CALCULATIONS IN TITRIMETRIC ANALYSIS

In order to save the analysed dosage forms and titrant, it is necessary to calculate the optimum amount of dosage forms and titrant before carrying out the analysis.

The weight of the dosage form for quantification is calculated according to the formula:

$$a = \frac{V * K * T * P}{b}$$

a - the sample weight, g or ml;

V - volume of titrant, ml;

T - titer of the working solution for the analyzed ingredient, g/ml;

b - quantity of the analysed ingredient as prescribed in the prescription, g;

P - mass or volume of the dosage form according to the prescription respectively g, ml;

K - correction factor for the titrated solution.

The titrant volume (V) in the case of individually prepared dosage forms must be between 0.5-2 ml. This is due to the express nature of intra-pharmacy quality control of medicines. The analyst should use a micro-, or semi-micro pipettes or micro-, semi-microburettes. The concentration of of the titrated solutions can vary from 0.1 mol/l to 0.01 mol/l.

The correction factor (K) of the prepared titrated solution is the ratio of the true (experimentally determined) and the theoretical concentration of the prepared titrated solution (or its true and theoretical titre):

$$K = \frac{M_E}{M_T} = \frac{T_E}{T_T}$$

M_E, M_T - experimentally determined and theoretical concentration of the titrated standardised solution, respectively, mol/l;

T_E, T_T - actual and theoretical concentration of the dissolved substance in the standardized titrated solution, g/ml.

- When determining the correction factor, at least three parallel titrations.
- If the titration results do not differ by more than 0,05 mL, the arithmetic mean of the results is taken and is calculated by K.
- If the discrepancy between the individual titrations exceeds 0.05 mL, the titration is repeated until the results are convergent.
- The relative error in determining the correction factor should not exceed ±0.1%. To do this, titrate at least 20-30 ml of solution and use measuring flasks and pipettes previously tested for accuracy.
- The Pharmacopoeia correction factor should fall within the range 0.98-1.02. In cases where the correction factor values do not fall within these limits, solutions should be strengthened or diluted.

    - In the case of ***diluted*** titrated solutions, subtract 1.0 from the calculated K value and multiply the resulting difference by the volume of solution prepared in ml. The result of multiplication shows the amount of solvent in ml that needs to be added to the prepared solution to bring K to the required value.
    - To ***strengthen*** a titrated solution (K less than 1.0), subtract K from 1.0 and multiply the resulting difference by the mass of the initial substance weight taken to prepare the given volume of titrated solution.
    - After addition of the calculated quantity of solvent or starting substance, the correction factor is determined again (three times). If K complies with the Pharmacopoeia, the titrated solution is ready for use.

After titration, the substance content of the dosage form is calculated.

DIRECT TITRATION CALCULATIONS

The percentage concentration of the ingredients (in liquid dosage forms, ointments) in direct titration is calculated according to the formula:

$$X(\%) = \frac{V * K * T * 100}{a}$$

X (%) - content of the determined substance, in %;

T - titer of the titrant for the determined substance , in g/ml;

V - volume of titrated solution, in ml;

K - the correction factor of the titrated solution;

a - sample weight of the test drug (in g or ml).

Calculate the ingredient content in grams using the following formulas the following formulas:

a) for liquid dosage forms:

$$X(g) = \frac{V * K * T * V_{DF}}{a}$$

b) for solid and soft dosage forms:

$$X(g) = \frac{V * K * T * P}{a}$$

X (g) - mass of the determined medicinal substance, in g;

V_{DF} - volume of liquid dosage form (according to the prescription), in ml;

P - total weight of powder, ointment according to the prescription, in g;

V - the volume of titrated solution, in ml;

T - titer for the substance being determined, in g/ml;

K - correction factor for the titrated solution;

a - volume, in ml or mass, in g, of the dosage form sampled for analysis.

Calculation of substance content in grams, taking dilution into account

In some cases, in order to reduce weighing errors when taking a sample, it is proposed in the normative documentation to carry out quantification of the active ingredient in an aliquot of solution or filtrate.

In such cases the volume of the volumetric flask (V_f, ml) and the volume of the aliquot (V_a, ml) taken for titration are added to the calculation formulae.

$$X(\%) = \frac{V * K * T * 100 * V_f}{a * Va}$$

$$X(g) = \frac{V * K * T * V_f * V_{DF}}{a * V_a}$$

X (g) - mass of the determined medicinal substance, in % or g;

V_{DF} - volume of liquid dosage form (according to the prescription), in ml;

P - total mass of powder, ointment according to the prescription, in g;

V - volume of titrated solution, in ml;

T - titer for the substance being determined, in g/ml;

K - correction factor for the titrated solution;

a - volume, in ml, or mass, in g, of the dosage form, sampled for analysis;

V_f - volume of the flask where the dilution was carried out, ml;

V_a - volume of dilution (aliquot) taken for determination, ml.

CALCULATIONS IN REVERSE TITRATION

When quantification by reverse titration two titrated solutions are used, one of which is added in excess. The calculation of the ingredient content is carried out according to the formulas:

a) in percentages:

$$X\,(\%) = \frac{(V1K1 - V2K2) * T * 100}{a}$$

b) in grams in liquid dosage forms:

$$X(g) = \frac{(V1K1 - V2K2) * T * V_{DF}}{a}$$

c) in grams in powders and ointments

$$X(g) = \frac{(V1K1 - V2K2) * T * P}{a}$$

V1 and V2 - the volumes of titrated solutions taken in excess and spent on titration, ml, respectively;

V_{DF} - volume of liquid dosage form according to the prescription, in ml;

K1 and K2 - respective correction factors;

T - titer for the substance being determined, in g/ml;

P - total mass of powder , ointment according to the prescription, in g.

The contents of the ingredients, taking into account the reference test, are calculated according to the formulas:

a) in percentages:

$$X(\%) = \frac{(V - V_{rt}\ ) * K * T * 100}{a}$$

b) in grams:

$$X(g) = \frac{(V - V_{rt}\ ) * K * T * V_{DF}}{a}$$

V rt - the volume of the second titrant used for the titration of the reference test, in ml;

V - volume of the second titrant used for the titration of the main experiment, ml;

P - weight of powder or ointment, g.

For medicinal products that contain crystallising water or are hygroscopic, the moisture content may be decreased or increased during storage.

However, the quantitative content of the above pharmaceutical substances as required by the Pharmacopoeia must be calculated in the sample to be analysed in terms of anhydrous substance.

In such cases the titre for the substance to be determined ($T_{B/A}$) is calculated according to the formula:

$$T_{B/A} = \frac{N_B * f_{equiv.}(\mathrm{A}) * [\mathrm{M}(A) - n * M(H_2O)]}{1000}$$

N_B - the molar concentration of the titrant equivalent, g-eq/mol;

M (A) - molar mass of the drug substance, g/mol;

$F_{equiv.}$ (A) - drug substance equivalence factor;

n - number of water molecules in the analyzed medicinal substance according to gross formula;

M (H_2O) - molar mass of water, g/mol.

The active ingredient content (X, %) is calculated in terms of dry substance. Calculation formula:

$$X(\%) = \frac{V * K * T * 100 * 100}{a * (100 - B)}$$

B - Actual moisture content.

Calculation of the approximate average titre.

The presence in mixtures of substances with similar structures and properties (e.g. sulphonamides, alkaloids, salts of hydrogen-halogenic acids) makes it difficult to determine them separately.

If the two substances in a mixture can be titrated with the same titrated solution and there is no method for determining one of them separately, the total content of the components may be calculated using an approximate average titre. Its shall be calculated according to the formulas given below:

1) If the determined total ingredients are prescribed in similar quantities and their titres differ very little from each other, then the average approximate titre is calculated according to the formula:

$$T = \frac{T_1 b_1 + T_2 b_2}{b_1 + b_2}$$

2) In the event that the prescribed quantities of both ingredients are the same, the formula is converted to the formula below:

$$T = \frac{T_1 + T_2}{2}$$

T1 - titer of the first component, in g/ml;

b1 - prescribed mass of the first component, in g;

T2 - titer of the second component, in g/ml;

b2 - prescribed mass of the second component, in g.