H^{+}][H_{3}Y^{-}]}{[H_{4}Y]} \\ H_{3}Y^{-} &\rightleftharpoons H^{+} + H_{2}Y^{2-} \quad K_{a2} = 2.2 \times 10^{-3} = \frac{[H^{+}][H_{2}Y^{2-}]}{[H_{3}Y^{-}]} \\ H_{2}Y^{2-} &\rightleftharpoons H^{+} + HY^{3-} \quad K_{a3} = 6.9 \times 10^{-7} = \frac{[H^{+}][HY^{3-}]}{[H_{2}Y^{2-}]} \\ HY^{3-} &\rightleftharpoons H^{+} + Y^{4-} \quad K_{a4} = 5.5 \times 10^{-11} = \frac{[H^{+}][Y^{4-}]}{[HY^{3-}]} \end{aligned}$$





$[T] = [H_4Y] + [H_3Y] + [H_2Y^{2-}] + [HY^{3-}] + [Y^4]$

$$\alpha_{2} = \frac{[H_{2}Y^{2}]}{[T]} , \quad \alpha_{3} = \frac{[HY^{3}]}{[T]} , \quad \alpha_{4} = \frac{[Y^{4}]}{[T]}$$

 $\alpha_0 = \frac{[H_4Y]}{[m_1]}$, $\alpha_1 = \frac{[H_3Y]}{[m_1]}$

 α = fraction of EDTA ion such as H₃Y⁻ or H₂Y⁻²U.



EDTA equilibria

The effect of the hydrogen ion can then be calculated using $\alpha_{\rm Y}.$

$$\alpha_{Y} = \frac{[Y^{4-}]}{[H_{4}Y] + [H_{3}Y^{-}] + [H_{2}Y^{2-}] + [HY^{3-}] + [Y^{4-}]}$$

With reciprocal the equation we got :

$$\frac{1}{\alpha_4} = \frac{[H_4Y]}{[Y^{4-}]} + \frac{[H_3Y^{-}]}{[Y^{4-}]} + \frac{[H_2Y^{2-}]}{[Y^{4-}]} + \frac{[HY^{3-}]}{[Y^{4-}]} + \frac{[Y^{4-}]}{[Y^{4-}]}$$







Determination of α_{γ}

The EDTA equilibria can be expressed using a series of stepwise formation constants.



Similar expressions can be written for the other two equilibria







We can proceed through a series of substitutions leading to an equation in terms of [H*].

$\frac{1}{\alpha_{Y}} = \frac{[H^{+}]^{4}}{\kappa_{1}\kappa_{2}\kappa_{3}\kappa_{4}} + \frac{[H^{+}]^{3}}{\kappa_{2}\kappa_{3}\kappa_{4}} + \frac{[H^{+}]^{2}}{\kappa_{3}\kappa_{4}} + \frac{[H^{+}]^{2}}{\kappa_{4}} + \frac{[H^{+}]}{\kappa_{4}} + 1$

We can then calculate α_{Y} and plotted as a function of pH. With the same method we can calculate $\alpha_{1}, \alpha_{2}...$

















ording to the relationship between fraction of Contraction of EDTA species) and pH value we got the following statement :

- In acidic media (pH = 3-6) H_2Y^{-2} is predominant.
- In Basic media (pH = 6-10) HY⁻³ is predominant.
- In strong basic media (pH > 10) Y^{4} is predominant .
- The reaction at pH more than 10 is fast complete.
- The complex which formulated between EDTA and Metal is more stable at pH more than 10.

• we need buffer to fixed the pH in Complexometric titration.







While the actual formation constant for a metal-EDTA complex is:

$$K_{MY} = \frac{[MY^{4-}]}{[M][Y^{4-}]}$$
, α₄ = [Y⁻⁴]/T \implies Y⁻⁴ = T x α₄

A conditional constant can be calculated at any known, constant pH as

$$K_{MY} \alpha_{4} = K_{MY}' = \frac{[MY^{4-}]}{[M][T]}$$

 $K_{MY} \circ = Conditional formation constantProf .J .Al-Zehouri$



Conclusion

Present of great amount of hydrogen will effect on the complex (make weaker) because it will react with Y:

$M + Y \Longrightarrow MY$ $H + \downarrow \uparrow$ $H + \downarrow \uparrow$ $HY, H_2Y \dots etc.$


The Conditional Formation Constant

- The Conditional formation constant value holds for only a specified pH
- We use the conditional formation constant to derivative the titration curve.







As with our other types of titrations, we have four regions to deal with.

0% titration >0% and < 100% titration The equivalence point Over-titration region

We'll outline the basic steps for each region using an example.







Exomple

100.0 ml of a 0.0100 M Ni²⁺ solution is buffered at a pH of 10.2.

Determine the pNi at 0, 50, 100 and 200% titration if titrated with a 0.0100M EDTA solution.

 $\alpha_4 = 0.47$ and $K_{NiY}^{-2} = 3.98 \times 10^{18}$

We'll be using pNi so that our titration curve can be directly compared to other types of titrations.







0% titration Start point This is pretty straight forward.

We know that we're starting with 0.0100 M Ni²⁺ so:

ρNi = -log[Ni²⁺] = -log[0.0100] = 2.00







50% titration Before the Equivalence point At > 0% and < 100%, we can assume that the amount if free Ni(II) is:</pre>

[Ni²⁺] = Initial [Ni²⁺] x VNi²⁺ - [EDTA] x V_{EDTA added} VNi²⁺ + V_{EDTA added}

<u>0.0100M x 100.0 ml - 0.0100M x 50.0ml</u> 100 ml + 50 ml

= 3.33x10⁻³ pNi = 2.48







100% titration - the equivalence point.

Now things get interesting!

To determine the [Ni²⁺], we need to use:

$$K_{MY} = K_{MY} \alpha_4 = \frac{[NiY^{2-}]}{[Ni^{2+}][-]}$$

 $K_{MY} = 3.98 \times 10^{18}$







We'll need to calculate $\alpha_{\rm Y}~$ at pH 10.2.

$\frac{1}{\alpha_{Y}} = \frac{[H^{+}]^{4}}{K_{1}K_{2}K_{3}K_{4}} + \frac{[H^{+}]^{3}}{K_{2}K_{3}K_{4}} + \frac{[H^{+}]^{2}}{K_{3}K_{4}} + \frac{[H^{+}]^{2}}{K_{4}} + \frac{[H^{+}]}{K_{4}} + 1$

- $K_1 = 1.02 \times 10^2$ $K_2 = 2.14 \times 10^3$
- $K_3 = 6.92 \times 10^7$ $K_4 = 5.50 \times 10^{-11}$
- [H⁺] = 6.31x10⁻¹¹







If you're willing to trust me, then $\alpha_4 = 0.47$ $\kappa_{MY} \alpha_4 = \frac{[NiY^{2-}]}{[Ni^{2+}][T]} = 3.98 \times 10^{18} \times 0.47$ $= 1.87 \times 10^{18}$

At the equivalence point, we also know that virtually all of our nickel exists as NiY²⁻.







So, [NiY²⁻] = 0.0050 M due to dilution.

In addition [Ni²⁺] = [T] so:

$1.87 \times 10^{18} = \frac{0.0050 \text{ M}}{[\text{N}^{i2+}]^2}$

$[Ni^{2*}] = (0.0050 \text{ M} / 1.87 \times 10^{18})^{1/2}$

= 5.17 x10-11 M

ρNi = 10.3







200% titration

Beyond the equivalence point, we are primarily building up excess EDTA and diluting everything.

At 200% over-titration, [NiY2-] = [T] so:

$$K_{MY}' = \frac{[NiY^{2}]}{[Ni^{2+}][\tau]} = 1.87 \times 10^{18}$$

[Ni²⁺] = 5.35 \times 10^{-19} pNi = 18.27















The 200% titration mark is useful for estimating the shape of a titration curve because:

ρM = log K_{MY}'

Since you also know the 0% value (-log[species]) and the general shape of a titration curve, a reasonable estimate is possible.







Example

Estimate what our previous titration curve would look like if our sample was Ca²⁺ rather than Ni²⁺.

 ρCa at 0% = 2.00 and α_{γ} = 0.47 since the same conditions were used.

 $\rho Co_{200\%}$ = log K_{MY}' = log(K_{MY} α_{Y}) = log(5.01x1010 x 0.47) = -10.4











Detection of The end point (Indicators)

We can measure the pM Potentiometrically if a suitable electrode is available, for example, an ion-selective electrode, but it is simpler if an indicator can be used.

Indicators used for chelometric titrations are themselves chelating agents.

They are usually dyes of 1,2-dihydroxy azo type. (metal-ion indicators)



INDICATORS

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







To be a viable indicator, we need a species that: Competes for our metal ion. Is a weaker complexer than EDTA. Exhibits a measurable change between the complexed and

uncomplexed form.

M-Ind + Y' → MY + Ind (color 1) (color 2)







In the presence of an indicator, our reaction proceeds in two steps.



Since it is easier to EDTA to react with the uncomplexed metal, that reaction occurs first.

M-Ind is harder for EDTA to react with so we must insure that only a small amount of indicator is used.



Indicators for EDTA titrations



Calmagite Will form a colored species with most metal cations.





Calmagite

- Used for Fe⁺⁺⁺ but we must masking the ions of Ni, Cu, and Al as the following :
 - 1- Cu and Ni with CN ion,
 - 2- Al with addition of trietanolamine







Eriochrom Black T

Closely related to Calmagite - same properties but less stable - air oxidation.



It can be use for the titration of Mg⁺⁺ , Ca⁺⁺ and Mn⁺⁺ with EDTA in basic media

Complexes are red Uncomplexed form is blue



Complexometric Indicators

Indicators	IND H ₂	Me-IND		
Eriochrome - black T	blue	red		
Murexide	blue 6	red		
Calmagite	red	blue		
Xylenol Orange	yellow	red		
Methylthemol blue	yellow	blue		
Calcon	violet	Deep blue		
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Types of EDTA Titration

- 1. Direct Titration M- ind + EDTA⁻²
- Buffer solution is necessary to use to prevent the ppt of Metal
- Mg,Zn,Cd (Eriochrom black-T)
- Ca (Catcon)
- CO, Ni, Cu (Murexid)

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TA + ind⁻²



Types of EDTA Titration 2- Back Titration burette M-EDTA + EDTA + ind Zn-EDTA + Zn-ind M-I

The reasons? (No suitable indicator available, difficulty of pH control, can not mask the undesirable ion, slow reaction, unstable complex,...)
 Hg. Pb, Mn and Al







Types of EDTA Titration

- 4- Simultaneous titration
 - determination of water Hardness (Mg+ Ca)
 - Mg will be first formed ppt with hydroxyl therefore we titrate the Ca, then we dissolve the ppt of Mg using Perhedrol and HCI and titrate the Mg in present of suitable indicator.



Pharmaceutical USES

- EDTA in Pharmacopeias is used to titrate most all Metals in pharmaceutical dosage form such as Ca,AI,Bi,Mn,Zn(ETDA forms stable 1:1 complex with all metals except alkali metals such as Na & K.
- Ca & Mg form complexes which are unstable at low pH therefore titrate in ammonium chloride buffered pH 10

Pharmaceutical USES

Titration in pharmacopeias:

(Direct)

- Calcium chloride
- Calcium gluconate
- Bismuth sub carbonate
- Magnesium carbonate
- Calcium acetate
- Zinc chloride

(Back): of metal and titrate the excess with Mg⁺²or Zn⁺² Aluminum hydroxide Aluminum Insoluble metal salts ,the sample heated with excess EDTA to form soluble complex sulphate

Calcium hydrogen
 phosphate

Pharmaceutical USES

- EDTA , used in Ampoule (anti catalyses)
- Anticoagulant.
- To treatment of heavy metal To determine Ca in blood.
- poisoning such as lead (The chelated lead is excreted via kidneys.



Aluminium Hydroxide Tablets 400 mg Action and use : Antacid

Assay Weigh and powder 20 tablets, avoiding frictional heating. Dissolve a quantity of the powder containing 0.4 g of Dried Aluminium Hydroxide as completely as possible in a mixture of 3 ml of *hydrochloric acid* and 3 ml of *water* by warming on a water bath, cool to below 20° and dilute to 100 ml with water. To 20 ml of this solution add 40 ml of 0.05M disodium edetate VS, 80, m of water and 0.15 ml of methyl red solution and neutralise by the dropwise addition of 1M sodium hydroxide VS. Heat on a water bath for 30 minutes, add 3 g of hexamine and titrate with 0.05M lead nitrate VS using 0.5 ml of xyleno/ orange solution as indicator. Each ml of 0.05M disodium edetate VS is equivalent to 2.549 mg of Al2O3.



Aluminium Hydroxide Tablet

- 1. If the Tablet average weight is 700 mg, What is the weight of analysis sample?
- 2. Wright the equation of this titration.
- 3. If we consumed to the end point 8 ml, what is the % content of the ingredient?

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Aluminium acetate,Ear drops	0.05M EDTA	Xylenol Orange	0.001349
Aluminium hydroxid ,Oral suspension	0.05M EDTA	Xylenol Orange	0.002549
Aluminium Phosphate,Oral Suspension	0.05M EDTA	Dithizone	0.06098
Aluminium hydroxid Tablets	0.05M EDTA	XylenolOrange	0.002549
Aromatic Magnesium Carbonate,(Mixture,Or al Suspension	0.05M EDTA	Mørdant black II	0.001215
Calcium Gluconate injection	0.05MEDTA	Calcon	0.00400
Calcium Gluconate Tablet	0.05M EDTA	Calcon	0.0242
Calcium Lactate Tablets	0.05M EDTA	Calcon	0.01541

Compound Aluminium Paste	0.05M EDTA	Dithizone	0.004068
Compound Magnesium Trisilicate,Oral Powder	0.05M EDTA	Xylenol Orange	0.02242
Effervescent Calcium Gloconate,Tablete	0.05M EDTA	Calcon	0.02152
Hexachlorophane dusting powder	0.05M EDTA	Xylenol Orange	0.004068
Magnesium Sulphate(Mixture,Oral Suspensiom	0.05M EDTA	Erochromblack-T	0.001232
Sodium Calciumedetate , I.V inj.	0.05MEDTA	Xylenol Orange	0.01871
Zinc Sulphate, Eye drops	0.05M EDTA	Mordant black II	0.002875
Zinc Sulphate Lotion	0.05M EDTA	Mordant black II	0.01438

Bismuth

Introduce the prescribed solution into a 500 ml conical flask. Dilute to 250 ml with water R and then, unless otherwise prescribed, add dropwise, with shaking, concentrated ammonia R until the mixture becomes cloudy. Add 0.5 ml of nitric acid. R. Heat to about 70 °C until the cloudiness disappears completely. Add about 50 mg of xylenol orange triturate R and titrate with 0.1 M sodium edetate until the colour changes from pinkish-violet to yellow.

1 ml of 0.1 M sodium edetate is equivalent to 20.90 mg of Bi.

Calcium

Introduce the prescribed solution into a 500 ml conical flask, and dilute to 300 ml with water R. Add 6.0 ml of strong sodium hydroxide solution R and about 15 mg of calconecarboxylic acid triturate R. Titrate with 0.1 M sodium edetate until the colour changes from violet to full blue.

1 ml of 0.1 M sodium edetate is equivalent to 4.008 mg of Ca.

Magnesium

Introduce the prescribed solution into a 500 ml conical flask and dilute to 300 ml with water R. Add 10 ml of ammonium chloride buffer solution pH 10.0 R and about 50 mg of mordant black 11 triturate R. Heat to about 40 °C then titrate at this temperature with 0.1 M sodium edetate until the colour changes from violet to full blue.

1 ml of 0.1 M sodium edetate is equivalent to 2.431 mg of Mg.

المشعر هو نفسه أسود الأيروكروم
Lead

Introduce the prescribed solution into a 500 ml conical flask and dilute to 200 ml with water R. Add about 50 mg of xylenol orange tritorate R and hexamethylenetetramine R until the solution becomes violet-pink. Titrate with 0.1 M sodium edetate until the violet pink colour changes to yellow.

1 ml of 0.1 M sodium edetate is equivalent to 20.72 mg of Pb.

Zinc

Introduce the prescribed solution into a 500 ml conical flask and dilute to 200 ml with water R. Add about 50 mg of xylenol orange triturate R and hexamethylenetetramine R until the solution becomes violet-pink. Add 2 g of hexamethylenetetramine R in excess. Titrate with 0.1 M sodium edetate until the violet-pink colour changes to yellow.

1 ml of 0.1 M sodium edetate is equivalent to 6.54 mg of Zn.

هو نفسه الهكز امين

2- EDTA, used in Ampoule (anti catalyses)

- 3- To determine Ca in blood
- 4- Anticoagulant.
- 5- To treatment of heavy metal poisoning such as lead (The chelated lead is excreted via kidneys).



Thank you

Prof. J. Al-Zehouri

