**Lesson 9.**

**Chemical methods of quantitative analysis.**

Volumetric methods of quantitative determination.

Chemical methods are widely used in the quantitative determination of medicinal substances. The purpose of quantitative analysis is to determine the amount of analyte in a single preparation or mixture of preparations. Quantitative determination is extremely important in the organization of quality control of medicines. After identification and determination of the purity of the analyte, a quantitative assessment is carried out by various methods, depending on its chemical properties.

Volumetric analysis (titrimetric analysis methods) are mainly used in determining the amount of drugs. In this case, the gravimetric (weight) method, the gasometric method and the elemental analysis method are also used.

Gravimetric (weight) method. The method is mainly used for the quantitative determination of barbiturates, quinine salts, inorganic compounds, rarely for the quantitative determination of certain alkaloids in the form of picrates or silicotungstates and vitamins (for example, thiamine bromide and rutin).

The essence of the method lies in the fact that a sample mass accurately weighed on an analytical balance or a certain volume of a drug solution accurately taken with a pipette is affected by chemical reagents to precipitate its main component. This precipitate is separated by filtration, dried to constant weight (sometimes calcination is carried out; the difference between the two following samples should not exceed 0.0005 g) and weighed.

The percentage of the substance (P) is calculated using the following formula:

**P=**

Where:

a is the mass of the analyte in the taken sample of the medicinal product, in grams;

b - weighed portion of the drug in grams.

Sometimes the following formula is used to find the value of a:

a=F ∙ j,

Where:

j is the amount of dried or calcined sediment in grams;

F is the weight coefficient, which is determined as the result of the ratio of the gram equivalent of the component to be determined to the gram equivalent of the sample, this number is indicated at the end of the definition in the regulatory document.

The gasometric method is based on the interaction of the studied medicinal substance with an absorbing solution. This method is used for the quantitative analysis of gaseous medicinal substances, including oxygen, nitrous oxide, cyclopropane, etc.

titrimetric methods.

Titrimetric (volumetric) methods of analysis are based on an accurate measurement of the amount of a reagent (titrant) consumed in a reaction with a certain substance. During titration, the titrant is added in small portions to a solution containing a precisely known mass (weight) of the analyte. After adding each new portion of the titrant in the system described by the chemical reaction equation, an equilibrium is established:

nA + mB = AnBm

Where

A is the analyzed substance;

B-titrant

n, m are stoichiometric coefficients.

As the reaction proceeds, the equilibrium concentrations of the analyte and titrant decrease, while the equilibrium concentrations of the reaction products increase. When an amount of titrant equivalent to the amount of the titrated substance is consumed, the reaction will end. This moment is called the equivalence point.

In practice, the end point of the titration (reaction) is fixed. Which, with some degree of approximation, corresponds to the equivalence point. In titrimetric methods of analysis, it is fixed visually by a noticeable analytical effect (change in color of the solution, precipitation) caused by any of the starting compounds, reaction products, or substances specially added to the solution - indicators. In physico-chemical methods of analysis, the end point of the titration, as we have already said. determined by some factor.

In titrimetry, there are three methods of titration: direct, reverse and indirect (substitutive).

In direct titration, analyte A reacts directly with titrant B:

A + B = C

If such a reaction is impossible for some reason (there is no chemical interaction of the analyte with the titrant, the reaction proceeds at an insufficiently high rate, there is no reliable way to determine the end of the titration, etc.), then the reverse or indirect method is used.

In Back titration, an excess of titrant B is added to the analyte, the unreacted residue of which is titrated with titrant D:

A + B = C

Excess

B + D = E

In INDIRECT (substitutive) titration with titrant B, the product of the intermediate reaction G of the analyte A reacts with the auxiliary reagent F:

A + F = G

G + B = K

For titration, titrimetric methods use solutions of exactly known concentration, called TITRANTS or TITRATING SOLUTIONS. The concentration of a titrated solution is denoted by the terms MOLAR, NORMAL, TITER or TITTER FOR THE SUBSTANCE TO BE DETECTED.

MOLAR CONCENTRATION is the number of moles of a solute contained in one liter of solution. It is calculated as the ratio of the amount of solute to the volume of the solution in liters (the unit is mol/l). A mole is the amount of a substance that contains as many specified structural units as there are atoms in 0.012 kg (12 g) of the carbon-12 isotope.

Elementary particles, as well as ions, atoms, molecules or their fractions can be chosen as specified structural units. In analytical chemistry, these fractions are chosen so that each of them is responsible for the transfer of one electron in a redox reaction or is equivalent to one hydrogen ion in an acid-base reaction. To designate such a fraction of an ion, atom or molecule, the term "conditional particle" is adopted. The conditional particle is otherwise called the EQUIVALENT. In the quantitative determination of drugs by volumetric methods, the equivalent (E) should first be calculated. To do this, determine the molecular weight of a substance by its basicity (in acids), acidity (in bases), the total valence of metal atoms (in salts), the number of electrons received and given away by 1 mole of an oxidizing agent or reducing agent in redox reactions, and in some reactions titration uses 1 mole of the substance divided by the number of moles of the solution.

In analytical practice, along with the molar concentration of solutions, the normal concentration of the solution is also used.

NORMAL CONCENTRATION of a solution is the number of moles of solute equivalent contained in one liter of solution. A solution containing 1 mole equivalents of substances A in 1 liter is called a normal solution of this substance and denoted - 1n.

TITR is the mass of a solute, expressed in grams, contained in 1 milliliter of a solution. The titer is calculated as the ratio of the mass of the solute to the volume of the solution (dimension g/ml).

To find the titer (T) of a solution of an analyte, use the following formula:

T=,

where: M is the molar mass;

mol/l is the concentration of the titrated solution (at present, according to the internationally accepted rule, the concentration of titrated solutions is expressed in mol/l).

The molar mass of the equivalent of a substance denotes the mass of one mole of the equivalent of this substance, equal to the product of the equivalence factor (feq) by the molar mass of the substance.

An equivalence factor is a number indicating what proportion of a molecule of a substance is equivalent to one hydrogen ion in a given acid-base reaction or one electron in a given redox reaction.

When carrying out the analysis, the sample must be taken exactly (exact weight, exact volume). The amount of sample is usually indicated in the method. As a rule, it is best to calculate the mass of the sample. If the mass obtained in the calculation is less than that specified in the method, the drug is taken in the calculated amount. The sample mass (P) is calculated using the following formula:

P=V∙T,

where: V is the amount of solvent taken to dissolve the medicinal product.

The calculation of the quantitative content of the analyzed individual substance in% (X) is carried out according to the formulas:

1. Direct and indirect (replacement titration):

In a direct titration, the percentage of substance (X) in the test solution is calculated using the following formula:

Where,

V is the volume of titrant used for titration, ml;

K-correction factor of the titrated solution (titrant);

T-titer of the titrant for the analyte;

P-mass of the analyte, taken for analysis (weighed portion), in grams;

The amount of substance in grams (X) in the test solution, powders and tablets is calculated using the following formula:

where: Q is the total weight of the powder or mixture, and in the case of tablets, the average weight of one tablet (Q is not taken into account in injection solutions).

To determine the average weight of tablets, 20 tablets are weighed to the nearest 0.001 g and the resulting weight is divided by 20. If it is necessary to determine the deviation of the weight of each tablet from the average weight, that is, the standard deviation, then the weight of each tablet is determined by weighing separately to the nearest 0.001.

The average weight of tablets and the deviation of the weight of each tablet from the average weight is calculated using the following formula:

mсредн =

*∆mi* =

where: maverage is the average weight of a tablet;

 mi is the mass of one tablet;

 ∆mi is the deviation from the weight of the tablet, expressed in %.

The deviation of the weight of individual tablets from the average weight of a tablet within the following limits is allowed (with the exception of tablets coated with a coating method of overlay):

for tablets weighing 0.1 g or less - ± 10%;

for tablets weighing more than 0.1 g and less than 0.3 g - ± 7.5%;

for tablets weighing 0.3 g or more - ± 5%

The difference in weight of individual overlay-coated tablets should not exceed ±15% of the average weight.

However, two tablets may differ from the average weight by no more than two times within the specified limits.

The deviation from the amount of medicinal substance in tablets depends on the dosage of medicinal substances and should be within the following limits (unless otherwise specified in the relevant article of the pharmacopeia): ± 15% at a dosage of up to 0.001 g; ±10% at 0.001–0.01 g; ±7.5% for 0.01-0.1 g; ±5% for 0.1 g or more.

If dilution is performed, then the formula in the denominator should indicate the volume of dilution (W) of the solution, and in the numerator the volume taken from the diluted solution for titration in ml (m)

Where,

W is the volume of the volumetric flask, ml;

m is the volume of the solution taken for titration (volume of the pipette), ml.

2. BACK titration

For back titration, the following formula is used:

X%=

As can be seen from the formula, since two titrated solutions are involved in the determination, the product of the second titrated solution (V2) by its correction factor (K2) is obtained from the product of the amount of titrated solution (V1) in milliliters, taken in excess by its correction factor (K1 ).

For titrated (standard) solutions, the correction factor (K) can be calculated in 2 ways:

Method 1. The determination is carried out by weighing the mass of a chemically pure substance and using the following formula:



Where:

a - the amount of substance in grams, taken to determine the titer;

T is the amount of a substance in grams per 1 ml taken to determine the titer of a solution of the desired molarity;

V is the volume of the prepared solution used for titration, ml.

Method 2. The determination is carried out on the basis of a titrated solution of known concentration and the following formula is used:



Where,

V0 is the volume of the solution of the substance taken to determine the titer, in ml;

V is the volume of the prepared solution used for titration, ml;

K0 is the correction factor for the solution of the substance taken to determine the titer.

If a control experiment is carried out during the quantitative determination (for the titrant and for the indicator), then formulas 2 and 3 take the form:

1. Direct and indirect titration
2. Back titration

where Vo is the volume of titrant used for titration in the main experiment, ml;

Vk is the volume of titrant used for titration in the control experiment, ml.

Titration methods used in pharmaceutical chemistry are usually divided into:

1. Acid-base titration (in aqueous, non-aqueous and mixed media):

Acidimetry, Alkalimetry, Reverse (substitutive) neutralization, Oxime method, Etherification, Hydrolysis of esters.

2. Redox methods (redoxmetry):

Iodometry, iodchlormetry, iodatometry, permanganatometry, bromatometry, cerimetry.

3. Precipitation titration methods:

Argentometry, thiocyanatometry, mercurometry, mercurometry.

4. Complexometric titration.

5. Nitritometry.

6. Non-aqueous titration.

7.Elemental analysis method:

Determination of nitrogen in organic compounds (Keldahl method), combustion method in a flask with oxygen.