Ministry of Health of the Russian Federation
Volgograd State Medical University

Department of Pharmaceutical and Toxicological Chemistry

GENERAL PHARMACEUTICAL CHEMISTRY

Alkalimetry. Acidimetry. Titration in non-aqueous solution.

Lesson 8

V term

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QUESTIONS FOR THE LESSON

1. The concept of the neutralisation method.
2. Acid-base titration in aqueous media.
    - 2.1 Classification of acid-base titration methods in aqueous media.
    - 2.2 Working solutions and standard substances for the acid-base titration method.
    - 2.3 Acid-base indicators.
    - 2.4 Application of acid-base titration in drug analysis.
    - 2.5 Advantages and disadvantages of the acid-base titration method in aqueous medium.
3. Acid-base titration in non-aqueous media.
    - 3.1 Classification of solvents used in non-aqueous titration.
    - 3.2 Titrants and solvents used for non-aqueous titration.
    - 3.3 Indicators in non-aqueous titration.
    - 3.4 Application of non-aqueous titration in pharmaceutical analysis.
    - 3.5 Advantages and disadvantages of non-aqueous titration.

INTRODUCTION

The neutralisation method is one part of quantitative analysis. The method is an acid-base titration based on a protolytic reaction:

$$SH_2^+ + S^- \longleftrightarrow 2SH,$$

particularly in aqueous solutions:

$$H_3O^+ + OH^- \longleftrightarrow 2H_2O$$

This method is used to make quantitative determinations:

- acids,
- bases,
- salts, cationic and anionic hydrolyses,
- Nitrogen and sulphur in organic compounds.

Strong acids or strong bases are used as titrants.

A distinction is made between aqueous and non-aqueous acid-base titration.

ACID-BASE TITRATION IN AQUEOUS MEDIUM

The method is used for the quantitative determination of acids and alkalis as well as for titrimetric determinations related to the neutralisation method, for example the determination of some salts formed by strong bases and weak acids (Na_2CO_3, $Na_2B_4O_7$) or ammonium salts.

Classification of acid-base titration methods in aqueous media.

I. Depending on the working solution, this method gets its specific name:

- *Alkalimetry*, where the working solution is alkali,
- *Acidimetry*, which uses an acid solution as the working solution.

II. According to the technique of quantitative analysis , there are:

- Direct titration,
- Reverse titration,
- Substitution titration.

The direct titration method is used to determine:

1. Strong and weak acids, including multi-acid and organic;
2. Strong and weak bases, including multi-acid and organic;
3. Salts formed by weak acids and/or weak bases;
4. The above-mentioned compounds in a mixture (singly or in total).

In a mixture of strong acids or bases, only the total combined concentration of the acids or bases can be determined by acid-base titration, and the components cannot be determined separately.

Substances which react with acids or alkalis but cannot be titrated directly for some reason are determined by *reverse titra*tion. These include:

1. Low water soluble oxides (CaO, MgO etc.) and carbonates ($CaCO_3$, $BaCO_3$ etc.) which are analysed according to the following scheme: A precisely measured excess of standard acid HCl solution is added to an oxide or carbonate sample. After the reaction is completed the acid residue is titrated with a standard alkaline solution.
2. Ammonium salts which are analysed according to the following scheme: To a solution containing ammonium ions a precisely measured excess of standard alkali solution is added. After completion of the reaction and removal of the ammonia, the alkali residue is titrated with a standard acid solution.

3. Certain esters to be analysed according to the following scheme: An alkaline saponification of the ester with a precisely measured excess of a standard alkali solution is carried out. After completion of the reaction the alkali residue is titrated with a standard acid solution.
4. Some metals (Ca, Sr, Ba, etc.) which react readily with acid. The following scheme is used for the analysis: A precisely measured excess of a standard acid HCl solution is added to a sample of the metal. After the reaction is complete the acid residue is titrated with a standard alkaline solution.

Substitution titration is the determination of substances which do not react with acids or alkalis, but which can react chemically and whose products have acid-base properties. The essence of the determination is to convert the substance to a product which is titrated with a standard solution of acid or alkali.

The following classes of substances are determined according to this scheme:

1. Certain organic and inorganic nitrogen-containing compounds (nitrites, nitrates, nitro compounds, amines, amino acids, etc.). For this purpose, the nitrogen from the compound is converted into ammonium ions or ammonia and the resulting substituents are titrated by reverse titration.
2. Cations and anions using ion exchange: The analysed solution shall be passed through a column filled with an ion-exchange material - an ion exchanger. To determine cations, a cation exchange resin with a mobile hydrogen ion (conventionally R-H) is used, which results in acidity at the output of the column and is titrated with a standard alkali solution. The determination of alkali metal ions (Na^+, K^+, etc.) and anions (NO_3^-, CH_3COO^-, etc.) is based on this principle.
3. Cations and anions that form precipitates with ions having acid-base properties. For example, the determination of cations that form water-insoluble carbonates is carried out by precipitation of metal carbonate followed by reverse titration.

Working solutions and standard substances of the acid-base titration method

The main working solutions in this method are strong acid solutions or alkaline solutions. These substances do not meet the requirements for standard substances and therefore titrated solutions cannot be prepared from an exact sample weight.

Therefore working solutions of approximate concentration are first prepared, after which the exact concentration of such solutions is established by titrating the solutions prepared from standard substances.

As standard substances for the standardisation of ***acid solutions*** are used:

- ✓ Sodium tetraborate $Na_2B_4O_7 \times 10H_2O$,
- ✓ Anhydrous sodium carbonate Na_2CO_3,
- ✓ Mercuric oxide HgO
- ✓ Potassium iodate KIO_3 and others.

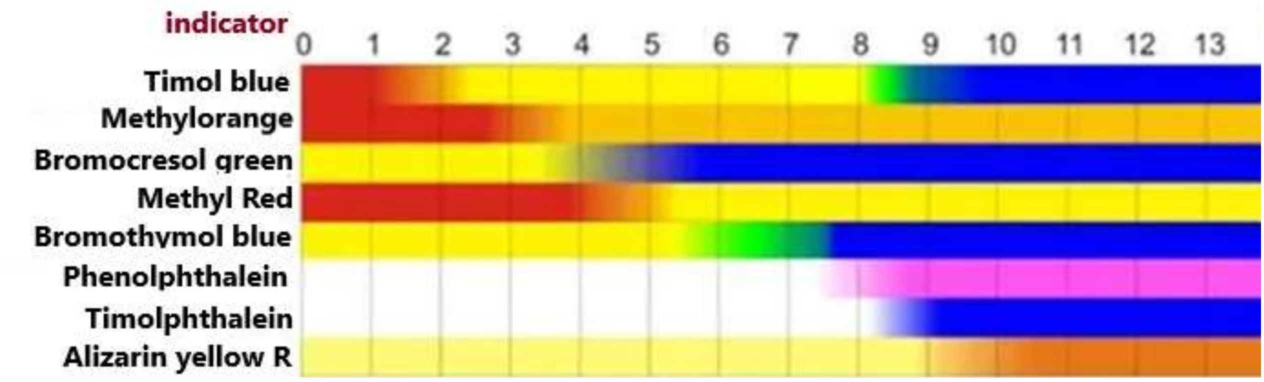
For the standardisation of ***alkaline solutions*** the following is used

- ✓ Oxalic acid $H_2C_2O_4 \times 2H_2O$,
- ✓ SUCCinic acid $H_2C_4H_4O_4$,
- ✓ Benzoic acid C_6H_5COOH (primary standards)
- ✓ and standardized solutions of hydrochloric or nitric acid (secondary standards).

Acid-base indicators

The equivalence point in neutralisation reactions is not accompanied by any external changes. Therefore, special indicators are used to determine the end of the reaction. At the point of equivalence the pH of the solution changes, so the indicators used in acid-base titration are organic compounds whose colouring changes according to the concentration of H^+ ions in the solution. These are acid-base (or pH) indicators.

The range of pH values of a solution in which there is a noticeable change in indicator colouration is called the transition range of the indicator.



Application of acid-base titration in drug analysis

Acid-base titration has found wide application in the analysis of pharmaceutical substances with acidic or basic properties.

These include

- ➢ inorganic and organic acids,
- ➢ salts of organic bases (hydrochlorides, nitrates, hydrophosphates, lactates, hydrotartrates etc.),

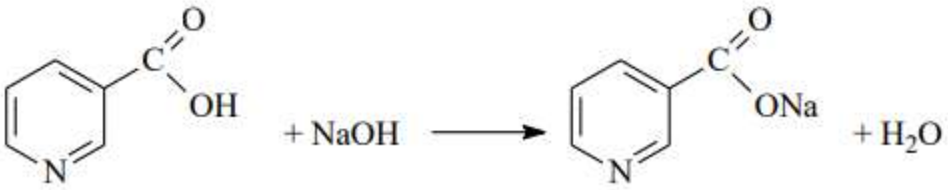
- organic bases exhibiting basic properties in aqueous or alcoholic media,
- sodium salts of weak inorganic and organic acids.

Titration of inorganic and organic acids.

Example: Quantification of nicotinic acid. Nicotinic acid exhibits amphoteric properties due to the nitrogen atom in the pyridine cycle and the mobile hydrogen atom in the carboxylic group.

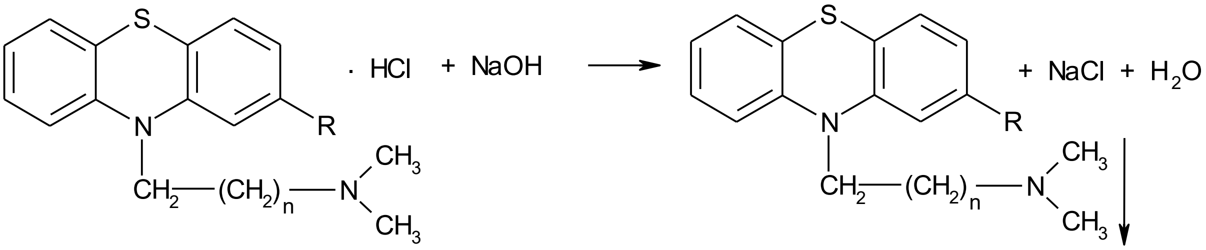
Quantification is based on titration of nicotinic acid with NaOH solution to form its sodium salt. The indicator is phenolphthalein.

The titration is carried out until a pink colour, which does not disappear within 1-2 minutes.



Titration of organic base salts.

Example: The determination of phenothiazine derivatives can be done alkalimetrically by titration with 0.1 M aqueous sodium hydroxide solution (indicator phenolphthalein). Chloroform is added to extract the released organic base:

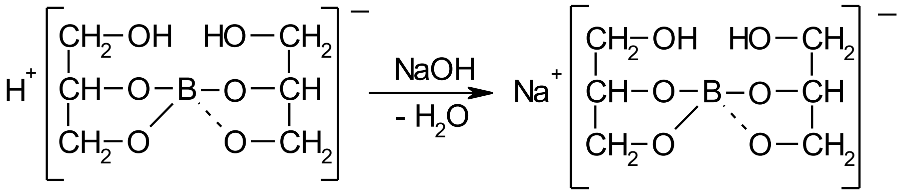


Titration of salts of weak inorganic and organic acids.

Example: Determination of sodium hydrogen carbonate. A sample of the preparation is dissolved in freshly boiled and cooled water (the water is boiled to remove dissolved carbon dioxide) and titrated with 0.1 M hydrochloric acid solution. The indicator is methyl orange.

$$NaHCO_3 + HCl \rightarrow NaCl + H_2O + CO_2\uparrow$$

Example: Determination of boric acid. Aqueous solutions of boric acid (1:50) have a slightly acidic reaction, so its titration is not possible directly. Therefore for the quantitative determination boric acid's ability to form with glycerol a strong uniaxial diglycerinoboric acid, which can be titrated with alkali with sufficient accuracy using phenolphthalein as indicator, is used:



Advantages and disadvantages of the acid-base titration method in aqueous medium

The ***advantages*** of the acid-base titration method include, in aqueous medium

- ✓ high accuracy (0.1-0.2%),
- ✓ The stability of the working solutions,
- ✓ A wide range of indicators for capturing the titration endpoint,
- ✓ Large area of practical application.

The main ***disadvantages*** of the method :

- ✓ Inselectivity in the titration of analyte mixtures,
- ✓ insufficiently high value of the equilibrium constant when titrating very weak acids and bases.

Acid-base titration in an aqueous medium has a number of ***limitations*****:**

- ➢ Weak acids and bases whose dissociation constants are < 10-7 cannot be titrated;
- ➢ Substances insoluble in water cannot be titrated;
- ➢ Strong acids or bases in mixtures as well as weak acids and bases with close dissociation constants cannot be titrated separately

In such cases, titrations in organic solvents, i.e. non-aqueous media, are resorted to.

ACID-BASE TITRATION IN A NON-AQUEOUS MEDIUM

A titration in which the medium is an organic solvent with little dissolved water (less than 0.5%) is called a **non-aqueous titration (non-aqueous titrimetry)**.

Classification of solvents used in non-aqueous titration

In terms of acid-base properties, solvents can be divided into two groups:

- **Aprotonic solvents** that exhibit neither acidic nor basic properties (benzene, hexane, chloroform, etc.),
- **Protolytic solvents**, which exhibit acidic and basic properties.

Protolytic solvents are in turn divided into 3 types:

- ✓ ***Protogenic solvents*** which exhibit acidic properties, i.e. which are proton donors. These are anhydrous carboxylic acids (acetic, formic, oily, etc.), acetic anhydride and phenol.
- ✓ ***Protophilic solvents*** that have basic properties, i.e. that can act as proton acceptors. These include ketones (acetone), esters (dioxane, diethyl ether), tertiary amines (pyridine);
- ✓ ***Amphiprotic solvents*** with both acidic and basic properties, of which alcohols, primary and secondary amines are typical representatives.

Titrants and solvents used for non-aqueous titration

- For titration of **weak acids** the **basic solvents** recommended are ethylenediamine, butylamine, pyridine, dimethylformamide, a mixture of methanol and benzene, and tertiary butanol. ***Sodium methylate in methanol***, for example, is used as a ***titrant***.
- For titration of **weak bases**, **solvents with acidic properties** are used. The most commonly used solvent is glacial (anhydrous) acetic acid. ***Perchloric acid in acetic acid*** or dioxane is the ***titrant***.
- **Both acids and bases** can be titrated in universal **inert solvents** such as methyl isobutyl ketone and methyl ethyl ketone, nitriles and nitromethane. In the inert solvents a differentiation effect can be seen, which makes it possible to titrate separately substances with similar constants. The ***titrants*** are ***tetrabutylammonium hydroxide, sodium methylate*** etc.

Fixing the titration end point

Indicators are used to fix the titration end-point, but mainly potentiometric titration. The colour transition intervals of the coloured indicators vary greatly in non-aqueous media and, although in principle a wide range of acid-base indicators can be used, the potentiometric method with a glass electrode is usually preferred.

The indicators that are used in non-aqueous titration, depending on the solvent/

In acidic solvents:

- ✓ Crystal violet,
- ✓ Tropeolin 00,
- ✓ Malachite green, etc.

In basic solvents:

- ✓ Thymol blue,
- ✓ Bromothymol blue, etc.

In inert solvents:

- ✓ Methyl orange,
- ✓ Thymol blue, etc.

Application of non-aqueous titration in pharmaceutical analysis

Aqueous titration is widely used in pharmaceutical analysis because many pharmaceutical substances are weak bases or acids and cannot be detected by the titrimetric method in aqueous media.

Acid-base titration in non-aqueous media is a pharmacopoeial method for the quantitative determination of many pharmaceutical substances:

- ➢ Salts of nitrogen-containing organic bases;
- ➢ Certain medicinal products of an acidic nature (barbiturates, sulphonamides etc.)
- ➢ Organic medicinal substances containing halide ions.

Titration of amino acid salts

The titration is carried out in glacial acetic acid.

The titrant is perchloric acid $HClO_4$ (solution in glacial acetic acid).

The detection of the titration end-point is done potentiometrically or by using crystal violet.

$$\overset{+}{N}H_3-CH_2-CH_2-CH_2-COO^- + CH_3COOH \rightarrow \overset{+}{N}H_3-CH_2-CH_2-CH_2-COOH + CH_3COO^-$$

$$\underset{\text{titrant}}{HClO_4} + \underset{\text{base}}{CH_3COOH} \longrightarrow \underset{\text{acilonium-ion}}{CH_3COOH_2^+} + \underset{\text{perchlorat-ion}}{ClO_4^-}$$

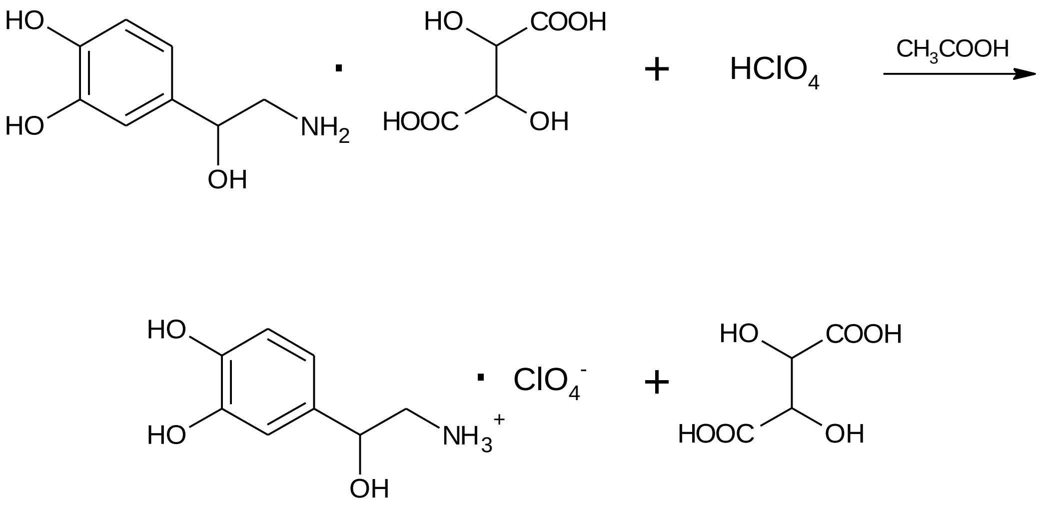
$$CH_3COO^- + CH_3COOH_2^+ \longrightarrow 2\,CH_3COOH$$

$$\overset{+}{N}H_3-CH_2-CH_2-CH_2-COOH + ClO_4^- \longrightarrow [\overset{+}{N}H_3-CH_2-CH_2-CH_2-COOH]ClO_4^-$$

$$\overline{\overset{+}{N}H_3-CH_2-CH_2-CH_2-COO^- + HClO_4 \longrightarrow [\overset{+}{N}H_3-CH_2-CH_2-CH_2-COOH]ClO_4^-}$$

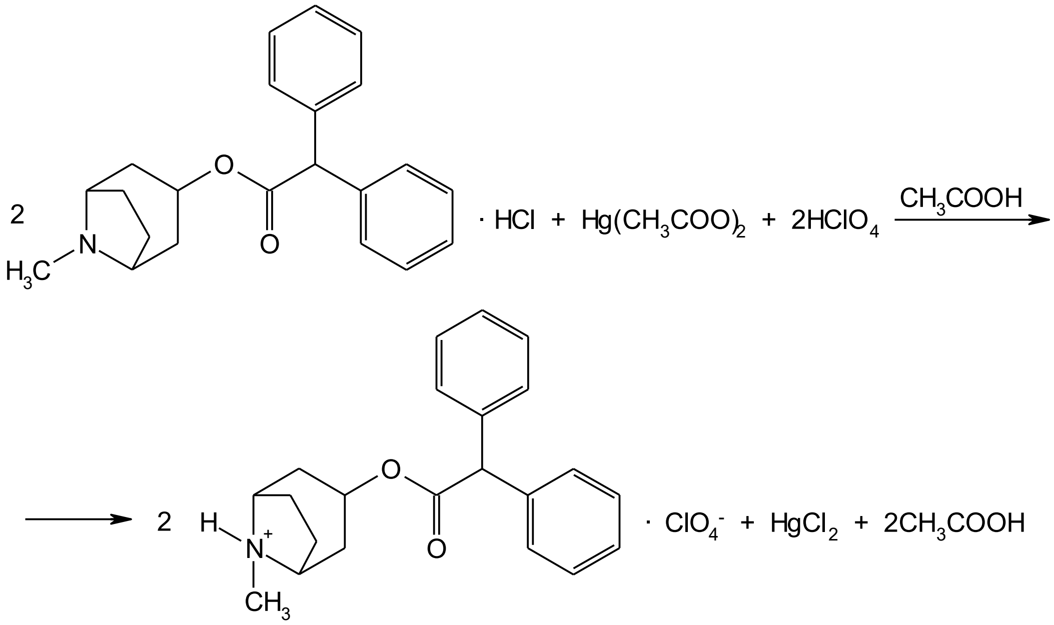
Titration of salts of nitrogen-containing organic bases

The quantitative determination of ***noradrenaline hydrotartrate*** is carried out by non-aqueous titration in glacial acetic acid by titration with 0.1 M perchloric acid solution (indicator methyl violet or crystal violet):

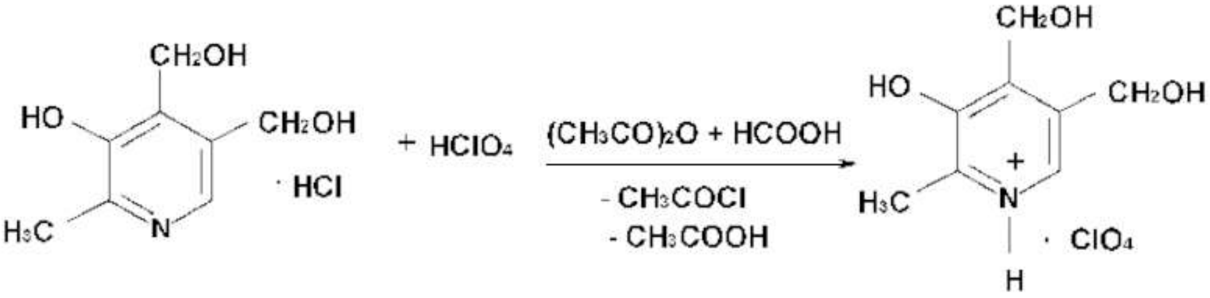


Hydrochlorides as well as hydrobromides are titrated in the presence of mercury (II) acetate, which inhibits the dissociation of the halide ions.

For example, the quantification of tropaphene. Titrated with perchloric acid solution in glacial acetic acid medium with addition of mercuric acetate. Crystal violet indicator.



Also, a *mixture of acetic anhydride and formic acid* can be used as a medium to inhibit the dissociation of the halide ions. ***For example, the quantification of pyridoxine hydrochloride.*** Titrate also with perchloric acid solution, crystal violet indicator.



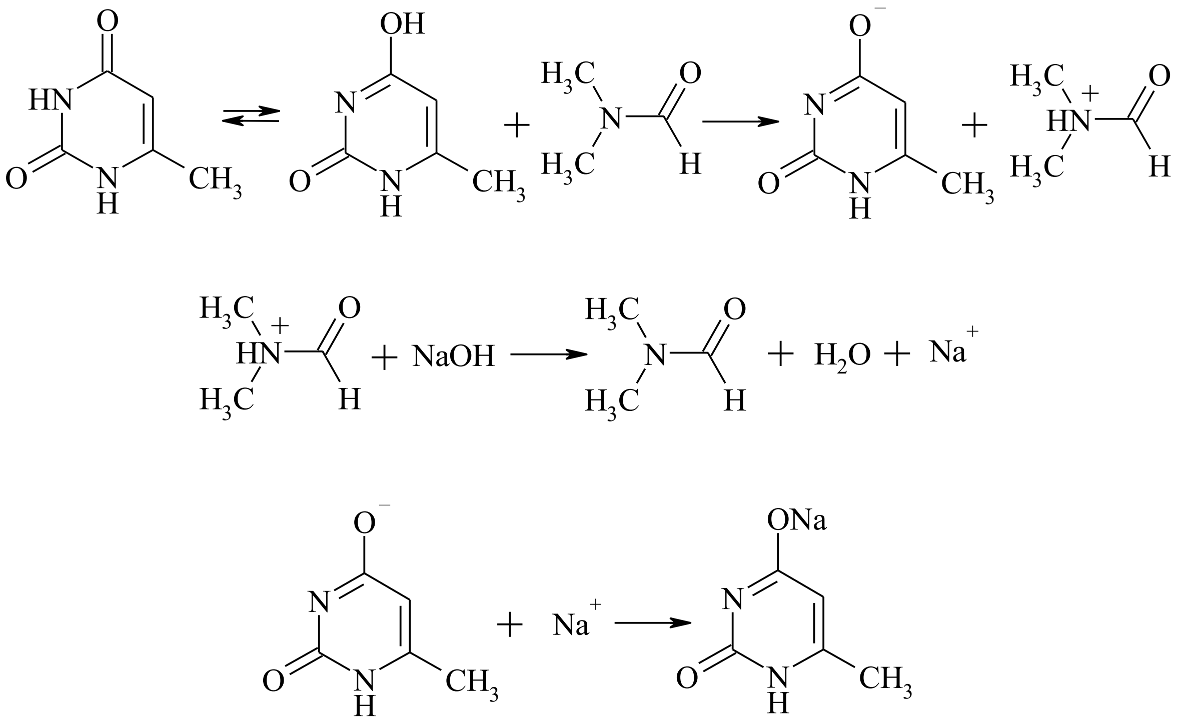
Titration of acidic medicinal substances

To enhance the acidic properties of the analyzed medicinal substances, protophilic solvents are usually used - solvents of a basic nature containing an unshared electron pair and capable of accepting a proton from the analyte. In pharmaceutical analysis, mainly dimethylformamide is used.

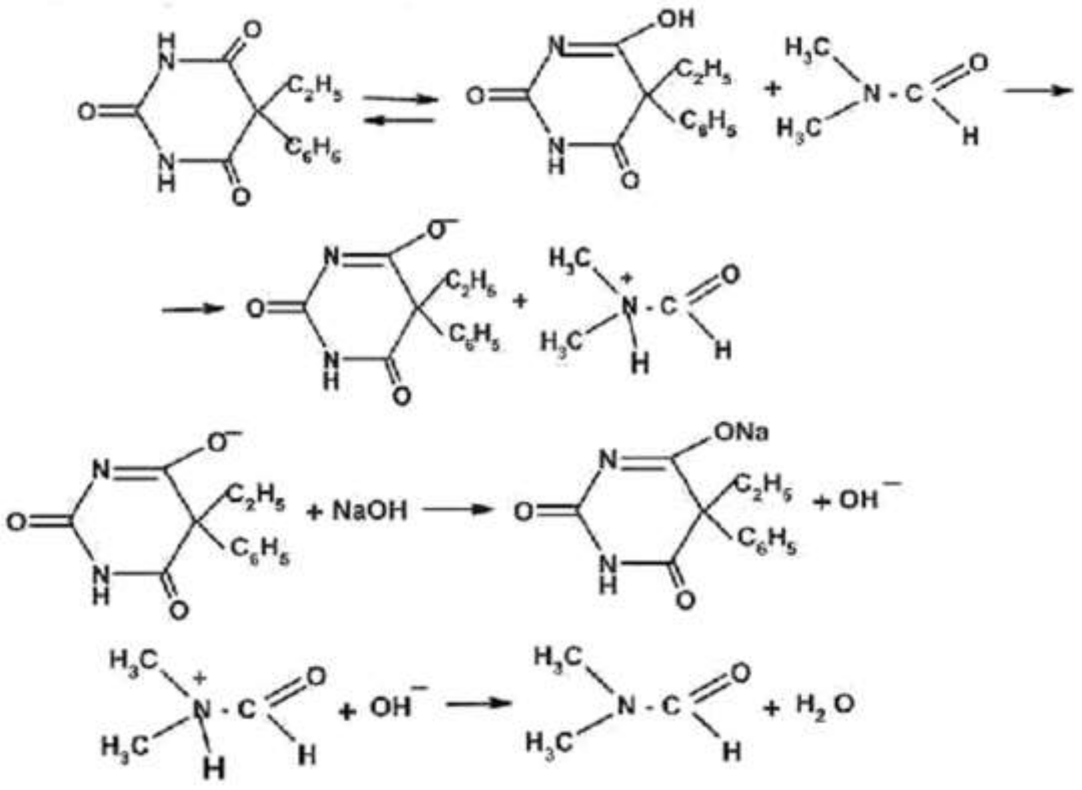
Dimethylformamide is used as a solvent in the determination of various drug substances which exhibit acidic properties, e.g:

- ✓ carboxylic acids,
- ✓ phenols,
- ✓ barbiturates (barbiturate, phenobarbital),
- ✓ sulfonamides,
- ✓ uracil derivatives (methyluracil, fluorouracil),
- ✓ xanthine (theobromine, theophylline),
- ✓ 5-nitrofuran (furadonine), etc.

Quantification ***of methyluracil*** is carried out in dimethylformamide medium, titrated with 0.1M sodium hydroxide solution in a mixture of methanol and benzene. The indicator is a solution of thymol blue in dimethylformamide.



The quantification ***of phenobarbital*** is carried out in dimethylformamide, titrated with sodium hydroxide solution. The indicator is a solution of thymol blue in dimethylformamide.



Advantages and disadvantages of non-aqueous titration

Titration in non-aqueous media has a number of advantages and disadvantages that should be considered when solving practical problems.

Advantages of non-aqueous titration:

1. Ability to analyse weak and very weak acids and bases, including those insoluble in water;
2. The possibility of unifying quantification methods for large groups of drugs;
3. Specificity of the method, as the determination is carried out on the pharmacologically active fragment of the structure of the molecule;
4. The possibility of separate titration of mixtures of substances with the same properties (acidic or basic).

Main **disadvantages** of non-aqueous titration :

1. Negative effects of organic solvents and mercury acetate on the human body;
2. Perchloric acid is explosive;
3. Careful preparation of solvents, protection of titrants (especially of basic nature) from atmospheric exposure is necessary;
4. Organic solvents are more expensive than purified water;
5. The possibilities of the method are noticeably narrowed when analysing dosage forms prepared on water (solutions, mixtures, solutions for injections).
6. The method does not provide objective information on the quality of substances which undergo hydrolytic decomposition (e.g. substances with ester groups) or other types of degradation during storage of aqueous dosage forms or sterilization process.