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Research/Review

A Review On Complexometric Titrations Used In Assay Of Various Drugs

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	Abstract
Published on: 16 May 2024	<p>Utilising complex-forming processes, complexometric titrations, also known as chelatometry, are a method for determining metal ions. In this kind of volumetric analysis, the formation of a coloured complex indicates the titration endpoint. The interaction between the metal ion and ligand, which leads to the creation of a complex, is the main idea in various types of titrations. The resultant compound is stable and dissolves in water. The complexometric titrations use a variety of indicators, including Solochrome black T, Eriochrome black T, Mordant black II, Murexide, and Cathechol violet. This method of titrations can be used to measure the hardness of the water as well as the amounts of calcium, magnesium, zinc, and copper ions in the sample. Complexometric titrations are frequently used to measure a mixture of many metal ions in solution.</p>
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INTRODUCTION

The complexometric titrations often called chelatometry, is the utilisation of complex-forming processes to determine metal ions. It is a type of volumetric analysis where the titration endpoint is indicated by the production of a coloured complex. This method converts a simple ion into a complex ion and uses electrometric or metal indicators to find the equivalency point. To find the titration endpoint, an indicator that may clearly change colour is typically utilised. The appropriate selection of indicators for endpoint detection determines the adaptability, sensitivity, and overall ease of complexometric titrations.[1] The measurement of a mixture of several metal ions in solution is often accomplished by complexometric titrations. The primary concept in these kinds of titrations is the interaction between the metal ion and ligand, which results in the formation of a complex. The resulting complex dissolves in water and is stable.



The metal ion functions as a Lewis acid by accepting an electron pair and the ligand functions as a Lewis base by donating an electron pair. Typically, the structure of the ligand molecule includes one or more numbers of oxygen, nitrogen, or sulphur. Coordinate linkage with metal ions occurs when a specific number of ligand molecules (such as 2, 4, 6, etc.) are connected to a metal ion. The ligand molecule may contain many sites that allow for the co-ordination connection with a metal ion. [2]

Different types of ligands were used. They are as follows:

Monodentate ligands

A single atom in a mono dentate ligand that is capable of binding to a central metal atom or ion. Examples of neutral mono dentate ligands are NH_3 and H_2O . Oxygen is the donor atom that binds to the metal when H_2O is a ligand. Nitrogen is the donor atom that binds to the metal when NH_3 is a ligand. [3] Halide ions like F^- , Cl^- , Br^- , I^- , and cyano (CN) are examples of electrically charged monodentate ligands.

Bidentate ligands

Bidentate ligands are composed of two atoms that can bind to a central metal atom or ion. Bidentate ligands include ethane-1, 2-diamine, which is depicted in the picture. This molecule's two nitrogens have the ability to donate electrons by attaching to a central metal atom or ion. [3] Further examples of bi dentate ligands are the oxalate ion (ox) and the acetylacetonate ion.

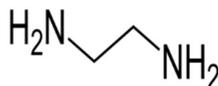


Fig 1: Ethane-1, 2-diamine



Fig 2: Acetylacetonone($C_5H_8O_2$)

Higher Polydentate Ligands and Tridentate Ligands

Tridentate ligands possess three atoms that can attach to a central metal atom or ion. Tetradentate ligands are molecules that consist of four donor atoms; pentadentate ligands are molecules that possess five donor atoms; and hexadentate ligands are compounds that possess six donor atoms. A chelate is a compound that has a polydentate ligand in it[3].

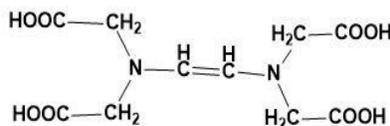


Fig 3: Structure of EDTA (Ethylene diamine tetracetic acid)

These days, a lot of industries, including biochemistry, agriculture, medicine, and the chemical industry, utilise chelators. In order to produce lone-paired electrons that are suitable for coordination, the majority of chelators have N, O, or S atoms in their chemical structure.[4,5,6]. It has been suggested from the beginning that in order for a reagent to function as a chelator in complexometric titrations, it has to satisfy the following criteria [4]

- (i) The reaction needs to occur kinetically quickly,
- (ii) It needs to progress stoichiometrically, and
- (iii) The change in free energy needs to be significant enough.

EDTA satisfies all the requirements listed above. EDTA generates 1:1 metal-chelator complexes and displays numerous coordinating groups. EDTA can combine with different metal ions to produce complexes. Nearly half of the elements in the periodic table have been analysed using EDTA, and its derivatives, such as ethylene glycol tetraacetic acid (EGTA) and diethylene triamine pentaacetic acid (DTPA), have similar use.[4] EDTA and its derivatives belong to the aminopolycarboxylic acid family.

Types of complexometric titration

- i. Direct titration method
- ii. Back titration methods
- iii. Replacement titration method
- iv. Alkalimetric titration of metals
- v. Indirect method

Direct titration method

- In this approach, the metal ion solution to which indicator is added is typically titrated against standardised disodium EDTA until the colour changes.
- It is the easiest and most practical approach.
- Cu, Zn, and Ni can be found using the direct titration method.
- The longer time required for complex formation and the observed interference from other ions are drawbacks.[7] Example: Calcium gluconate injection is assayed for determining the calcium chloride.

Back titration

- This technique involves back titrating an excess of complexing agent with a typical metal ion solution.
- Using this procedure, the pH is adjusted by adding an excess of the standard edta solution to the sample solution. After that, the final solution is back-titrated using a suitable titrant.
- Metal ion solutions of ZnCl₂, ZnSO₄, MgCl₂, and MgSO₄ are utilised as standard.
- Al₂O₃, Co₂O₃, Pb₂O₃, Mn₂O₃, Hg₂O, and Ni₂O can be determined via back titration method.[7] Example: Mn determination and ZnO determination.

Replacement titration

- As the name suggests, this approach substitutes other metal ions for metal ions, however it lacks precise endpoints.
- The determination of Ca²⁺ ions can benefit from this technique.[7] Example: $Mn^{+2} + MgEDTA^{-2} \longrightarrow Mg^{+2} + MnEDTA^{-2}$

Alkalimetry titration of metals

- This technique makes use of the idea that free H⁺ ions are released during complexation.
- Instrumental techniques can also be used to determine the H⁺ ions.[7]

Indirect titration

- It is possible to test some anions indirectly if they precipitate with metal cations and do not react with EDTA. To create the metal, the anion is first precipitated with a metal cation. The precipitate is then rinsed and boiled with an excess of disodium EDTA solution.
$$Mn^{+} + H_2Y_2 \longrightarrow M^{+}(n-4) + 2H^{+}$$
- Here, the heavy metal displaces protons from the complexing agent (EDTA), which is then titrated with sodium alkali.
- This approach can be used to determine barbiturates.
- Na, K, Ag, Au, As, Cl, Br, and F are all analysed using this approach.[7]

MATERIALS & METHODOLOGY**Methods Of End Point Detection**

Indicators: pM indicators (Metallochromic indicators) are used in complexometric titrations to indicate the end point.[8]

S.No	Name of the indicator	Colour change	pH range	Metals detected
1	Mordant Black II Eriochrome black T Solochrome black T	Red to Blue	6-7	Ca, Ba, Mg, Zn, Cd, Mn, Pb, Hg
2	Murexide (or) Ammonium purpurate	Violet to Blue	12	Ca, Cu, Co
3	Catechol – violet	Violet to Red	8-10	Mn, Mg, Fe, Co Pb
4	Methyl Blue Thymol Blue	Blue to Yellow Blue to Grey	4-5 10-12	Pb, Zn, Cd, Hg
5	Alizarin	Red to Yellow	4.3	Pb, Zn, Co, Mg, Cu
6	Sodium Alizarin sulphonate	Blue to Red	4	Al, Thorium
7	Xylenol range	Lemon to Yellow	1-3 4-5 5-6	Bi, Thorium Pb, Zn Cd, Hg

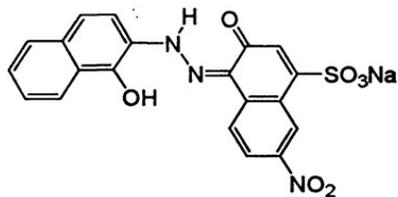


Fig 4: Structure of Mordant black II

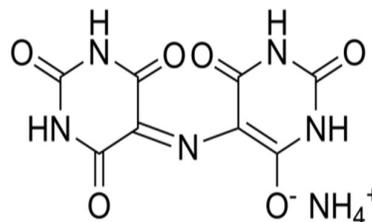


Fig 5: Structure of murexide(Ammonium purpurate)

Spectrophotometric detection

Compared to visual methods, Spectrophotometric methods typically provide a more accurate and diluted solution for the detection of changes in the absorption spectrum caused by the conversion of a metal ion of a complexing agent to a metal complex or the conversion of one complex to another. Therefore, 0.001M solutions can be used to reach an accurate end point in disodium edta titrations. In actuality, a visible-range indicator is often used; however, spectrophotometric techniques can be used to titrate coloured ions in the absence of an indicator. Additionally, for ions and complexes that are colourless in the visible spectrum, it is occasionally feasible to employ an end point in the UV range.[9]

Amperometric Titration

The amperometric titration method shows that complex formation causes an ion's half-wave potential to become more negative. The diffusion current will decrease gradually until it reaches the residual current, or until the last trace of the free cation has been complexed, if the electrode potential is set to a value between the half-wave potential of the complex and that of the free cation and disodium edetate solution is added gradually. This is the final stage, and the quantity of standard disodium edetate solution supplied corresponds to the quantity of metal that is there.[10]

Potentiometric titration

Applying the equation $E = E_0 + \log_e [\text{Ox}]/[\text{Red}]$, disodium edetate will lower the redox potential since it preferentially interacts with an ion's higher valency state.

Where, E represents the electrode's potential.

E_0 is the electrode potential standard.

[Ox] is the oxidised state's ion activity.

[Red] denotes the ion activity in the reduced state.[10]

Preparation and standardization of Disodium EDTA

Preparation of Disodium EDTA

- Disodium EDTA preparation involves dissolving 18.6 grammes of the substance in water.
- To create a 0.05M solution, adjust the volume to 1000 ml.
- Make the prepared solution standardised.[11]

$$372.24 \text{ g } \text{C}_{10}\text{H}_{14}\text{N}_2\text{Na}_2\text{O}_8 \cdot 2\text{H}_2\text{O} \approx 1000\text{ml} \approx 1\text{M disodium EDTA}$$

$$18.612 \text{ g } \text{C}_{10}\text{H}_{14}\text{N}_2\text{Na}_2\text{O}_8 \cdot 2\text{H}_2\text{O} \approx 1000\text{ml} \approx 0.05\text{M disodium EDTA}$$

Standardisation of EDTA

- Precisely weigh 200 mg of CaCO_3 in a titration flask.
- To dissolve CaCO_3 , add 50 ml of water and a minimum amount of dil. HCl.
- Use NaOH to bring the solution's pH down to 12.
- Add 300 mg of the blue indicator hydroxy naphthol.
- Titrating should be done using the prepared M/20 disodium EDTA solution until a deep blue colour is achieved.

CaCO_3 is converted to CaCl_2 by the HCl, which solubilizes it. In order to ensure that the Ca-EDTA combination remains stable and that any possible contaminants, such as magnesium, do not react, the NaOH turns the solution alkaline and keeps the pH at roughly 12. In order to release the free, uncomplicated indicator, which is blue, the coloured Ca-indicator complex releases Ca to EDTA. [11]

Assay of drugs using edta

Determination of copper

Chemicals Required

Acetone(99.9%), Anhydrous sodium acetate (99.9%), Disodium ethylenediamine tetra acetic acid (99.9%), Copper (II) sulphate pentahydrate (99.999%), Perchloric acid (99.9985%), Tris (hydroxymethylaminomethane)–Buffer (99.5%), Ethyl alcohol (95% V/V), and murexide (ammonium purpurate) (99.9%).

Procedure

Because of their solubility, 10 ml of Copper (II) solution was diluted to 30 ml using either an acetone-water (reg no. viii) or an ethanol-water mixture (reg nos. i to vii, ix). The pH was adjusted using 1.0% tris-buffer and 1.0% perchloric acid solution. When 5 to 6 drops of Hydroxytriazenes were added, the colour turned yellow. An equimolar EDTA solution was used for the titration, which was conducted slowly at room temperature. To improve the endpoint's perceptibility, one or two more drops of indication were applied towards the finish. The end point was marked as the point at which the colour abruptly turned green.[12]

Determination of zinc

Making a Standard 0.01M Zn²⁺ Solution

In order to prevent hydrolysis, a little amount of glacial acetic acid was added after the necessary amount of zinc acetate dihydrate had been dissolved in ultra-pure water. After that, the solution was gravimetrically standardised using 8-hydroxyquinoline, which was produced by hydrolyzing 8-acetoxyquinoline at a pH of 4.4 and a temperature range of 60 to 700 degrees Celsius. The precipitate was then washed. After drying the precipitate at 105–110°C, an analytical balance was used to weigh it.[13]

Standard EDTA 0.01M Solution

Using Xylenol orange indicator, the proper quantity of disodium salt of EDTA, which had been first dried at 80 degrees Celsius, was dissolved in ultra-pure water to a specified volume and standardised against zinc acetate dehydrate solution (0.01M).[13]

Orange Xylenol Indicator (0.1%)

After dissolving 0.1g of Xylenol orange in 100 ml of ultra-pure water, the mixture was filtered.[13]

The indicator hydroxytriazene (0.1%)

100 ml of ethanol and 100 ml of acetone were used to dissolve 0.1 g of each hydroxytriazene.[13]

1% Hexamine solution

After dissolving 1.0g of hexamine in the smallest volume of ultra-pure water, ethanol was added to get the mixture up to the 100 mark. [13]

1.0% Perchloric Acid Solution

Ethanol was used to dilute 1.0 ml of perchloric acid to the 100 mark.[13]

Procedure

Depending on how soluble the indicator was, a mixture of ethanol, water, or acetone was used to dilute 10 ml of zinc (II) solution to 30 ml. 1.0% Hexamine solution and 1.0% Perchloric acid solution were used to alter the pH. When five or six drops of hydroxytriazene were added, a yellow colour is developed right away. An equimolar EDTA solution was added to the solution very gradually while it was at room temperature. To improve the end point's perceptibility, one or two more indicator drops were added to the mixture towards the finish. In every instance, the point at which colour abruptly turned colourless was noted as the end point. These outcomes were contrasted with those attained with an indication, Xylenol orange.[13]

Determination of bismuth

Bismuth nitrate solution 0.05M

Stock bismuth nitrate solution was prepared by dissolving bismuth nitrate pentahydrate 24.25 gm in 50ml of 16M nitric acid and diluting to 1000ml with distilled water.

Xylenol orange indicator

It was prepared by dissolving 0.25gm of solid in 100ml of water.

Tartaric acid (20% w/w)

20gm of solid was dissolved in 100ml of water.

Procedure

To the sample solution 5ml of tartaric acid solution was added along with a few drops of xylenol orange indicator. Colour of contents is in yellow at this stage which were diluted with water until the intense red colour is developed (pH was around 2). In cases where concentration of acid in original bismuth solution was high (above 0.5M), the solution was neutralised with 1M KOH or NaOH solution after the addition of indicator and tartaric acid solution, till a faint pink colour is obtained. Then it was diluted with water for the development of intense red colour. The contents was titrated against 0.05M EDTA solution until the colour change to sharp yellow.[14]

Determination of aluminium**Mn(II)SO₄ Solution 0.01M**

1 L of water was used to dilute 1.7 g of 1-hydrate, which had been dissolved in 0.01 M Mn(II)SO₄ solution. Using an EBT indicator, the stock solution of 0.01 M Mn(II)SO₄ was standardised against standard aluminium using the traditional approach. In a similar manner, standard lead solution was used to standardise 0.005 M Mn(II)SO₄ solution.

Standard Aluminium Solution

After being thoroughly cleaned with pure alcohol, 0.6745 g of polished aluminium foil were dissolved in 25 mL of hydrochloric acid and 150 mL of deionized water. The mixture was then further diluted to 500 mL.

Erichrome Black T indicator

This was made by dissolving 1.2 g of hydroxylamine hydrochloride and 0.12 g of EBT in ethanol.

Procedure

The solution left over from the previous titration was mixed with 5 mL of 10% (w/v) hydroxyl amine and 20 mL of triethanolamine, and it was then brought to a boil for one minute in order to measure the amount of aluminium. The released EDTA was then titrated using Erichrome Black-T as the indicator and a standard 0.01 Mn(II)SO₄ solution. At the finish line, a blue colouring was observed to turn red. The amount of manganese solution ingested matched the sample's aluminium content.[15]

Table 1: Substances assayed by direct titration with Disodium- EDTA

S.No	Name of substance	Qty	Indicator	Calculations
1	Calcium Carbonate	0.1g	Calcon mixture	Each ml of 0.05M EDTA \equiv 0.005004g of CaCO ₃
2	Dibasic Calcium Phosphate	0.2g	Hydroxy naphthol blue	Each ml of 0.05M EDTA \equiv 0.002004g of Ca
3	Magnesium chloride	0.5g	Mordant black II mixture	Each ml of 0.05M EDTA \equiv 0.017017g of MgCl ₂ .6H ₂ O
4	Heavy magnesium oxide	0.1g	Mordant black II mixture	Each ml of 0.05M EDTA \equiv 0.002015g of MgO
5	Magnesium trisilicate	1.0g	Mordant black II mixture	Each ml of 0.05M EDTA \equiv 0.002015g of MgO
6	Zinc chloride	3.0g	Erichrome black T	Each ml of 0.05M EDTA \equiv 0.006815g of ZnCl ₂
7	Zinc stearate	1.0g	Erichrome black T	Each ml of 0.05M EDTA \equiv 0.004069 of ZnO
8	Zinc sulphate	0.3g	Erichrome black T	Each ml of 0.05M EDTA \equiv 0.001438g of ZnSO ₄ .7H ₂ O
9	Zinc undecylenate	0.5g	Erichrome black T	Each ml of 0.05M EDTA \equiv 0.002160 of C ₂₂ H ₃₈ O ₄ Zn

Table 2: Substances Assayed by residual Titration with EDTA

S.no	Name of substance	Qty	Indicator	Calculations
1	Aluminium Glycinate	0.25g	Methyl red	Each ml of 0.05M EDTA \equiv 0.002549g of Al ₂ O ₃
2	Dried aluminium hydroxide	0.8g	Methyl red	Each ml of 0.05M EDTA \equiv 0.005098g of Al ₂ O ₃
3	Aluminium sulphate	0.5g	Methyl red	Each ml of 0.05M EDTA \equiv 0.01711g of Al ₂ (SO ₄) ₃

4	Bismuth Subcarbonate	0.5g	Methyl red	Each ml of 0.05M EDTA \equiv 0.02090g of Bi
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Applications

- Complexometric titrations have been successfully used to determine the hardness of water as well as a number of metals, including Ca, Mg, Pb, Zn, Al, Fe, Mn, and Cr, in several official I.P. formulations.
- Calculating the Calcium Content of Various Formulations
- Determining the Hardness of Water[16]
- Titanium dioxide is used in many cosmetic products which can be analysed by complexometric titrations.
- It is widely used in analytical chemistry.

CONCLUSION

Complexometric titration is the volumetric titration through which the end point can be determined by different stabilities of metal-indicator and metal-titrant complex. Buffer solutions resist the change in pH. The individual metal ions can be analysed by EDTA titration. Complexometric titration had made it possible for man to be exposed to an advanced method of titration which not only enables us to analyze more ions, but also do them in very small quantities.

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