«General pharmaceutical chemistry »

ALKALIMETRY. ACIDIMETRY.

TITRATION IN NON-AQUEOUS SOLUTION.

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NEUTRALISATION

The neutralisation method is based on the protolytic reaction:

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

Particularly in aqueous solutions:

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

This method is used to quantify:

- acids,
- bases,
- salts hydrolysed by cation or anion,
- nitrogen and sulphur in organic compounds.

ACID–BASE TITRATION IN AQUEOUS MEDIUM

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.

ACID–BASE TITRATION IN AQUEOUS MEDIUM

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**.

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,
- mercury oxide HgO,
- potassium iodate KJO_3 and others.

To standardise alkaline solutions, the following are used

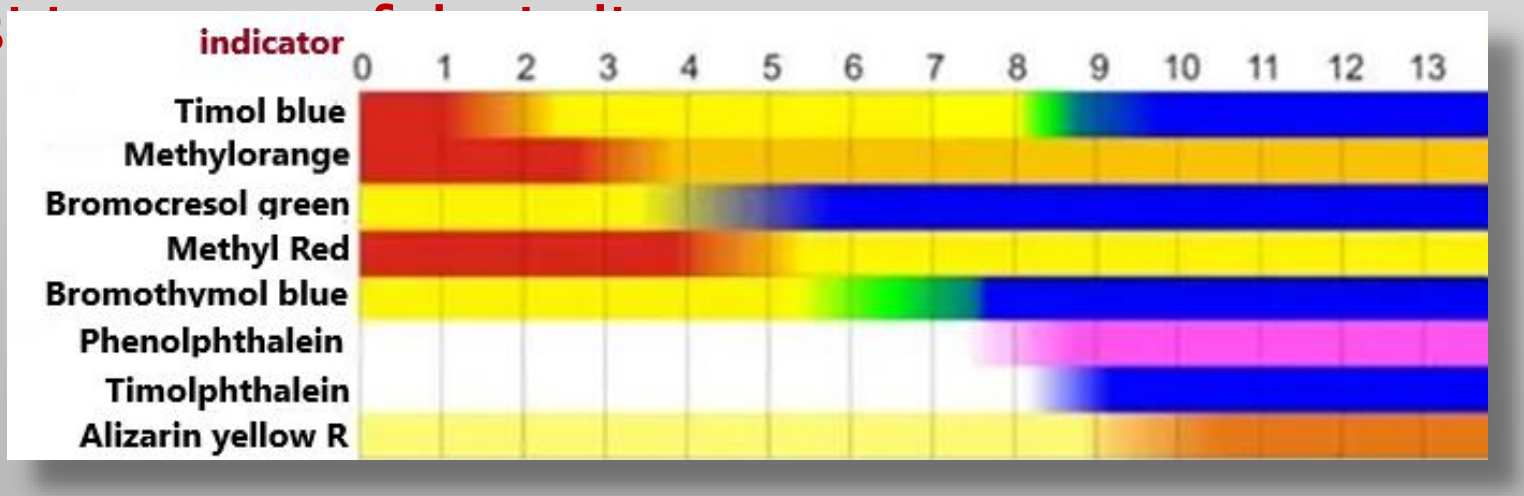
- oxalic acid $H_2C_2O_4 \times 2H_2O$,
- succinic acid $H_2C_4H_4O_4$,
- benzoic acid C_6H_5COOH (primary standards),
- as well as standardised solutions of hydrochloric or nitric acid (secondary standards).

ACID–BASE TITRATION IN AQUEOUS MEDIUM

ACID–BASE INDICATORS

Acid–base indicators are organic compounds whose colouring changes according to the concentration of H+ ions in the solution.

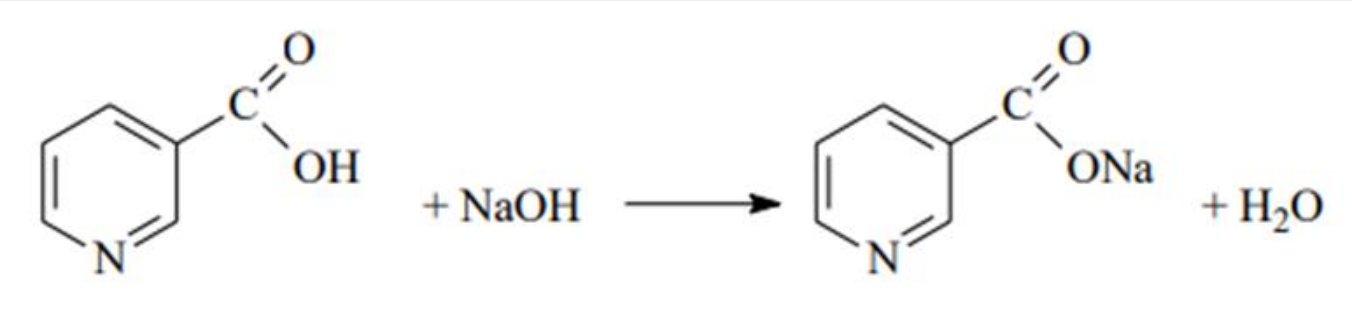
The range of pH values of a solution in which there is a noticeable change in indicator colouration is called the **trans**



ACID–BASE TITRATION IN AQUEOUS MEDIUM

APPLICATION OF ACID–BASE TITRATION IN DRUG ANALYSIS

Titration of inorganic and organic acids

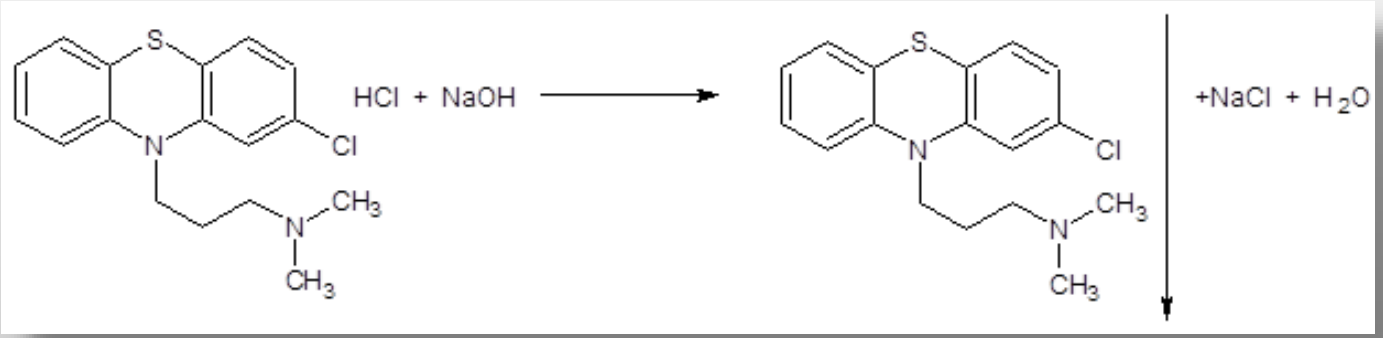


Nicotinic acid
Titrant: NaOH
Indicator: phenolphthalein

ACID–BASE TITRATION IN AQUEOUS MEDIUM

APPLICATION OF ACID–BASE TITRATION IN DRUG ANALYSIS

Titration of organic base salts



Chlorpromazine
Titrant: NaOH
Indicator: phenolphthalein

ACID–BASE TITRATION IN AQUEOUS MEDIUM

APPLICATION OF ACID–BASE TITRATION IN DRUG ANALYSIS

Titration of salts of weak inorganic and organic acids

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

Sodium hydrogen carbonate
Titrant: Hydrochloric acid
Indicator: Methyl orange

ACID–BASE TITRATION IN AQUEOUS MEDIUM

ADVANTAGES AND DISADVANTAGES OF THE ACID–BASE TITRATION METHOD IN AQUEOUS MEDIUM

Advantages of the acid–base titration method:

- ✓ High accuracy (0.1–0.2%),
- ✓ The stability of the working solutions,
- ✓ Wide choice of indicators for fixing the titration endpoint,
- ✓ Large area of practical application.

Disadvantages of the method:

- ✓ non-selectivity when titrating mixtures of analytes,
- ✓ Insufficiently high value of the equilibrium constant when titrating very weak acids and bases.

ACID–BASE TITRATION IN AQUEOUS MEDIUM

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).

ACID–BASE TITRATION IN A NON–AQUEOUS MEDIUM

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.

ACID–BASE TITRATION IN A NON–AQUEOUS MEDIUM

CLASSIFICATION OF SOLVENTS USED IN NON–AQUEOUS TITRATION

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 water, alcohols, primary and secondary amines are typical representatives.

ACID–BASE TITRATION IN A NON–AQUEOUS MEDIUM

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. **Chloric 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

ACID–BASE TITRATION IN A NON–AQUEOUS MEDIUM

FIXING THE TITRATION END POINT

Indicators are used to fix the titration end–point, but mainly **potentiometric titration**.

Indicators

In acidic solvents:

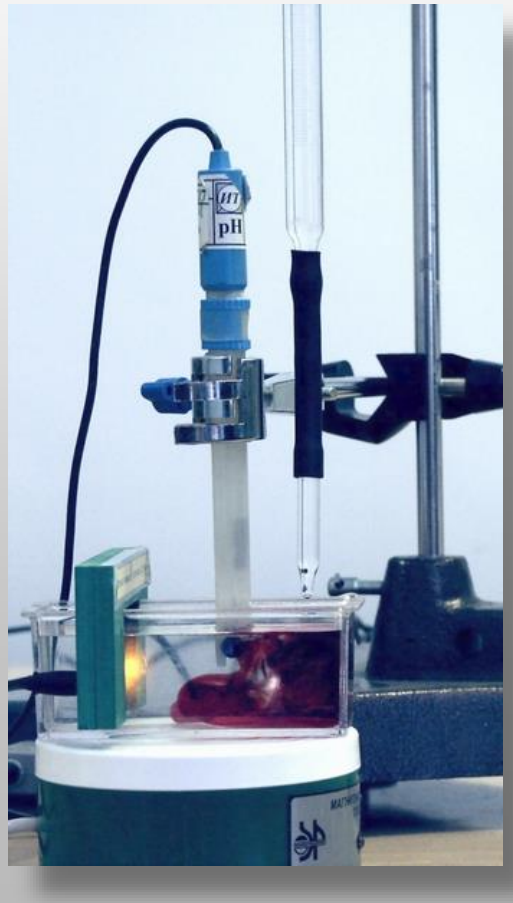
- ✓ Crystal violet,
- ✓ Tropeolin 00,
- ✓ Malachite green, etc.

In basic solvents:

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

In inert solvents:

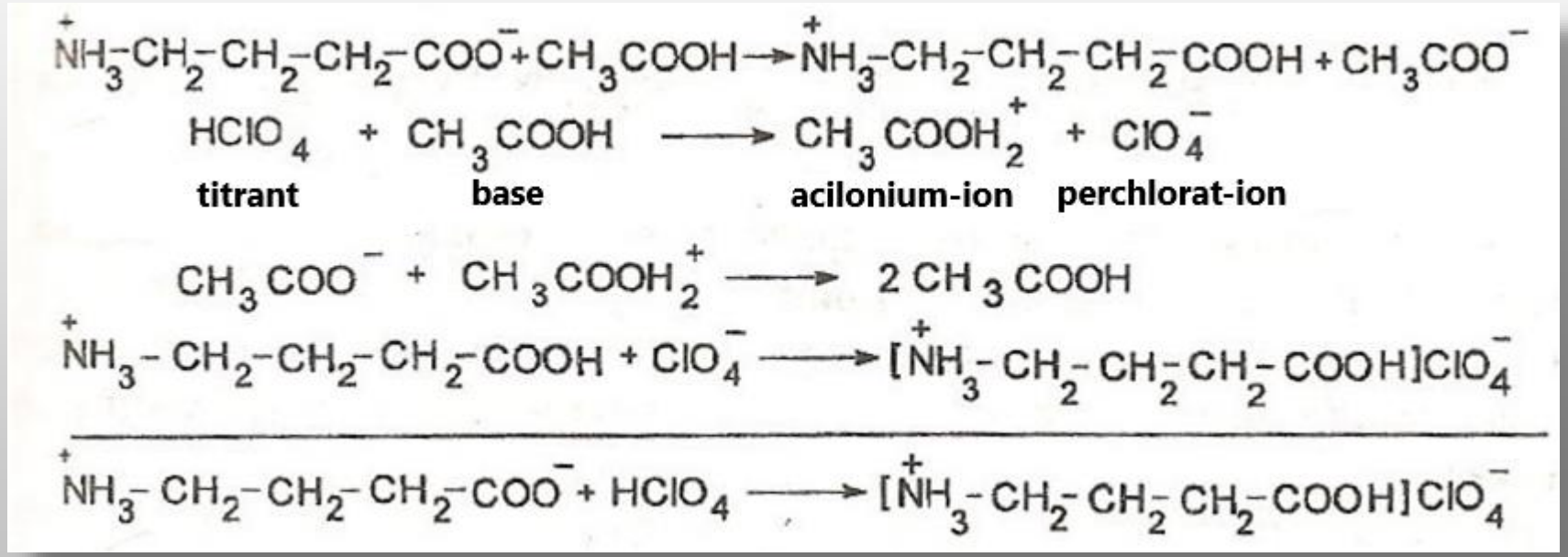
- ✓ Methyl orange,
- ✓ Thymol blue, etc.



ACID–BASE TITRATION IN A NON–AQUEOUS MEDIUM

APPLICATION OF NON–AQUEOUS TITRATION IN PHARMACEUTICAL ANALYSIS

Titration of amino acid salts

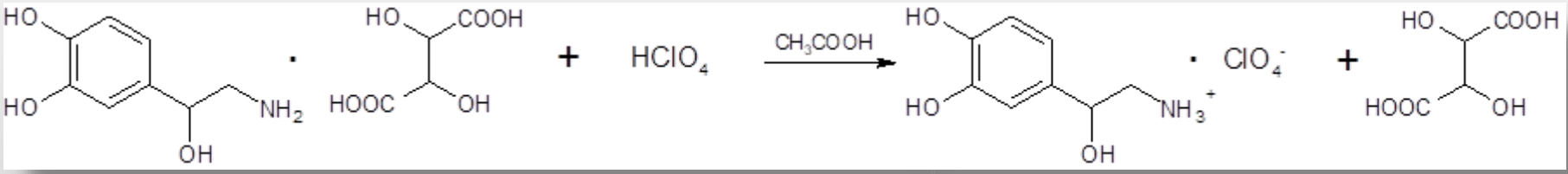


GABA
Solvent: glacial acetic acid
Titrant: $HClO_4$
Indicator: crystal violet

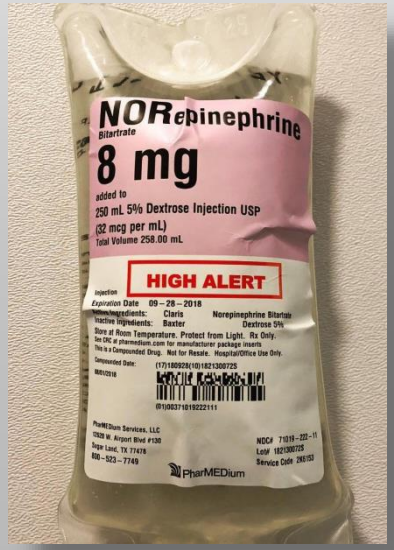
ACID–BASE TITRATION IN A NON–AQUEOUS MEDIUM

APPLICATION OF NON–AQUEOUS TITRATION IN PHARMACEUTICAL ANALYSIS

Titration of salts of nitrogen–containing organic bases



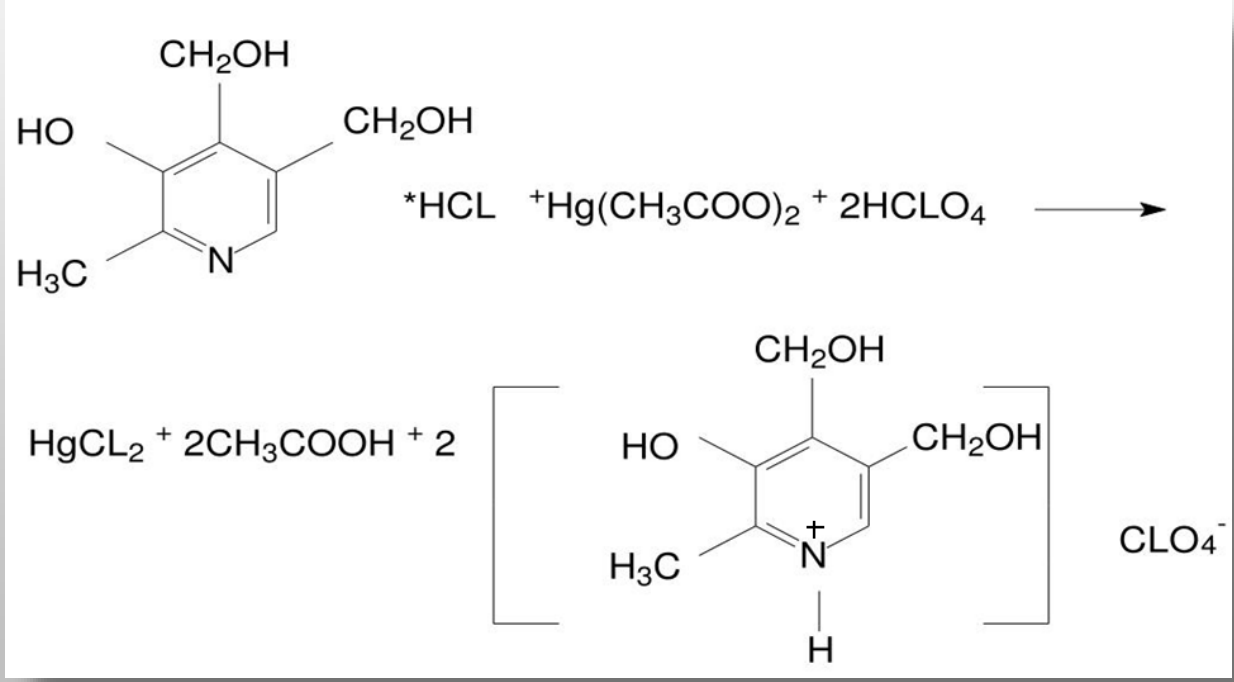
Norepinephrine hydrotartrate
Solvent: glacial acetic acid
Titrant: chloric acid
Indicator: crystal violet



ACID–BASE TITRATION IN A NON–AQUEOUS MEDIUM

APPLICATION OF NON–AQUEOUS TITRATION IN PHARMACEUTICAL ANALYSIS

Titration of nitrogen–containing organic base hydrohalides



Pyridoxine hydrochloride

Solvent: glacial acetic acid

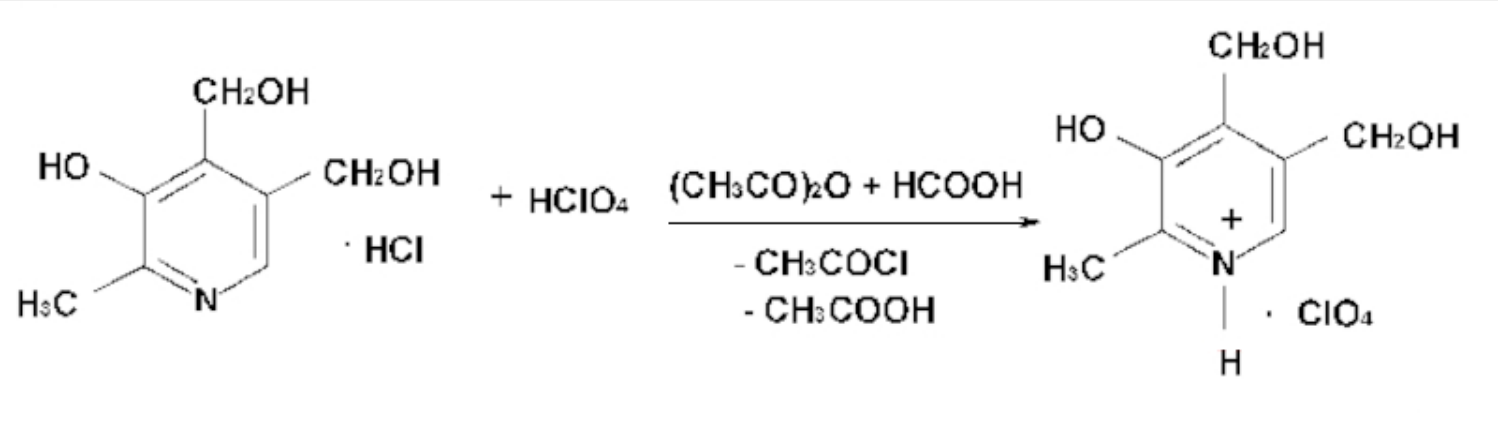
Titrant: HClO4

Indicator: crystal violet

ACID–BASE TITRATION IN A NON–AQUEOUS MEDIUM

APPLICATION OF NON–AQUEOUS TITRATION IN PHARMACEUTICAL ANALYSIS

Titration of nitrogen–containing organic base hydrohalides



Pyridoxine Hydrochloride

Solvent: formic acid with acetic anhydride

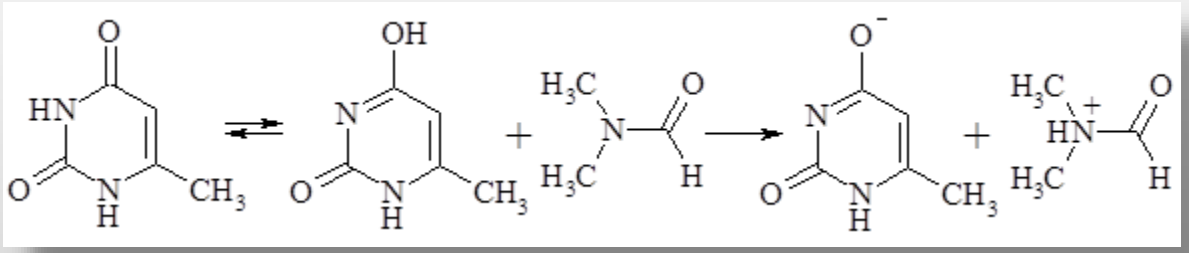
Titrant: $HClO_4$

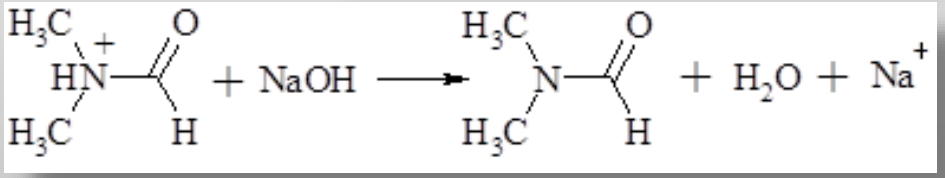
Indicator: Crystal violet

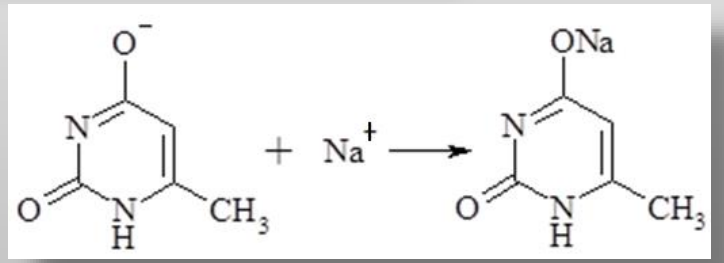
ACID–BASE TITRATION IN A NON–AQUEOUS MEDIUM

APPLICATION OF NON–AQUEOUS TITRATION IN PHARMACEUTICAL ANALYSIS

Titration of acidic medicinal substances







Methyluracilum

Solvent: DMFA

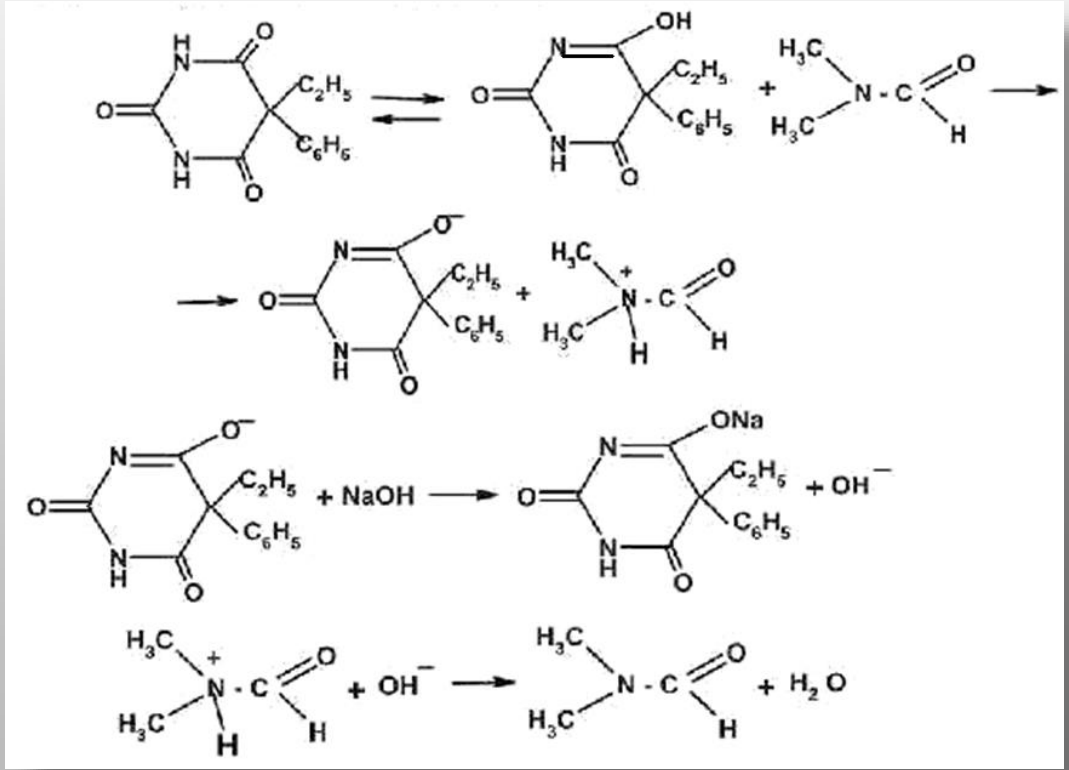
Titrant: NaOH in a mixture of methanol and benzene

Indicator: Bromothymol blue

ACID–BASE TITRATION IN A NON–AQUEOUS MEDIUM

APPLICATION OF NON–AQUEOUS TITRATION IN PHARMACEUTICAL ANALYSIS

Titration of acidic medicinal substances



Phenobarbital
Solvent: DMF
Titrant: NaOH
Indicator: Thymol blue

ACID–BASE TITRATION IN A NON–AQUEOUS MEDIUM

ADVANTAGES AND DISADVANTAGES OF NON–AQUEOUS TITRATION

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).

ACID–BASE TITRATION IN A NON–AQUEOUS MEDIUM

ADVANTAGES AND DISADVANTAGES OF NON–AQUEOUS TITRATION

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

1. Negative effects of organic solvents and mercury acetate on the human body;
2. Chloric 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

Thank you for attention!