Ministry of Health of the Russian Federation

Volgograd State Medical University

Department of Pharmaceutical and Toxicological Chemistry

GENERAL PHARMACEUTICAL CHEMISTRY

Precipitation titration.
Argentometry.

Lesson 14

V term

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QUESTIONS FOR THE LESSON

1. General characteristics of precipitation titration.
2. Classification of precipitation titration methods.
3. Argentometry.
4. Determination of the end point of titration.
5. Mohr method. The essence of the method.
6. Conditions of titration by the Mohr method.
7. Mohr method application in pharmaceutical analysis.
8. Volhard's method. The essence of the method.
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10. Determination of Ag^+ ions by the Volhard's method (direct titration).
11. Application of the Volhard's method (direct titration) in pharmaceutical analysis.
12. Determination of anions by the Volhard's method (reverse titration).
13. Application of the Volhard's method (reverse titration) in pharmaceutical analysis.
14. Fajans method.
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16. Application of the Fajans method in pharmaceutical analysis.

1. General characteristics

Precipitation titration is a group of titrimetric methods of analysis based on the formation of low solubility compounds that are released from solution as precipitate.

Precipitation methods are used for the quantitative determination of inorganic compounds of halides, cyanides, thiocyanates, soluble silver salts, including NaCl, KBr, KI, AgNO3, etc. These methods are also used for the quantitation of drugs: diphenhydramine hydrochloride, bromocamphora, novocaine hydrochloride and others. Titrimetric precipitation methods are based on the use of titration reactions accompanied by the formation of unsolvable compounds.

The difference from the gravimetric method: during titration, an equivalent amount of precipitator is added to the substance in the form of a standard solution. The amount of the determined component (substance) is calculated by the volume of the titrant consumed for the precipitation of the determined substance.

Requirements:

Only a few of the precipitation formation reactions are suitable for titrimetry. In order to use the precipitation reaction in titrimetric analysis, the following conditions must be met:

1. The precipitate must be practically insoluble, i.e. the solubility of the precipitate must not exceed 10^{-5} mol/l;
2. The precipitation shall be sufficiently rapid;
3. The titration results should not be distorted by adsorption (co-precipitation) phenomena;
4. It shall be possible to fix the point of equivalence in the titration.

These requirements significantly limit the range of precipitation reactions used in titrimetric analysis.

2. Classification of precipitation titration methods

According to the nature of the active reagent interacting with the substances to be determined:

- ✓ Argentometry ($AgNO_3$),
- ✓ Thiocyanatometry ($KNCS$ or NH_4NCS),
- ✓ Mercurometry ($Hg_2(NO_3)_2$),
- ✓ Hexacyanoferratometry ($K_4[Fe(CN)_6]$)
- ✓ Sulfatometry (H_2SO_4)
- ✓ Barimetry ($BaC1_2$).

Among all methods of precipitation titration, argentometric and mercurometric titration are of practical importance.

According to the technique of execution, as in other methods of titrimetric analysis, direct and reverse titrations are distinguished.

3. Argentometry

Argentometric titration is a titrimetric method of analysis based on the formation of low soluble silver compounds.

The argentometric titrimetric method of analysis is based on the use of a standard solution of silver nitrate as precipitant:

$$Ag^+ + Hal^- \leftrightarrow AgHal\downarrow$$

A 0.1 mol/l standard solution of silver nitrate can be prepared:

- as a primary standard solution;
- secondary standard solution.

To prepare the ***primary standard*** AgNO3 solution, the calculated weight of chemically pure AgNO3 salt is weighed on an analytical balance, transferred to a measuring flask, dissolved in purified water, the volume of the solution is brought to the mark, thoroughly mixed and transferred to a dark glass flask.

When preparing a ***secondary standard solution*** of AgNO3, the calculated weight of salt is weighed on a technical scale, transferred through a funnel into a dark glass flask, the necessary volume of purified water is added with a cylinder and thoroughly mixed. The resulting secondary standard solution of $AgNO_3$ is standardized by chemically pure standard substances KCl or NaCl or by their solutions.

The concentration of standard silver nitrate solutions varies with prolonged storage. The reason for the instability of silver nitrate solutions is their photosensitivity, therefore these solutions should be stored in dark glass flasks or in dishes wrapped with black paper or covered with black varnish, and in a place protected from light. Their concentration should be checked periodically.

4. Determination of the end point of titration

In the method of argentometry, both indicator-free and indicator methods of fixing the end point of titration are used.

Indicator-free methods

Chloride ions are determined by the so-called equal clouding method (Gay-Lussac method). In this method the analysed solution is titrated with a standard solution of silver nitrate, the end of the titration is determined by taking two samples of the titrated solution into two tubes near the titration endpoint:

- in one of them a drop of a standard solution of silver nitrate is added,

- in the other one a drop of a standard solution of sodium chloride of the same concentration.

The under-titrated solution shows clouding in the tube with silver nitrate, the over-titrated solution shows clouding in the tube with sodium chloride. At the final titration point, the solution in both tubes has the same turbidity.

Bromide and iodide ions are determined by the method of enlightenment. Its essence lies in the fact that when small portions of a standard silver nitrate solution are added to the analyzed solution from the burette, a colloidal silver bromide solution is formed at the beginning, and at the moment of equivalence, colloidal particles coagulate and precipitate in the form of curd flakes, while the solution is clarified.

Of the modern Indicator-free methods in argentometry, ***potentiometric determination of the equivalence point*** using silver or halide-selective electrodes is most often used.

Indicator methods

Depending on the indicator used in argentometry , the following methods are distinguished:

- Mohr method based on the reaction between silver ions and halide ions in the presence of an indicator - a solution of potassium chromate;
- Volhard’s method (thiocyanatometry), based on the reaction between silver ions and thiocyanate ions in the presence of iron (III) ions as an indicator;
- Fajans method is based on the use of adsorption indicators.

Sedimentary indicators are substances released from a solution in the form of a precipitate in a well-marked form at or near the equivalence point.

5. Mohr method

Mohr's method is direct titration.

The titrant of the method is a solution of 0.1 (or 0.05; 0.02; 0.01) mol/l of silver nitrate.

A solution of 0.01 mol/l of potassium chromate is used as an indicator.

The essence of the method is that when titrating halide ions in the presence of chromate ions, the halide ions precipitate first.

$$Ag^+ + Hal^- \leftrightarrow AgHal\downarrow$$

$$Cl^- + Ag^+ \leftrightarrow AgCl\downarrow \quad \text{white}$$

$$Br^- + Ag^+ \leftrightarrow AgBr\downarrow \quad \text{yellowish white}$$

When the halide ions to be determined are almost completely precipitated as AgHal, only then does a brick-red precipitate of Ag_2CrO_4 begin to precipitate. This is due to the different solubility of AgHal and Ag_2CrO_4

$$K_2CrO_4 + 2AgNO_3 = \underset{\text{brick-red sediment}}{Ag_2CrO_4\downarrow} + 2KNO_3$$

In order to take into account the amount of titrant required to form the minimum visually detectable amount of Ag_2CrO_4, a control experiment is carried out.

Conditions of titration by the Mohr method:

1. Titration should be carried out in a neutral or slightly alkaline medium ($6.5 \leq pH \leq 10$).
2. The solution should be free of:

a) Pb^{2+}, Ba^{2+}, Hg^{2+} cations and others forming chromate precipitates with indicator anions

b) PO_4^{3-}, CO_3^{2-}, $C_2O_4^{2-}$, AsO_4^{3-} anions and others forming precipitates with silver ions.

3. Near the end point of titration, the solution must be titrated slowly, with vigorous stirring, in order to reduce the error due to adsorption.
4. It is impossible to titrate colored solutions, as they will mask the Ag_2CrO_4 coloring, which will make it difficult to fix the end point of titration.

The Mohr method is **applicable** for the determination of chlorides and bromides, including pharmaceutical preparations that contain chloride and bromide ions.

Application in pharmaceutical analysis

The Mohr method is mainly used for the quantification of sodium and potassium chlorides and bromides in neutral or weakly alkaline solutions.

The drugs potassium chloride, sodium chloride, potassium bromide and sodium bromide are titrated in a neutral medium, potassium chromate is used as an indicator. The reactions follow a scheme:

$$NaCl + AgNO_3 \rightarrow AgCl\downarrow + NaNO_3$$

$$KCl + AgNO_3 \rightarrow AgCl\downarrow + KNO_3$$

$$NaBr + AgNO_3 \rightarrow AgBr\downarrow + NaNO_3$$

$$KBr + AgNO_3 \rightarrow AgBr\downarrow + KNO_3$$

The excess titrant (the first drop) interacts with the indicator to form an orange-red precipitate, according to which the end point of titration is set:

$$2AgNO_3 + K_2CrO_4 \rightarrow Ag_2CrO_4\downarrow + 2KNO_3$$

6. Volhard's method

The Volhard's method is based on titration of a solution containing silver ions with **standard solutions of NH_4NCS или KNCS**:

$$Ag^+ + NCS^- \leftrightarrow AgNCS\downarrow$$

The indicator in this method is ***iron-ammonium alum*** **$NH_4[Fe(SO_4)_2] \cdot 12H_2O$**. After the precipitation of silver ions as a white AgNCS precipitate, an excess drop of titrant reacts with the indicator to form a soluble red complex.

$$NH_4[Fe(SO_4)_2] + 3NH_4NCS \leftrightarrow Fe(NCS)_3 + 2(NH_4)_2SO_4$$

The Volhard's method uses forward and reverse titration. As standard solutions are used:

- in the method of **direct titration** - a solution of **ammonium thiocyanate or potassium thiocyanate**;
- in the **reverse titration** method – the solutions of **silver nitrate and ammonium or potassium thiocyanate**.

Preparation of NH_4NCS solution.

Ammonium thiocyanate is not a standard substance, since the salt is hygroscopic. Therefore, a solution of the required concentration is prepared from it

- approximately 0.1 or 0.05 mol / l, and then it is standardized according to the standard substance $AgNO_3$ or according to the standard solution $AgNO_3$.

Conditions of titration by the Volhard’smethod:

1. Titration should be performed in an acidic environment to prevent hydrolysis of the indicator .
2. During titration, the solution must be vigorously mixed to reduce the error due to the adsorption of ions on the surface of the precipitate.
3. The analyzed solution should be free of:
   - mercury salts (I) and (II) reacting with NCS-ions:
   - oxidants $KBrO_3$, $KMnO_4$ and other oxidizing NCS-ions;
   - anions F^-, PO_4^{3-}, $C_2O_4^{2-}$ and others forming strong complexes with the indicator

Determination of Ag+ ions by the Volhard’s method (direct titration)

The concentration of silver ions is determined by direct titration with a standard solution of ammonium thiocyanate (or potassium thiocyanate) in the presence of Fe3+ ions.

The ammonium thiocyanate standard solution reacts primarily with the silver ions to form a low soluble compound:

$$Ag^+ + NH_4NCS \leftrightarrow AgNCS + NH_4^+$$

At the titration endpoint an excess drop of titrant reacts with the Fe3+ ions and stains the solution red:

$$NH_4[Fe(SO_4)_2] + 3NH_4NCS \leftrightarrow Fe(NCS)_3 + 2(NH_4)_2SO_4$$

Application of the Volhard’s method (direct titration) in pharmaceutical analysis

An example of direct titration by the Volhard’s method is the quantification of silver cations in colloidal solutions (collargol and protargol). The colloidal preparations are first destroyed by boiling in a mixture of concentrated sulphuric and nitric acids. The resulting silver ions are then titrated with ammonium thiocyanate. The indicator is ferric ammonium alum.

$$Ag^+ + NH_4NCS \leftrightarrow AgNCS + NH_4^+$$
$$NH_4[Fe(SO_4)_2] + 3NH_4NCS \leftrightarrow Fe(NCS)_3 + 2(NH_4)_2SO_4$$

Collargol should contain at least 70% silver, and protargol — 7.5-8.5%.

Determination of anions by the Volhard's method (reverse titration)

Reverse titration is used for the determination of anions. The essence of the determination is that to the solution to be analysed a double of the minimum, precisely measured volume (35.00 or 40.00 mL) of standard silver nitrate solution (1st working solution) is added which reacts with the anions to be determined, e.g. chloride ions:

$$AgNO_3 + Cl^- \leftrightarrow AgCl\downarrow + NO_3^-$$

The unreacted silver nitrate residue is titrated with a second standard solution of ammonium thiocyanate:

$$AgNO_3 + NH_4NCS \leftrightarrow AgNCS\downarrow + NH_4NO_3$$

at the end of titration, an excess drop of NH_4NCS solution reacts with the indicator:

$$NH_4[Fe(SO_4)_2] + 3NH_4NCS \leftrightarrow Fe(NCS)_3 + 2(NH_4)_2SO_4$$

and the solution turns red.

Advantages of the Volhard's method

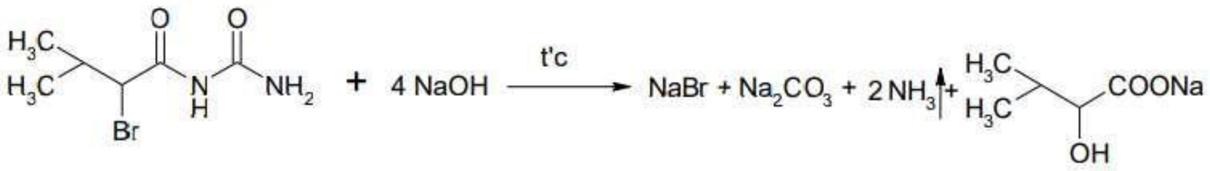
In comparison with the Mohr method, the Folgard method has a number of advantages:

- ✓ the determination of Ag^+, Cl^-, Br^-, I^-, NCS^- is performed in an acidic medium;
- ✓ the cations Ba^{2+}, Pb^{2+} and others that interfere with the determination of anions by the Mohr method do not interfere with their determination by Volhard's.

Application of the Volhard's method (reverse titration) in pharmaceutical analysis

According to the Pharmacopoeia, the Volgard's method is used for the quantification of iodoform, bromisoval, bromocamphora.

The quantification of bromisoval is based on the titration of sodium bromide produced by alkaline hydrolysis of the drug substance:



After pretreatment the reaction mixture is cooled down, acidified with diluted nitric acid, an excess of titrated silver nitrate solution is added, stirred vigorously and titrated with standard ammonium thiocyanate solution in the presence of ironammonium alum:

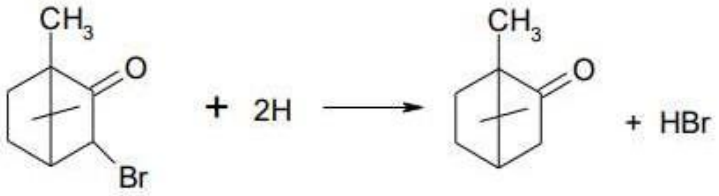
$$NaBr + AgNO_3 \rightarrow AgBr\downarrow + NaNO_3$$

$$AgNO_3 + NH_4SCN \rightarrow AgSCN\downarrow + NH_4NO_3$$

$$3NH_4SCN + FeNH_4(SO_4)_2 \rightarrow Fe(SCN)_3 + 2(NH_4)_2SO_4$$

Quantification of bromocamphora. The method is based on the determination of sodium bromide formed by heating bromocamphor with zinc dust in an alkaline medium.

$$Zn + 2KOH + 2HOH \longrightarrow K_2[Zn(OH)_4] + 2H$$



$$HBr + KOH \longrightarrow KBr + HOH$$

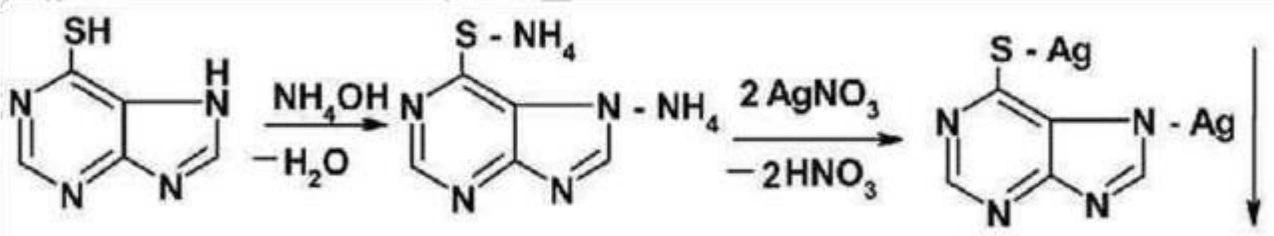
After the reaction is finished, the zinc dust is filtered off and the filtrate is titrated with potassium bromide by the Volgard’s method:

$$KBr + AgNO_3 \longrightarrow KNO_3 + AgBr\downarrow$$

$$AgNO_3 + NH_4SCN \rightarrow AgSCN\downarrow + NH_4NO_3$$

$$3NH_4SCN + FeNH_4(SO_4)_2 \rightarrow Fe(SCN)_3 + 2(NH_4)_2SO_4$$

The quantification of mercaptopurine by the reverse argentometric method is based on the formation of a double-substituted silver salt. The sample is dissolved in ammonia solution and determined by reverse argentometric method, titrating an excess of 0.1 M silver nitrate solution with ammonium thiocyanate solution of the same concentration (indicator ferric ammonium alum):



$$AgNO_3 + NH_4CNS \longrightarrow AgCNS + NH_4NO_3$$

$$3NH_4CNS + FeNH_4(SO_4)_2 \longrightarrow Fe(CNS)_3 + 2(NH_4)_2SO_4$$

7. Fajans method

The Fajans method is based on **direct titration** of anions (halides, cyanides, thiocyanates) with a **standard silver nitrate solution** in the presence of **adsorption indicators.**

Silver halides are prone to the formation of colloidal solutions. In the presence of an excess of Hal ions due to the adsorption of AgHal particles acquire a negative charge:

$$nAgHal + Hal^- \rightarrow (AgHal)_n \cdot Hal^-$$

In the presence of an excess of Ag^+ ions, they acquire a positive charge:

$$nAgHal + Ag^+ \rightarrow (AgHal)_n \cdot Ag^+$$

Charged particles are highly adsorptive and attract particles carrying opposite electric charges and form insoluble compounds with them.

The colloidal properties of silver halides are the basis for the use of adsorption indicators.

Adsorption indicators are substances whose adsorption or desorption by sediment is accompanied by a change in color at or near the equivalence point.

As adsorption indicators are used:

- Bromophenol blue, bromocresel blue - in acetic acid medium;
- Sodium eosinate - in acetic acid medium;
- Fluorescein - in neutral and slightly alkaline media.

The action of the indicators in the Fajans method is related to their adsorption as counter-ions on the charged surface of the sediment.

For example, fluorescein in solution has a yellow colour, while fluorescein adsorbed on sediment has a pink colour; eosin has orange and red-violet colours, respectively.

Conditions of titration by the Fajans method

1. **Titration should be performed at a certain pH value**, as this significantly affects the ionization of the indicator.
2. **Titration with an adsorption indicator should be carried out with a large sediment surface.** This is achieved when the precipitate is present in the form of colloidal particles. For this purpose, protective colloids are added to the titrated solution - dextrin, starch, etc.
3. **It is necessary that the indicator ions are adsorbed by the sediment much weaker than the ions being determined**, otherwise the indicator ions will be adsorbed much earlier than the moment of equivalence, which will lead to underestimated analysis results.
4. **Fluorescein** can be used in the determination of chlorides, bromides, iodides and rhodanides, **eosin** - only in the titration of bromides, iodides and rhodanides. Titration of chlorides in the presence of eosin does not give accurate results, since in this case the staining of the precipitate occurs before the end of the reaction.
5. **Titration cannot be carried out in direct sunlight**, since adsorbed indicators greatly increase the sensitivity of salts to light.

The Fajans method is applicable for the determination of Cl^-, Br^-, I^-,CN^- and NS^- ions.

Application of the Fajans method in pharmaceutical analysis

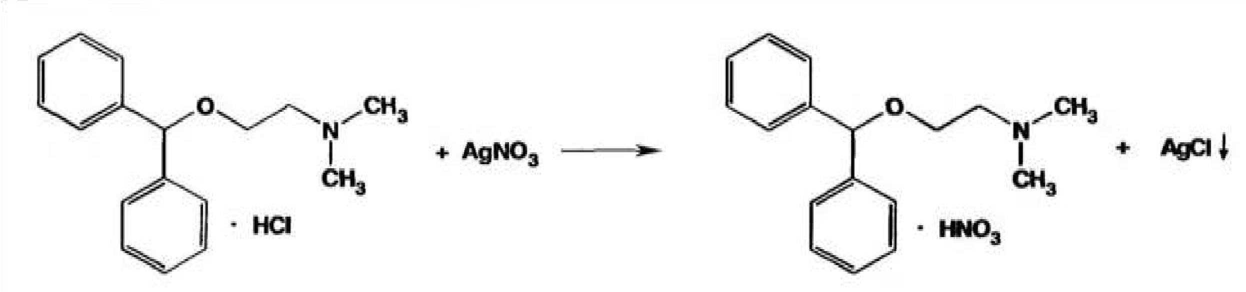
The Fajans method quantifies alkaloid salts, salts of nitrogenous bases (dimedrol, novocaine, papaverine, dicaine, pilocarpil, ephedrine). The Fayans method is pharmacopoeial for sodium and potassium iodides.

Quantification of sodium and potassium iodides. Determined by the Fayans method in acetic acid medium, using 0.1 M silver nitrate solution as a titrant and sodium eosinate as an adsorption indicator. After precipitation of the iodide ions the resulting colloidal silver iodide particles become positively charged from the addition of excess silver ions:

$$[AgI \cdot I^-] \xrightarrow{Ag^+} [AgI \cdot Ag^+]$$

At the same time the colloid [AgI Ag+] attracts the negatively charged sodium eosinate indicator anion with a positive charge. At the titration endpoint the colouring of the surface of the colloidal particles (i.e. the precipitate) changes abruptly from yellow to pink.

Quantification of dimedrol. The method is based on the ability of bound hydrochloric acid to react with silver nitrate to form silver chloride. To the drug add 1 drop of bromophenol blue, drop by drop diluted acetic acid to greenish yellow colouring and titrate with 0.1 mol/l silver nitrate solution to violet colouring.



Quantification of novocaine. To a solution of the drug add 0.1 ml of bromophenol blue solution, drop by drop acetic acid diluted to a greenish yellow colour and titrate with 0.1 mol/l silver nitrate solution to a violet colour.