Ministry of Health of the Russian Federation

Volgograd State Medical University

Department of Pharmaceutical and Toxicological Chemistry

GENERAL PHARMACEUTICAL CHEMISTRY

Complementometry

Lesson 17

V term

Volgograd, 2022

QUESTIONS FOR THE LESSON

1. Essence of the method
2. Preparation of trilon b standard solution
3. Fixing the titration end point
4. Eriochrome black t
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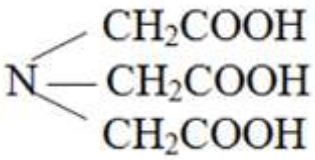
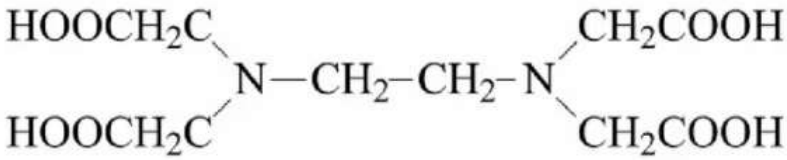
ESSENCE OF THE METHOD

Complexometric titration is a method of titrimetric analysis based on the complexation reaction of metal cations with complexones - aminopolycarboxylic acids and their salts.

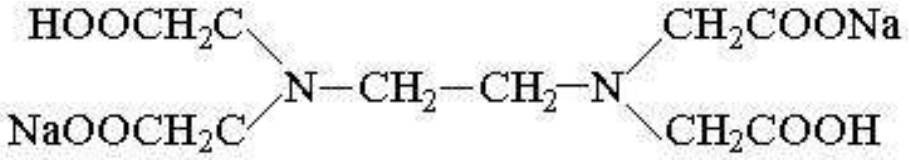
Complexons. The simplest complexon, known as **complexon I**, is **tri-basic nitrilotriacetic acid** (abbreviated H_3Y):



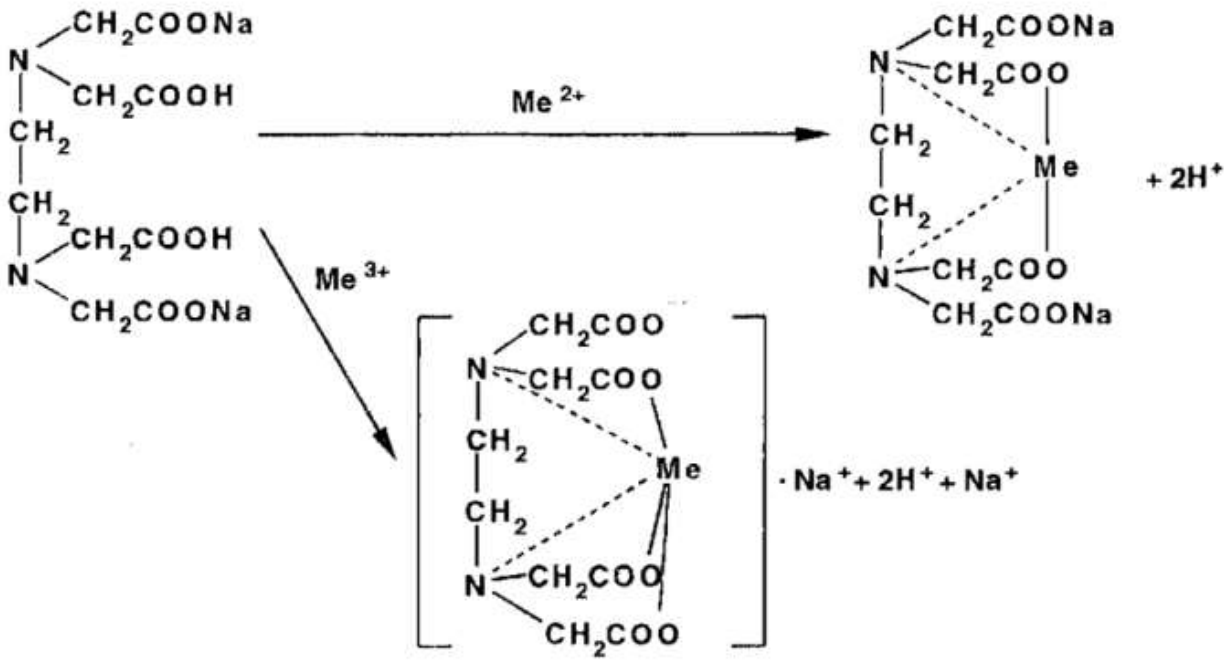
Ethylenediaminetetetraacetic acid (EDTA), **complexone II**, quaternary basic acid (abbreviated H_4Y) has become most important:



As a titrant in complexometry, solutions of the **disodium salt of ethylenediaminetetraacetic acid**, called **complexon III, Na_2EDTA**, or **trilon B** (abbreviated Na_2H_2Y) are used:



Chemistries. Complexon III, like other complexons, forms soluble intracomplex salts with many metal ions. The metal substitutes hydrogen atoms of carboxy groups and also forms donor-acceptor bonds with nitrogen and oxygen atoms according to the scheme:



Such binding leads to the formation of very strong complexes. In addition, the composition of the resulting complexes is, with few exceptions, 1:1. This eliminates stepwise complexation and simplifies the analysis and accompanying calculations. Many metal complexes with EDTA are easy to form, sufficiently stable and in most cases soluble in water.

The complexometric titration method is highly sensitive (up to 10^{-3} M) and accurate (0.1-0.3 % error), fast and easy to perform, and has a sufficiently high selectivity.

A number of features of the reaction should be noted which have made complexometry widely used in chemical analysis:

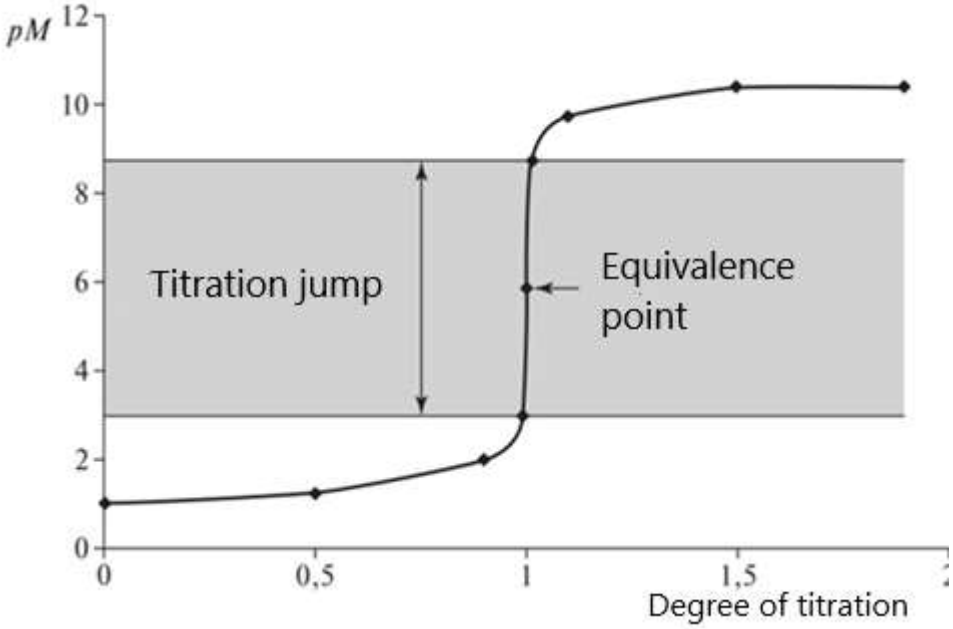
- the reaction produces complexes of only one composition with a metal-complexing - ligand-complexon (M:L) component ratio of 1:1.
- The complexonates are colourless, water-soluble and highly stable, as the central metal atom is firmly bound to the polydentate chelate ligand.
- The reaction is a reversible process and can be shifted both towards the formation and destruction of the complexonate. This is easily achieved by varying the pH of the solution: acidification shifts the equilibrium to the left

towards the parent reagents, while alkalinisation promotes the formation of the complexonate:

$$M^{2+} + Na_2H_2Y \longleftrightarrow Na_2[MY] + 2H^+$$

- The reaction generates hydrogen ions, so it should be carried out in a buffer medium, maintaining an optimum pH value determined by the complexonate's stability constant.

Titration curves. The degree of reaction depends on the pH and the stability constant of the complex compound.



The magnitude of the jump in the titration curve is affected:

- initial concentration of the ion to be determined in the solution
- the stability constant of the resulting compound with EDTA

The higher the concentration of the ion to be determined and the stronger the complex, the greater the jump.

PREPARATION OF TRILON B STANDARD SOLUTION

The diisodium salt of ethylenediamine-tetraacetic acid is hygroscopic, so a *secondary* standard solution is prepared from it.

Then determine its exact concentration using standard substances - chemically pure Zn, ZnO, $CaCO_3$ or standard solutions of $ZnSO_4$ or $MgSO_4$.

FIXING THE TITRATION END POINT

The titration end-point is set with metal indicators - indicators that change colour depending on the concentration of the metal ion.

These are organic compounds that contain chromophore groups in their molecules and are therefore coloured. Such indicators form complexes with metal ions less strong than the titrant and the colour of these complexes differs from the colour of the indicators themselves.

Metal indicators can be divided into two groups:

- **Indicators which are not themselves coloured, but form coloured complexes with metal ions.** The colour intensity of the resulting complexes is usually low. Therefore, the concentration of the indicator must be about 10 times the concentration of the titrated metal in order to observe the colouration of the complex.

  For example, in the complexometric titration of iron(III) salicylic and hydroxamic acids are used as indicators; in the determination of bismuth(III) thiourea is used. Iron(III) complexes with salicylic and hydroxamic acids are red. Thiourea complexes of bismuth(III) are yellow.

- **metallochromic indicators -** organic substances with chromophore groups that form intensely coloured complexes with metal ions, which are less stable than complexonates.

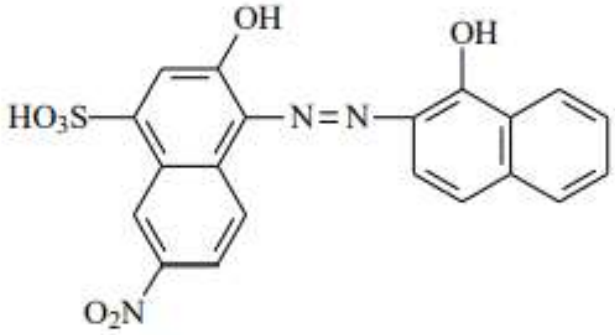
Requirements for metal indicators

1. In the selected pH region they should form sufficiently stable complexes with metal ions with the ratio M:Ind=1:1.
2. The complex of the metal ion with the indicator must be kinetically labile and rapidly break up on addition of the complexons;
3. The colour change of the solution in the titration end-point should be contrasting.

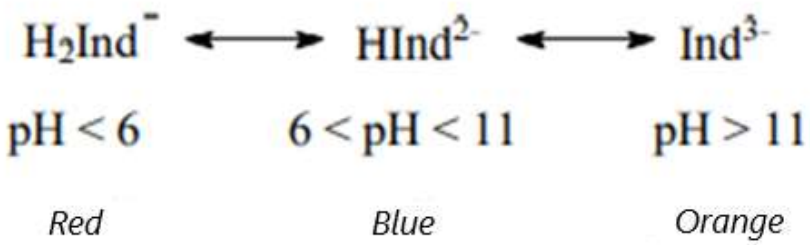
Eriochrome black T and murexide are the most common metallochrome indicators, while pyrocatechin purple and xylene orange are also used.

ERIOCHROME BLACK T

Eriochrome black T is an azo dye with the properties of a weak tri-base acid (H_3Ind):

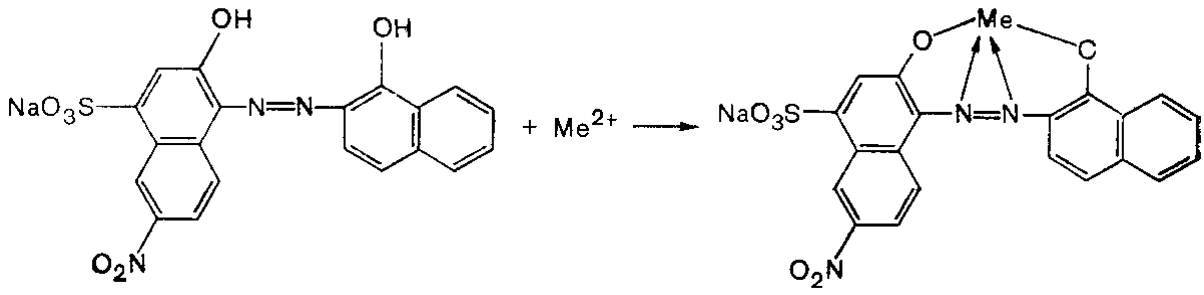


As the pH of the solution increases, it changes from one coloured form to another according to the following scheme:



The predominance of one or another form of indicator is determined by the values of its acid dissociation constants and the pH value of the solution. At pH = 6-11 the blue coloured $HInd^{2-}$ ion will be dominant.

In this pH range, most metal ions (Mg^{2+}, Ca^{2+}, Cu^{2+}, Zn^{2+}, etc.) form 1:1 wine-red complexes with the eriochrome black T:



During titration with a complexon III solution near the point of equivalence the indicator is displaced by the complexon with the formation of a colourless complexonate and a blue coloured form of the free indicator $HInd^{2-}$:

$$MInd^{n-3} + [H_2Y]^{2-} \leftrightarrow [MY]^{n-4} + HInd^{2-} + H^+$$

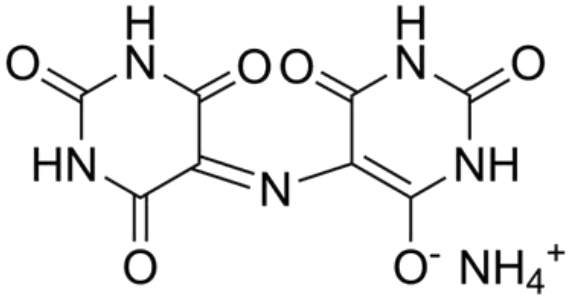
Wine red **Colourless** **Blue**

Thus, when titrating metal ions with complexon III in a neutral and slightly alkaline medium in the presence of eriochrome black T the colour change of the indicator from wine-red to blue indicates the titration end-point.

As a rule, complexometric titration with eriochrome black T is carried out in the presence of ammonia buffer solution (pH ~ 9).

MUREXIDE

Murexide is the ammonium salt of purple acid (H_4Ind^-).



It is a dark red powder whose aqueous solution is coloured violet, varying with the pH of the medium:

$$H_4Ind^- \longleftrightarrow H_3Ind^{2-} \longleftrightarrow H_2Ind^{3-}$$

$pH < 9$ $9 < pH < 11$ $pH > 11$

Red-Purple **Purple** **Blue**

Murexide forms stable coloured complexes with calcium, nickel, cobalt, copper and other cations.

Calcium complexes are **red**,

complexes of nickel, cobalt and copper are **yellow**.

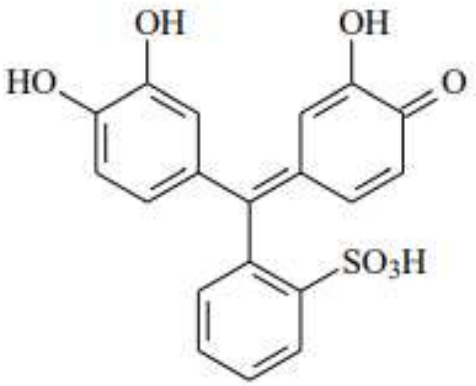
Murexide is used in the complexometric determination:

- Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+} (pH 8-9),
- Ca^{2+} (pH >12).

The indicator is used as a 1% aqueous solution or as a dry mixture with sucrose (or sodium chloride) in a 1:500 ratio.

PYROCATECHIN PURPLE

Pyrocatechin purple is a metal indicator of the sulphophthalein dye class and is a quad-base acid (H_4Ind).



The colour changes are due to a stepwise dissociation of the indicator depending on the pH of the medium.

H_4Ind	H_3Ind^-	H_2Ind^{2-}	$HInd^{3-}$	Ind^{4-}
$pH < 1$	$1 < pH < 8$	$8 < pH < 10$	$10 < pH < 11$	$pH > 11$
Red	**Yellow**	**Purple**	**Red-purple**	**Blue**

The complexes with the metals are usually coloured blue. The indicator can be used to determine the end-point of a complexometric titration at different pH values.

For the determination of Bi^{3+} the titration at pH 2-3, Cu^{2+} in acetate buffer solution at pH 5-6 and under these conditions the colour change from blue to yellow is fixed. Mg^{2+}, Ni^{2+} and Zn^{2+} are determined in ammonia buffer solution at pH 9-10 and the colour change from blue to red-purple is observed in the titration endpoint.

COMPLEXOMETRIC TITRATION CONDITIONS

1. The complexation reactions should be fast, quantitative and stoichiometric so that near the equivalence point the determined cations are almost completely bound to the complex.
2. Detectable ions should form less strong complexes with the metalindicator than their complexes with trilon B.

3. The complexometric titration must be conducted at a certain pH value (pH < 10), because precipitation of hydroxides of determined cations or their basic salts can form in an alkaline environment.

In order to maintain a certain pH value the titration should be carried out in the presence of buffer solutions having a certain pH value. Most cations are titrated with Trilon B in the presence of ammonia buffer solution $NH_4OH + NH_4Cl$ at pH 9.2.

METHODS OF COMPLEXOMETRIC TITRATION

Direct titration

Ammonia buffer solution and the metal indicator are added to the test solution and titrated with a standard trilon B solution.

At the point of equivalence the colouring of the solution changes from the colouring of the cation complex with the metal indicator to the colouring of the free metal indicator.

The cations $Cu^{2+,}$ Co^{2+}, Pb^{2+}, Ni^{2+}, Zn^{2+}, Fe^{3+}, Ba^{2+}, Cr^{3+},Ca^{2+}, Mg^{2+} etc. are determined by direct titration.

Reverse titration

To the analysed solution add

- ✓ Ammonia buffer solution,
- ✓ Exactly measured double of the minimum volume of Trilon B standard solution, which reacts with the determined ions,
- ✓ Excess Trilon B is titrated with a standard solution of magnesium sulphate or zinc sulphate in the presence of a metal indicator.

In the process, reactions occur:

$$Me^{2+} + H_2Y^{2-} \leftrightarrow [MeY]^{2-} + 2H^+$$

$$\text{изб. } H_2Y^{2-} + Zn^{2+} \leftrightarrow [ZnY]^{2-} + 2H^+$$

Change from free indicator colouring to colouring of the metal indicator complex with the titrant cation.

The reverse titration method is used:

- ✓ when the complexation reaction is slow;
- ✓ there is no suitable indicator for fixing the titration end-point in the direct titration method;

- ✓ The indicator forms a very strong complex with the determined ion, which is not destroyed by the complexon;
- ✓ for the determination of cations in water-insoluble sediments for example Ca^{2+} in CaC_2O_4, Mg^{2+} in $MgNH_4PO_4$, Pb^{2+} in $PbSO_4$.

Substitution titration

The method is based on the fact that most ions form more stable complex compounds with trilon B than the complex of Mg^{2+} cations with trilon B $[MgY]^{2-}$. After the addition of the $[MgY]^{2-}$ complex to the analysed solution, an exchange reaction takes place:

$$\mathbf{[MgY]^{2-} + Me^{2+} \rightarrow [MeY]^{2-} + Mg^{2+}}$$

The released Mg^{2+} ions are titrated with a standard solution of Trilon B in the presence of a metal-chromium indicator:

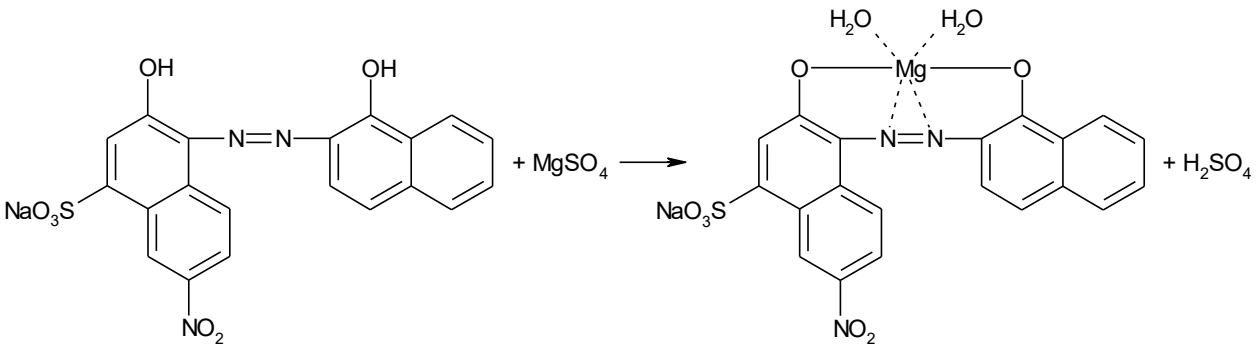
$$\mathbf{Mg^{2+} + H_2Y^{2-} \rightarrow [MgY]^{2-} + 2H^{+}}$$

At the point of equivalence, the colouring of the solution changes to the colouring of the free metal indicator.

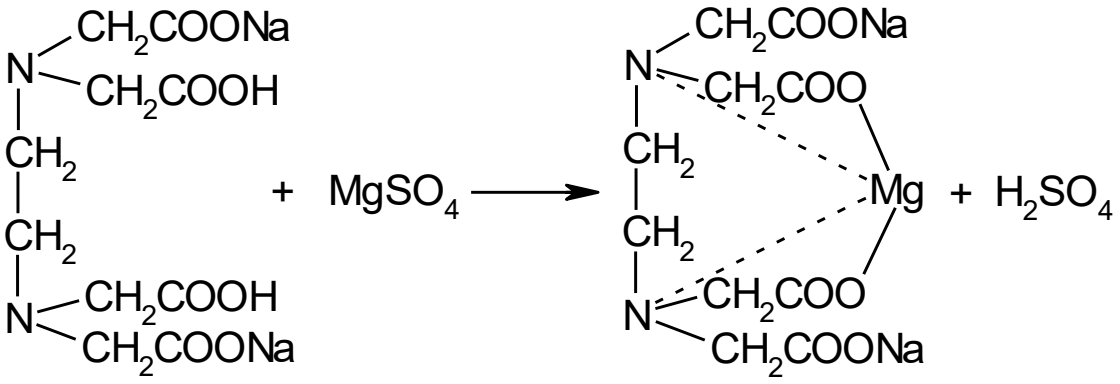
APPLICATIONS IN PHARMACEUTICAL ANALYSIS

Complementometry is a pharmacopoeial method of analysis. The method is characterised by its expressiveness and accuracy, which makes it suitable for the analysis of substances and drugs. In particular it is used for the analysis of pharmaceuticals such as magnesium sulphate, gluconate, calcium lactate and chloride, bismuth basic nitrate.

Magnesium sulphate is quantified by direct complexometric method using a special acid chromium black indicator (eriochrome black T). After adding the indicator to the titrated solution the magnesium ions form a weak complex compound with it:

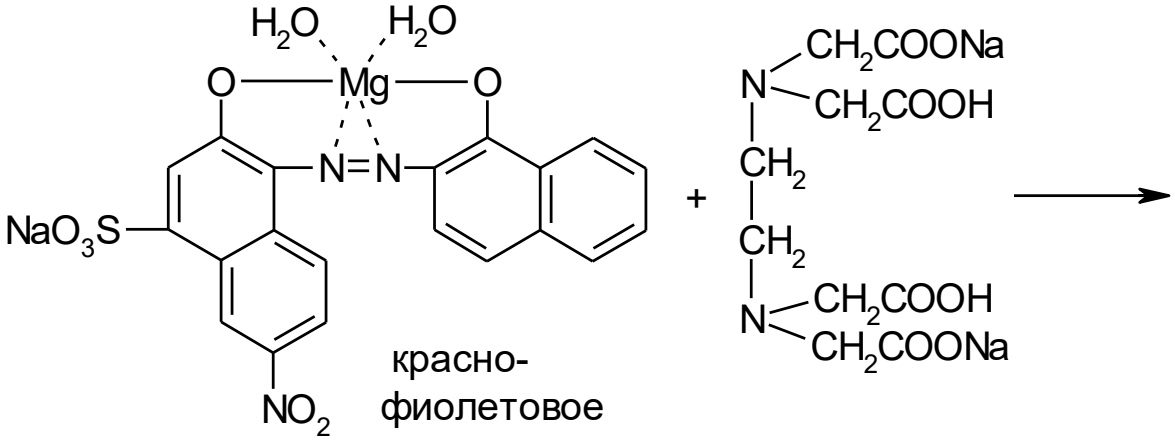


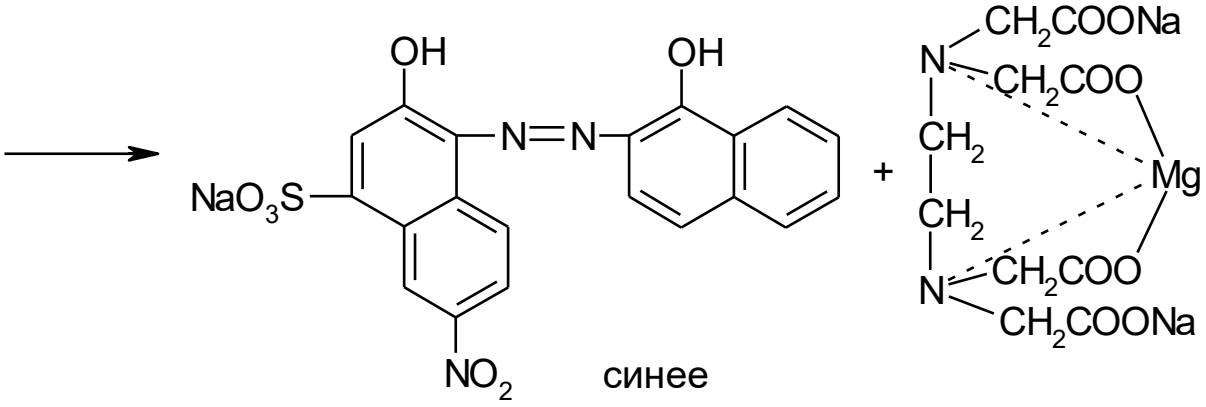
The titrant, a 0.05 M solution of Trilon B (EDTA-Na2), binds the magnesium ions in solution into a complex compound:



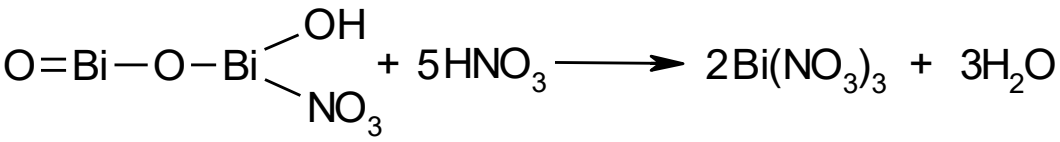
At the equivalent point, when all the magnesium ions are bonded to the metal-EDTA-Na_2 complex, the titrant interacts with the magnesium ions contained in the metal-indicator complex.

The complex between the indicator and the magnesium ions breaks down. The red-violet colouring of the solution changes to the blue colouring of the free indicator:

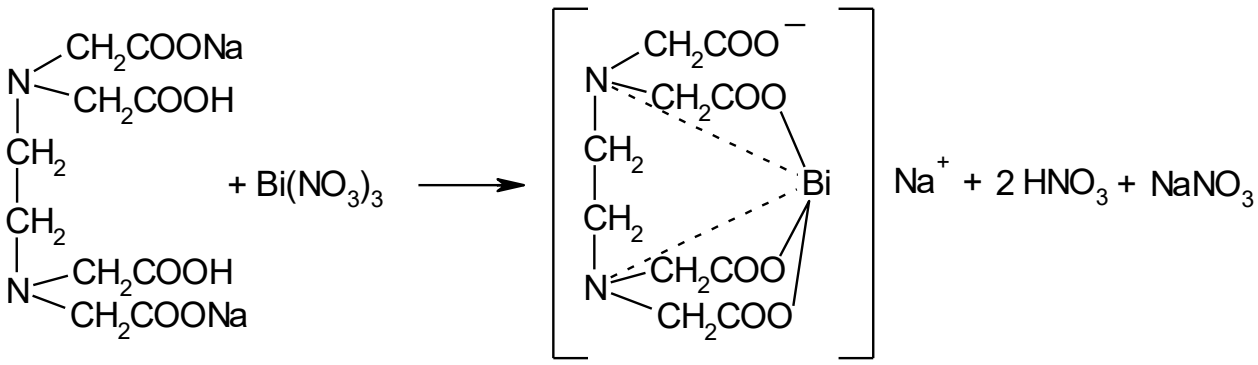




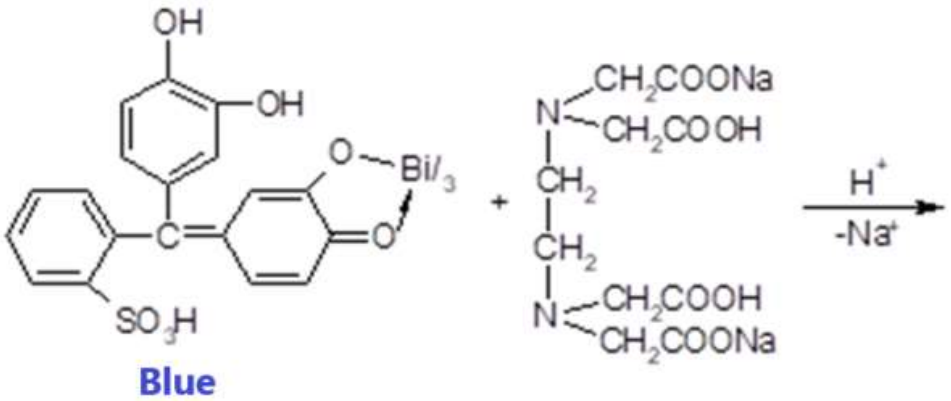
***Quantification of bismuth nitrate basic*.** A sample dissolved in heated nitric acid.

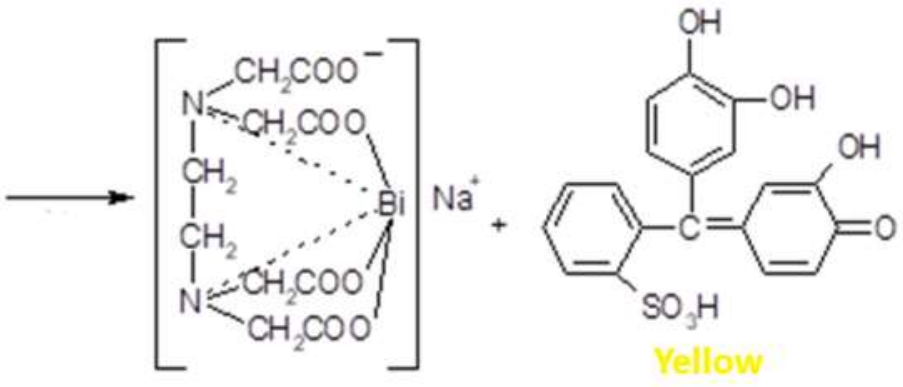


Titration with 0.05 M Trilon B solution (EDTA-Na_2) in the presence of xylenol orange or pyrocatechin purple indicator. During titration, the titrant binds the bismuth ions formed when the drug substance is dissolved in nitric acid into a complex compound:



When titrated with EDTA-Na_2 it takes the bismuth ion away from the indicator and binds it into a stronger complex which is not coloured. At the equivalent point a free indicator is released which gives a yellow colour to the solution:

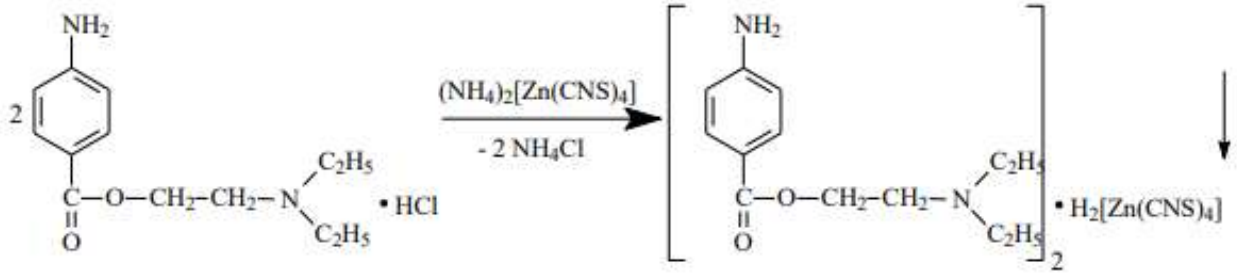




Determination of organic bases. Many organic compounds (e.g. novocaine, papaverine hydrochloride) can form slightly soluble complexes with salts of heavy metals, with Marmet reagents (CdI_2 solution in potassium iodide, i.e. $K_2[CdI_4]$) and Dragendorf (BiI_3 solution in potassium iodide, i.e. $K[BiI_4]$), with ammonium tetradanocinkat etc.

After separating the precipitate formed, the filtrate containing an excess of unreacted reagent is titrated with a complexon III solution (reverse titration method).

For example, in the determination of ***novocaine***, it is precipitated with ammonium tetrorhodanozincate



nd after separating the precipitate, the reagent residue is titrated with complexone III in ammonia buffer solution in the presence of eriochrome black T.

$$(NH_4)_2[Zn(CNS)_4] + Na_2[H_2Y] = Na_2[ZnY] + 2NH_4CNS + 2HCNS$$