МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РЕСПУБЛИКИ БЕЛАРУСЬ
БЕЛОРУССКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ
КАФЕДРА ФАРМАЦЕВТИЧЕСКОЙ ХИМИИ С КУРСОМ ПОВЫШЕНИЯ КВАЛИФИКАЦИИ
И ПЕРЕПОДГОТОВКИ

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ФАРМАЦЕВТИЧЕСКАЯ ХИМИЯ

PHARMACEUTICAL CHEMISTRY

Сборник задач
для студентов 3-го курса медицинского факультета иностранных учащихся,
обучающихся по специальности «Фармация»

В двух частях

Часть 1

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Л84

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Включает примеры решения типовых задач по фармацевтической химии, условия задач и место для их решения. Содержатся задачи на химические и инструментальные методы анализа. Студенты приобретают навык расчета по результатам контроля качества лекарственных средств.

Предназначен для студентов 3-го курса медицинского факультета иностранных учащихся, обучающихся по специальности «Фармация» на английском языке.

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EDUCATIONAL CARD

Student _____ group _____

(FULL NAME)

No.	Laboratory lesson topic	Teacher's signature
4	Reagents used in pharmacopoeial analysis. Properties of pharmaceutical substances.	
5	Titrimetric methods used in pharmaceutical analysis. Gravimetry	
6	Spectrometric and thermal methods used in pharmaceutical analysis.	
7	Chromatographic and biological methods used in pharmaceutical analysis.	
9	Methods for identifying inorganic cations and anions used in pharmacopoeial analysis.	
10	Methods for identifying organic ions and functional groups used in pharmacopoeial analysis. Instrumental identification methods.	
11	Pharmacopoeial tests of pharmaceutical substances.	
12	Pharmacopoeial tests of pharmaceutical substances and electrochemical methods used in pharmaceutical analysis.	
15	Pharmacopoeial water quality control. Statistical processing of chemical experiment results, validation of methods and the principle of choosing a quantitative determination method.	
16	Pharmacopoeial analysis of pharmaceutical substances of inorganic nature: s-elements.	

PREFACE

This problem book is an example of organizing a student's independent work on calculations of the results of medicines studied for Faculty of Medicine for foreign students with English as the language of instruction in the specialty «Pharmacy» quality control.

Purpose of the book: facilitate and accelerate acquisition of calculation skills for the results of medicines quality control necessary for the professional activity of a pharmacist-analyst.

This problem book contains a sample solution for a typical problems and tasks to be solved at lessons in accordance with the pharmaceutical chemistry curriculum. Space is provided for reaction equations and calculations.

Using the problem book students acquire the skill of calculating results of medicines quality control obtained by means of chemical and instrumental methods (titration, spectrophotometry, polarimetry, refractometry, etc.), which is necessary in the future for the professional activities of a pharmacist-analyst. Students solve problems at home on their own; during the lesson, the most difficult ones that caused difficulties, or typical mistakes, are discussed.

At the end of the lesson the teacher checks solved problems and signs educational record card. If questions arise, the student contacts the teacher for clarification.

EXAMPLES OF SOLUTIONS TO TYPICAL PROBLEMS IN PHARMACEUTICAL CHEMISTRY

Titration tasks

Solution sequence:

1. Write the equation for the reaction that occurs during titration.
2. See in what ratio the test sample reacts with the titrant.
3. Calculate titer (mg/ml) using the formula:

$$T = C_{(titrant)} \times M_{(subst)} \times f,$$

where f is the equivalence factor, which shows the ratio in which the test sample reacts with the titrant, and is calculated by dividing the coefficient in the reaction equation before the analyte by the coefficient before the titrant (be careful when multiple reactions occur during the titration!).

This stage can be omitted only if the compliance title is already given in the task conditions.

4. Calculate what is required by the conditions of the problem (for example, the mass fraction of a substance in the sample or the volume of titrant). There are basic formulas for this:

Direct titration	
No control experiment	**With control experiment**
$\omega = \frac{T \times V_T \times k}{g \times (1-\omega')} \times 100\ \%$	$\omega = \frac{T \times (V_T - V_{c.e.}) \times k}{g \times (1-\omega')} \times 100\ \%$
Reverse titration	
No control experience	**With control experience**
$\omega = \frac{T \times (V_{1st\ titr} - V_{2nd\ titr}) \times k}{g \times (1-\omega')} \times 100\ \%$	$\omega = \frac{T \times (V_{c.e.} - V_T) \times k}{g \times (1-\omega')} \times 100\ \%$

In these formulas, V_T is the volume of the titrant, k is the correction factor of the titrant, g is the mass of the sample being tested, w′ is the proportion of water or loss in mass during drying (in fractions), $V_{c.e.}$ — volume of titrant spent in the control experiment.

Since titer measurement units correspond to mg/ml, the mass of the sample is expressed in mg, and volume in ml.

If the method involves dilution, then the volume of the volumetric flask is taken into account in the numerator, and the volume of the pipette is taken into account in the denominator.

If a liquid sample is used and it is necessary to calculate the concentration in the original solution, we use the above formulas, but instead of the sample mass we use the sample volume and do not multiply by 100 %.

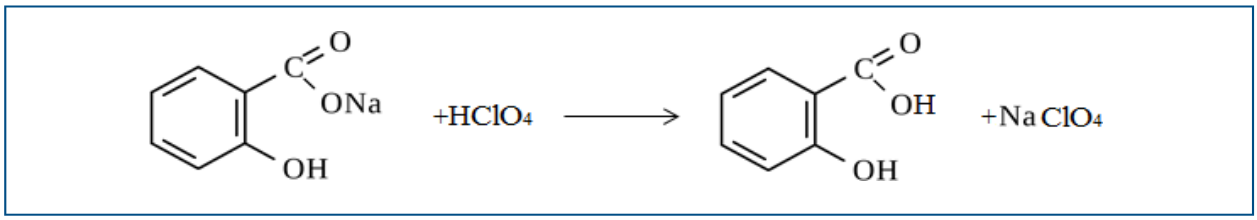
An example of solving a problem:

A sample weighing 130.0 mg of sodium salicylate substance (M = 160.1 g/mol) was dissolved in 30 ml of anhydrous acetic acid and titrated

with a 0.1 M solution of perchloric acid (k = 0.9850) with potentiometric detection of the titration end point. For titration, 7.90 ml of titrant solution was used. Calculate the mass fraction of sodium salicylate in the sample in terms of dry matter if the loss in mass upon drying is 2.50 %.

The technique describes direct acidimetric titration without a control experiment.

Chemical reaction equation:



Sodium salicylate and perchloric acid react in a 1 : 1 ratio, i. e. equivalence factor = 1.

Titer calculation:

$$T_{match.} = 0{,}1 \times 160{,}1 = 16{,}01 \text{ мг/мл}$$

Calculation of mass fraction:

$$\omega = \frac{16{,}01 \times 7{,}90 \times 0{,}9850}{130{,}0 \times (1 - 0{,}0250)} \times 100\ \% = 98{,}3\ \%$$

Spectrophotometry tasks

Solution sequence:

1. Read the methodology carefully and select the required values. Important are the optical density (A), the thickness of the absorbing layer (l), the mass (g) or volume (V) of the sample of the analyzed sample, the volumes of volumetric flasks (V_f) and the volumes of pipettes (V_p) (with the help of which the solution is transferred from one volumetric flasks into another), specific absorbance ($A_{1см}^{1\%}$), water content (w') (weight loss on drying), weight of the tablet (m_{1tab}) (or several tablets).

2. Calculation required by the conditions of the problem. To do this, we use the transformed Bouguer-Lambert-Beer law.

$$A = A_{1см}^{1\%} \times l \times C,$$

where l is expressed in cm, C is the concentration of the substance in the solution after dilution, g/100 ml.

To calculate the concentration in g/100 ml, we use the formula

$$C = \frac{m \times V_p \times 100}{V_f},$$

where m is the actual mass of the substance in the sample (g), if there are several pipettes, they are multiplied in the numerator, if there are several volumetric flasks, they are multiplied in the denominator.

Note that if the procedure calls for the first flask to be 100.0 mL, it is reduced from 100 in the numerator when expressing concentration.

We combine the two formulas and get an equation from which, with minor additions, we can express everything that is asked in the problem:

$$A = \frac{A_{1см}^{1\%} \times l \times m \times V_p \times 100}{V_f}.$$

Conversion example. If the problem requires calculating the mass fraction of a substance in a sample, we express from this equation the real mass of the substance in the sample and divide it by the mass of the sample (in grams) taking into account the water content (mass loss during drying):

$$\omega = \frac{m}{g \times (1 - \omega')} = \frac{A \times V_f}{A_{1см}^{1\%} \times l \times V_p \times 100 \times g \times (1 - \omega')} \times 100\ \%.$$

If a liquid sample is used and it is necessary to calculate the concentration in the original solution, we use the above formulas, but instead of the sample mass, we use the sample volume and do not multiply by 100% (concentration will be in g/ml).

If it is necessary to calculate content in terms of one tablet/capsule/suppository, use the mass fraction formula (without multiplying by 100 %) and multiply by the average weight of one tablet/capsule/suppository.

If it is necessary to calculate both the specific absorption rate and the molar absorption rate, then from this equation we express the specific absorption rate, calculate it, then substitute the resulting value into the formula for calculating the molar absorption rate:

$$\varepsilon = \frac{A_{1см}^{1\%} \times M_{subst}}{10}.$$

An example of solving a problem:

A sample weighing 250.0 mg of the sodium sulfacetamide substance was dissolved in a phosphate buffer solution (pH 7.0), obtaining 250.0 ml of solution. Then 1.00 ml of the resulting solution was adjusted with phosphate buffer solution (pH 7.0) to a volume of 100.0 ml. The optical density of the final solution at a wavelength of 255 nm and an absorbing layer thickness of 1.00 cm was found to be 0.640. Calculate the mass fraction of sodium sulfacetamide in the original substance in terms of an anhydrous substance, if the mass fraction of water is 7.00 %. The specific absorbance at a wavelength of 255 nm is 703.

The technique involves the use of two volumetric flasks (250.0 and 100.0 ml) and one 1.00 ml pipette. We also use the mass of the sample, the thickness of the absorbing layer, optical density, specific absorbance and mass fraction of water.

$$\omega = \frac{0{,}640 \times 250{,}0 \times 100{,}0}{703 \times 1{,}00 \times 1{,}00 \times 100 \times 0{,}2500 \times (1 - 0{,}0700)} \times 100\ \% = 97{,}9\ \%.$$

Polarimetry tasks

Solution plan:

1. Read through the problem carefully and select the required values. The important ones are the optical rotation angle (α), specific optical rotation (α_D^{20}), layer thickness (l), sample mass (m), solution volume (V), water content (w') (weight loss on drying).

2. Calculation required by the conditions of the problem. To do this, we use the basic formula (when calculating other parameters, we express them from it).

$$\alpha = \alpha_D^{20} \times l \times C,$$

where l is expressed in dm, C is the concentration of the substance in the solution, g/ml.

If the concentration of the solution is not given, divide the mass of the substance (g) by the volume of the solution (ml), if necessary, taking into account the water content (mass loss upon drying) and the mass fraction of the substance (in fractions):

$$C = \frac{m}{V} = \frac{g \times \omega \times (1 - \omega')}{V}.$$

We obtain the basic equation for polarimetry:

$$\alpha = \frac{\alpha_D^{20} \times l \times g \times \omega \times (1 - \omega')}{V}.$$

Example task:

A 1.00 g sample of ascorbic acid substance (ascorbic acid content 99.8 %) was dissolved in water to obtain a solution with a volume of 50.0 ml. Calculate the specific optical rotation of ascorbic acid if the angle of rotation of the resulting solution in a cuvette with a layer thickness of 20.0 cm was +0.96º.

From the basic equation we express the specific optical rotation.

$$\alpha_D^{20} = \frac{\alpha \times V}{l \times g \times \omega} = \frac{0{,}96 \times 50{,}0}{2{,}00 \times 1{,}00 \times 0{,}998} = 24.$$

Refractometry tasks

The basic formula for calculations in refractometry:

$$C = \frac{n - n_0}{F},$$

where C is the concentration of the solution (g/100 ml), n is the refractive index of the test solution, n_0 is the refractive index of the solvent, F — refractive index factor.

If the problem requires calculating the mass of a substance (g) in a certain volume of the dosage form (V_{df}), the formula takes the following form:

$$m = \frac{(n - n_0) \times V_{df}}{F \times 100}.$$

If there are other substances in the solution, which also affect the refractive index of the analyzed solution, then the formula for calculating the concentration of the main substance will change as follows:

$$C = \frac{n - n_0 - C_x \times F_x}{F},$$

where C_x is the concentration of the «interfering» substance, g/100 ml, F_x is the refractive index factor of the «interfering» substance.

Example task:

The concentration of magnesium sulfate in an aqueous solution was determined refractometrically. The measured refractive index at 20 ºC was 1.3550. The refractive index factor for the assumed concentration is 0.00089. Calculate the concentration of magnesium sulfate (%) in the test solution.

The problem deals with an aqueous solution of magnesium sulfate, so n_0 water = 1.3330 is used. We use the basic formula.

$$C = \frac{1{,}3550 - 1{,}3330}{0{,}00089} = 24{,}7\%$$

REAGENTS USED IN PHARMACOPOEIAL ANALYSIS. PROPERTIES OF PHARMACEUTICAL SUBSTANCES

1. Standardization of a 0.1 M perchloric acid solution was carried out according to the method from the State Pharmacopoeia of the Republic of Belarus (SPh RB). A sample weighing 350.0 mg of a standard sample of potassium hydrophthalate (M = 204.2 g/mol) was dissolved in 50 ml of anhydrous acetic acid and titrated with solution of perchloric acid using 0.05 ml of a solution of crystal violet R as an indicator. For titration it was required 16.7 ml of perchloric acid solution. Calculate the correction factor for the solution being standardized.

2. Standardization of a 0.1 M sodium thiosulfate solution was carried out according to the method from the State Pharmacopoeia of the Republic of Belarus. To 10.0 ml of 0.03333 M potassium bromate solution 40 ml of water R, 10 ml of potassium iodide solution R, 5 ml of hydrochloric acid R1 were added and titrated with the prepared sodium thiosulfate solution using 1 ml of starch solution R as an indicator. For titration it was required 20.1 ml of titrant solution. Calculate the correction factor for the solution being standardized.

3. When preparing a standard potassium solution, a sample of potassium sulfate was dissolved in water and brought to a volume of 50.0 ml with the same solvent. Immediately before use the resulting solution was diluted with water 20 times. Calculate the mass of a sample of potassium sulfate (M = 174.3 g/mol) that must be taken so that the potassium content (M = 39.1 g/mol) in the final solution is 200 ppm.

4. Pharmacist-analyst carried out quality control of the pharmaceutical substance of bendazole hydrochloride according to the section «Description» of the State Pharmacopoeia of the Republic of Belarus. When assessing the degree of hygroscopicity the following results were obtained: mass of the empty bottle = = 20.0510 g, mass of the bottle with the test sample before placement in the climatic chamber = 20.5568 g, mass of the bottle with the test sample after keeping in the climatic chamber = 20.6020 g. Calculate increase in the mass of bendazole hydrochloride and name the term that characterizes hygroscopicity based on the results obtained.

5. Pharmacist-analyst carried out quality control of the sodium chloride pharmaceutical substance according to the section «Description» of the State Pharmacopoeia of the Republic of Belarus. When assessing water solubility, 101.0 mg of finely ground test sample was placed in a test tube, 0.1 ml of solvent

was added, shaken vigorously for 1 min and kept at 25 °C for 15 min, then shaken and kept again. The test sample did not dissolve completely. Another 0.9 ml of solvent was added to it, as a result of which the sample was completely dissolved. Calculate the solubility of sodium chloride in water and provide the corresponding descriptive term.

TITRIMETRIC METHODS USED IN PHARMACEUTICAL ANALYSIS. GRAVIMETRY

1. Pharmacist-analyst carried out quality control of sodium citrate (M anhydrous substance = 258.06 g/mol) according to the «Quantitative determination» indicator in accordance with the methodology from the pharmacopoeial monograph. 0.150 g of the test sample containing 12.0 % water was dissolved in 20 ml of anhydrous acetic acid R, heated to a temperature of 50 °C, cooled and titrated with a 0.1 M solution of perchloric acid (k = 0.9870) until a green color appears using 0.25 ml of naphtholbenzein solution R as an indicator. 15.5 ml of titrant was used for titration. Write the equation for the reaction that take place. Calculate the mass fraction of sodium citrate in the test sample in terms of dry matter with a preliminary calculation of titer.

2. Pharmacist-analyst carried out quality control of the PhS of procaine hydrochloride (M = 272.8 g/mol) according to the indicator «Quantitative determination» in accordance with the methodology from the SPh RB. 0.400 g of the test sample was dissolved in 50 ml of diluted hydrochloric acid R, 3 g of potassium bromide R was added. Cooled in ice water and then slowly titrated under constant stirring with 0.1 M sodium nitrite solution (k = 0.9955) maintaining the temperature of the solution about 15 °C (a solution of tropeolin 00 R mixed with

methylene blue R (0.2 ml of a solution of tropeolin 00 R and 0.1 ml of a solution of methylene blue R) was used as an indicator — titrated until the color changed from red-violet to blue). 14.6 ml of titrant was used for titration. Write the equation for the reaction that take place. Calculate the mass fraction of procaine hydrochloride in the test sample (mass loss on drying is 0.30%) relative to dry matter with a preliminary calculation of titer.

3. Pharmacist-analyst carried out quality control of PhS calcium gluconate for injection (M = 448.4 g/mol) according to the «Quantitative Determination» indicator in accordance with the methodology from the SPh RB. 0.350 g of the test sample was dissolved in 20 ml of hot water R, cooled and diluted with water R to a volume of 300 ml. Add 6.0 ml of concentrated sodium hydroxide solution R and 50 mg of calcone carboxylic acid indicator mixture R. Titrate with 0.1000 M sodium edetate solution until violet color changes to deep blue. 7.80 ml of titrant was used for titration. Write the equation for the reaction that take place. Calculate the mass fraction of calcium gluconate in the test sample with a preliminary calculation of titer.

4. Pharmacist-analyst carried out quality control of the PhS of hydrogen peroxide of a 30 % solution (M = 34.01 g/mol) according to the indicator «Quantitative determination» in accordance with the methodology from the SPh RB. 1.0000 g of the test sample was diluted with water R to a volume of 100.0 ml. To 10.0 ml of the resulting solution 20 ml of diluted sulfuric acid R was added and titrated with 0.02 M potassium permanganate solution (k = 0.9952) until a pink color appeared. 17.7 ml of titrant was used for titration. Write the equation for the reaction that occurs. Calculate the mass fraction of hydrogen peroxide of a 30 % solution in the test sample with a preliminary calculation of titer.

5. Pharmacist-analyst carried out quality control of the PhS of acetylsalicylic acid (M = 180.2 g/mol) according to the indicator «Quantitative determination» in accordance with the methodology from the SPh RB. 1.0000 g of the test sample was placed in a flask with a ground glass stopper, dissolved in 10 ml of 96% alcohol R, 50.0 ml of 0.5 M sodium hydroxide solution was added, the flask was capped and kept for 1 hour. Titrated with 0.5 M solution of hydrochloric acid (k = 0.9867), using 0.2 ml of phenolphthalein solution R as an indicator. A control experiment was carried out in parallel. For titration with the test sample 27.2 ml of titrant was consumed, in the control experiment — 49.5 ml. Write the equations for the reactions that occur. Calculate the mass fraction of acetylsalicylic acid in the test sample (mass loss on drying is 0.500 %) in terms of dry matter with a preliminary calculation of titer.

SPECTROMETRIC AND THERMAL METHODS USED IN PHARMACEUTICAL ANALYSIS

1. Pharmacist-analyst carried out quality control of the pharmaceutical substance of chloramphenicol according to the indicator «Quantitative determination» in accordance with the methodology from the SPh RB. 0.1000 g of the test sample was dissolved in water R and made up to a volume of 500.0 ml with the same solvent. 10.0 ml of the resulting solution was diluted with water R to a volume of 100.0 ml. Optical density of the resulting solution was measured at a maximum of 278 nm and an absorbing layer thickness of 10.0 mm, which turned out to be equal to 0.583. Calculate the mass fraction of chloramphenicol in the test sample (weight loss on drying is 0.32 %) in terms of dry matter taking into account the specific absorption index of 297.

2. Pharmacist-analyst carried out quality control of glucose in a 10 % solution without a stabilizer according to the «Quantitative Determination» indicator using the refractometric method. The refractive index of the solution at 20 °C turned out to be 1.3490. Calculate the mass (g) of anhydrous glucose in 500 ml of such a solution if the refractive index factor for anhydrous glucose is 0.00142.

3. Pharmacist-analyst carried out quality control of glucose in a 10 % solution with potassium chloride according to the «Quantitative Determination» indicator using the refractometric method. The refractive index of the solution at 20 °C turned out to be 1.3502. When argentometrically determining potassium chloride (M = 74.56 g/mol) in 1.00 ml of the drug, 3.20 ml of 0.1000 M silver nitrate solution was required for titration. Calculate the mass of anhydrous glucose in 1000 ml of the drug if the refractive index factor for potassium chloride is 0.00127 and for anhydrous glucose is 0.00142.

4. A sample weighing 2.50 g of the levomenthol substance was dissolved in 10 ml of 96 % alcohol and brought to a volume of 25.0 ml with the same solvent. The angle of optical rotation of the resulting alcohol solution with a polarimetric tube length of 100 mm was –4.20°. Calculate specific optical rotation value of the test sample.

5. Pharmacist-analyst carried out quality control of the triamcinolone PhS according to the «Quantitative Determination» indicator using the spectrophotometric method. 50.0 mg of the test sample was dissolved in ethyl alcohol and diluted to 50.0 ml with the same solvent. Then 2.00 ml of the resulting solution was diluted to 100.0 ml with ethyl alcohol. Optical density of the final solution at 238 nm and an absorbing layer thickness of 1.00 cm was found to be 0.760. Calculate the mass fraction of triamcinolone in the sample (weight loss on drying is 1.40 %) in terms of dry matter. The specific absorption index of triamcinolone at 238 nm is 389.

CHROMATOGRAPHIC AND BIOLOGICAL METHODS USED IN PHARMACEUTICAL ANALYSIS

1. Pharmacist-analyst carried out quality control of the pharmaceutical substance of fluoxetine hydrochloride according to the indicator «Quantitative determination» using the liquid chromatography method. A sample weighing 50.0 mg of the test substance was dissolved in the mobile phase obtaining 50.0 ml of solution. Then 10.0 ml of this solution was diluted with the mobile phase to

100.0 ml. The ratio of the peak areas for the test solution and the standard solution of fluoxetine hydrochloride (0.100 mg/ml in the final solution) was found to be 0.990. Calculate the mass fraction of fluoxetine in the test sample in terms of an anhydrous and acetonitrile-free substance, if the mass fraction of water in the sample is 0.40 % and acetonitrile is 0.05 %.

2. Calculate number of theoretical plates (N), height of equivalent theoretical plate (H), degree of separation (R), mass fraction (W) in percent (using the internal normalization method) when separating a mixture of isopropanol and n-propanol under gas chromatography conditions in a packed column 1000 mm long, if the following characteristics of the peaks of the separated components are obtained on the chromatogram (l is the retention time, h and $\alpha 1/2$ are the height and half-width of the peaks, respectively), expressed in the same units of measurement: for isopropanol l = 17.5, h = 52.5, $\alpha 1/2$ = 2.5; for n-propanol l = 32.5, h = 40, $\alpha 1/2$ = 3.75.

3. When chromatographing atropine on a Sorbfil chromatographic plate, the following results were obtained: distance from the start line to the center of the spot is 49.6 mm, distance from the start line to the bottom border of the spot is 46.8 mm, distance from the bottom to the top border of the spot is 5.6 mm. Distance between the start line and the solvent front line is 90.0 mm. Calculate the Rf of atropine.

4. Pharmacist-analyst carried out quality control of the PhS of sitagliptin phosphate monohydrate according to the indicator «Quantitative determination» using the liquid chromatography method. When preparing the test solution, 25.40 mg of the test sample containing 3.5 % water was placed in a volumetric flask with a capacity of 250.0 ml, dissolved in a solvent (acetonitrile — phosphoric acid diluted 0.1 % 5:95) and volume of the solution was brought to tags. Then, using a similar procedure, a solution of a standard sample of sitagliptin phosphate monohydrate was prepared from 24.90 mg of the standard sample. The ratio of the peak areas of sitagliptin phosphate in the test and standard solutions turned out to be 0.978. Calculate content of sitagliptin phosphate in the test sample as a percentage in terms of anhydrous and free of residual organic solvents substance. According to the requirements of the SPh RB content of sitagliptin phosphate must be no less than 98.0% and no more than 102.0 %. Make a conclusion about the compliance of the test sample with the requirements of regulatory documentation.

5. Pharmacist-analyst carried out quality control of amlodipine besylate PhS according to the indicator «Quantitative determination» using liquid chromatography. When preparing the test solution, 49.8 mg of the test sample was placed in a 50.0 ml volumetric flask, dissolved in the mobile phase, volume of the solution was adjusted to the mark with the mobile phase and mixed. 5.00 ml of the resulting solution was transferred to a 100.0 ml volumetric flask, volume of the solution was adjusted to the mark with the mobile phase and mixed. Then a standard solution was prepared. 50.00 mg of a standard sample of amlodipine besylate was placed in a 50.0 ml volumetric flask, dissolved in the mobile phase, volume of the solution was adjusted to the mark with the mobile phase and mixed. 5.00 ml of the resulting solution was transferred to a 100.0 ml volumetric flask, volume of the

solution was adjusted to the mark with the mobile phase and mixed. The peak area of amlodipine besylate in the standard solution was 1.02 times greater than in the test solution. Calculate the mass fraction of amlodipine besylate in the test sample in terms of an anhydrous substance free of residual organic solvents (the total content of water and residual organic solvents in the substance is 0.40 %). According to the requirements of the SPh RB content of amlodipine besylate must be no less than 97.0 % and no more than 102.0 %. Make a conclusion about the compliance of the test sample with the requirements of regulatory documentation.

METHODS FOR IDENTIFICATION OF INORGANIC CATIONS AND ANIONS USED IN PHARMACOPOEIAL ANALYSIS

1. The test sample was dissolved in water, 1 ml of diluted hydrochloric acid and 1 ml of barium chloride solution were added — a white precipitate was formed. When adding iodine solution, yellow color did not disappear; when adding tin chloride, the solution did not become discolored. Guess which ion was detected. Give equations for the reactions that take place.

2. The test sample was dissolved in water, acidified with dilute nitric acid, a solution of silver nitrate was added, mixed, allowed to stand, a light yellow cheesy precipitate was formed, which, after separation and washing with water, slowly dissolved with the addition of ammonia. Guess which ion was detected. Give equations for the reactions that take place.

3. The test sample was dissolved in water. Diluted hydrochloric acid and thioacetamide reagent was added, but no precipitate formed. Then a diluted sodium hydroxide solution was added dropwise, a gel-like white precipitate formed, which dissolved with the subsequent addition of a diluted sodium hydroxide solution. When ammonium chloride solution was gradually added to the solution, a gel-like white precipitate again formed. Guess which ion was detected. Give equations for the reactions that take place.

4. The test sample was dissolved in water. Added 0.2 g of magnesium oxide. Air was passed through the liquid and the escaping air was directed into a mixture of 1 ml of 0.1 M hydrochloric acid solution and 0.05 ml of methyl red solution; Indicator color turns yellow. Then 1 ml of a freshly prepared solution of 100 g/l sodium cobaltinitrite was added; a yellow precipitate formed. Guess which ion was detected. Give equations for the reactions that take place.

5. 20 mg of the test sample was dissolved in 5 ml of acetic acid. 0.5 ml of potassium hexacyanoferrate (II) solution was added to the resulting solution — the solution remained transparent. 50 mg of ammonium chloride was added to the solution and a white crystalline precipitate formed. The same test sample after wetting with hydrochloric acid and when introduced into a colorless flame turned it orange-red. Guess which ion was detected. Give the equation for the reaction that take place.

METHODS FOR IDENTIFYING ORGANIC IONS AND FUNCTIONAL GROUPS USED IN PHARMACOPOEIAL ANALYSIS. INSTRUMENTAL IDENTIFICATION METHODS

1. Pharmacist-analyst carried out quality control of the pharmaceutical substance of paracetamol according to the indicator «Authenticity (Identification)» in accordance with the methodology from the SPh RB. 0.1000 g of the test sample was dissolved in methanol R and made up to a volume of 100.0 ml with the same solvent. To 1.0 ml of the resulting solution was added 0.5 ml of a solution of 10.3 g/l hydrochloric acid R and diluted with methanol R to a volume of 100.0 ml. Optical density of the resulting solution was measured at a maximum at 249 nm and absorbent layer thickness 10.0 mm, which turned out to be equal to 0.900. Calculate the specific absorption value of paracetamol under the conditions for measuring optical density. According to the requirements of the SPh RB specific absorption index can be in the range from 860 to 980. Make a conclusion about the compliance of the test sample with the requirements of regulatory documentation.

2. Pharmacist-analyst carried out quality control of glutamic acid PhS according to the indicator «Authenticity (Identification)» in accordance with the methodology from the SPh RB using the polarimetric method. 5.0000 g of the test sample was dissolved in 1 M hydrochloric acid solution under gentle heating and

made up to a volume of 50.0 ml with the same solvent. The optical rotation angle measured with a polarimetric tube length of 10.0 cm turned out to be +3.10°. Calculate value of the specific optical rotation of the test sample (mass loss on drying is 0.33 %) in terms of dry matter. According to the requirements of the SPh RB specific optical rotation can be in the range from +30.5 to +32.5. Make a conclusion about the compliance of the test sample with the requirements of regulatory documentation.

3. Pharmacist-analyst carried out quality control of the hydrochlorothiazide pharmaceutical substance according to the indicator «Authenticity (Identification)» in accordance with the methodology from the SPh RB spectrophotometric method. 50.00 mg of the test sample was dissolved in 10 ml of 0.1 M sodium hydroxide solution and diluted with water R to a volume of 100.0 ml. 2.00 ml of the resulting solution was brought to a volume of 100.0 ml with 0.01 M sodium hydroxide solution. The absorption spectrum was recorded in the wavelength range from 250 nm to 350 nm. The solution had two absorption maxima — at 273 and 323 nm. The optical density of the solution at a wavelength of 273 nm turned out to be 0.320, and at a wavelength of 323 nm — 0.113. According to the requirements of the SPh RB ratio of optical densities at wavelengths of 273 and 323 nm should be from 5.4 to 5.7. Calculate ratio of the optical densities of the solution at wavelengths of 273 and 323 nm. Make a conclusion about the compliance of the test sample with the requirements of regulatory documentation.

4. A solution of iron (III) chloride was added to the solution of the test sample and a violet color was observed, which did not disappear after adding acetic acid and disappeared with the addition of diluted hydrochloric acid; a white crystalline precipitate formed. Guess which ion was detected. Give equations for the reactions that take place.

5. The test sample was dissolved in water, concentrated sulfuric acid and a solution of potassium permanganate were added, heated until discolored, a solution of sodium nitroprusside in diluted sulfuric acid and sulfamic acid were added. A concentrated ammonia solution was added to the mixture until the medium was alkaline and the sulfamic acid was completely dissolved. Addition of an excess of concentrated ammonia solution led to the appearance of a violet color turning into violet-blue. Guess which ion was detected. Give equations for the reactions that take place.

PHARMACOPOEIAL TESTS OF PHARMACEUTICAL SUBSTANCES

1. Pharmacist-analyst carried out quality control of the Vaseline PhS according to the «Test» indicator. When determining its kinematic viscosity, it was found that when using a viscometer with a constant of 0.82 mm^2/s^2 flow time of the test sample is 22 s. Calculate kinematic viscosity m^2/s for the test sample.

2. Pharmacist-analyst carried out quality control of the isopropyl myristate pharmaceutical substance according to the «Test» indicator. When determining the dynamic viscosity of a sample with a relative density of 0.853, it was found that when using a viscometer with a constant of 0.82 mm^2/s^2 flow time of the test sample is 8 s. Calculate value of dynamic viscosity mPa × s for isopropyl myristate.

3. Pharmacist-analyst carried out quality control of refined sunflower oil PhS according to the indicator «Description (Properties)». Density determination was carried out using a pycnometer at a temperature of 20 °C. The difference in mass between pycnometer with the test sample and the empty pycnometer was 54.3300 g, and difference in mass between the pycnometer with water and the empty pycnometer was 59.1900 g. Calculate relative density of the test sample.

4. Pharmacist-analyst carried out quality control of the PhS chlorhexidine digluconate solution according to the «Test» indicator. Relative density of the test sample was found to be 1.07. Calculate density g/cm^3 of this sample at 20 °C.

5. Pharmacist-analyst carried out quality control of the pharmaceutical substance of morphine sulfate according to the «Test» indicator. 500.0 mg of the test sample containing 12.0 % water was dissolved in carbon dioxide-free water to obtain 25.0 ml of solution. According to the requirements of the SPh RB permissible value of specific optical rotation for morphine sulfate is from –107 to –110 in terms of dry matter. Calculate permissible value of the optical rotation angle of the resulting solution for a 10.0 cm layer thickness.

PHARMACOPOEIAL TESTS OF PHARMACEUTICAL SUBSTANCES AND ELECTROCHEMICAL METHODS USED IN PHARMACEUTICAL ANALYSIS

1. Pharmacist-analyst carried out quality control of the isopropyl myristate pharmaceutical substance according to the «Test» indicator. When determining content of total ash the following results were obtained: mass of the crucible is 17.8000 g, weighed portion of the test sample is 5.00020 g, mass of the crucible after drying and burning to a constant mass is 17.8045 g. Calculate content of total ash in the test sample and make a conclusion whether it meets the requirements of the SPh RB (no more than 0.1 %)?

2. Pharmacist-analyst carried out quality control of aminocaproic acid PhS according to the «Test» indicator. When determining sulfate ash, mass of the empty crucible was 11.2800 g, mass of the crucible with the sample was 12.2810 g. Calculate content of sulfate ash in the test sample if mass of the crucible with the sample after calcination until complete ashing of the residue was 11.2879 g. Does this correspond content of sulfate ash in the test sample according to the requirements of the SPh RB (no more than 0.1 %)?

3. Pharmacist-analyst carried out quality control of the zinc gluconate PhS according to the «Test» indicator. Water content was determined by micromethod. A sample weighing 80.0 mg was dissolved in anhydrous methanol. To interact with the water contained in the prepared solution, iodine was required, for the production of which 102.0 C of electricity was consumed. Calculate mass fraction of water in the test sample and make a conclusion whether its content meets the requirements of the SPh RB (no more than 12.0 %).

4. Pharmacist-analyst carried out quality control of the pharmaceutical substance aluminum chloride hexahydrate according to the «Test» indicator. Water content in the sample was determined using the semi-micro method. Write the equations for the reactions that take place. Calculate mass fraction of water in the test sample if, when titrating a sample weighing 50.0 mg of the substance morphine hydrochloride, 5.10 ml of Karl Fischer reagent (iodosulfur reagent) was consumed, titer of which in water is 4.500 mg/ml. Does water content in the test sample meet the requirements of the SPh RB (not less than 42.0 % and not more than 48.0 %)?

5. Pharmacist-analyst carried out quality control of the pharmaceutical substance aluminum chloride hexahydrate according to the «Test» indicator. When determining the weight loss during drying, the following results were obtained: mass of an empty bottle = 20.5123 g, mass of a bottle with a sample of the test sample before drying = 21.5155 g, mass of a bottle with a sample of the test sample after drying = 21.4988 g. Calculate weight loss during drying and make a conclusion whether its value meets the requirements of the SPh RB (no more than 3.0 %).

PHARMACOPOEIAL WATER QUALITY CONTROL. STATISTICAL PROCESSING OF CHEMICAL EXPERIMENT RESULTS, VALIDATION OF METHODS AND PRINCIPLE OF CHOOSING A QUANTITATIVE DETERMINATION METHOD

1. During spectrophotometric determination of the active substance in omeprazole capsules the following results were obtained: 19.8 mg, 19.6 mg, 21.4 mg, 20.1 mg, 20.6 mg, 20.5 mg, 21.7 mg, 21.2 mg, 21.4 mg. It is necessary to check homogeneity of the sample (remove outliers if necessary) and present results in the form of the mean value and the half-width of its confidence interval (presenting all necessary calculations). Metrological characteristics during statistical processing include: number of degrees of freedom, average value, dispersion, standard deviation, standard deviation of the sample average, relative standard deviation of analysis results, confidence interval boundaries (95 % confidence level), uncertainty of the average result.

2. During the titrimetric determination of sodium bicarbonate PhS the following results were obtained: 99.4 %, 98.9 %, 99.6 %, 99.5 %, 99.2 %, 99.0 %. It is necessary to check homogeneity of the sample (remove outliers if necessary) and present results in the form of the mean value and the half-width of its confidence interval (presenting all necessary calculations). Metrological characteristics during statistical processing include: number of degrees of freedom, average value, dispersion, standard deviation, standard deviation of the sample average, relative standard deviation of analysis results, confidence interval boundaries (95 % confidence level), uncertainty of the average result.

3. It is necessary to compare two analysis methods for reproducibility. Using the first method the following values were obtained: 18.5 mg, 19.8 mg, 19.6 mg, 21.4 mg, 20.1 mg, 20.6 mg; for the second: 20.5 mg, 20.6 mg, 21.7 mg, 21.2 mg, 21.4 mg, 22.0 mg.

4. It is necessary to compare two analysis methods for reproducibility. Using the first method the following values were obtained: 99.4 %, 98.8 %, 99.6 %, 95.4 %, 99.2 %; for the second: 97.3 %, 98.1 %, 97.5 %, 94.7 %, 97.4 %.

5. During the chromatographic determination of the PhS atorvastatin calcium trihydrate the following results were obtained: 98.2 %, 96.4 %, 97.9 %, 97.6 %. It is necessary to check homogeneity of the sample (remove outliers if necessary) and present results in the form of the mean value and the half-width of its confidence interval (presenting all necessary calculations).

PHARMACOPOEIAL ANALYSIS OF PHARMACEUTICAL SUBSTANCES OF INORGANIC NATURE: S-ELEMENTS

1. Pharmacist-analyst carried out quality control of the PhS calcium chloride dihydrate (M = 147.0 g/mol) according to the indicator «Quantitative determination» in accordance with the methodology from the SPh RB. 0.285 g of the test sample was dissolved in 100 ml of water R and diluted with the same solvent to a volume of 300 ml. Add 6.0 ml of concentrated sodium hydroxide solution R and 15 mg of calcone carboxylic acid indicator mixture R. Titrate with 0.1 M sodium edetate solution (k = 1.0100) until violet color changes to deep blue. 19.1 ml of titrant was used for titration. Write the equation for the reaction that take place. Calculate mass fraction of calcium chloride dihydrate in the test sample with a preliminary calculation of titer. According to the requirements of the SPh RB content of calcium chloride dihydrate must be no less than 97% and no more than 103.0 %. Make a conclusion about the compliance of the test sample with the requirements of regulatory documentation.

2. Pharmacist-analyst carried out quality control of the PhS magnesium light oxide (M = 40.30 g/mol) according to the indicator «Quantitative determination» in accordance with the methodology from the SPh RB. 300.0 mg of the test sample was dissolved in 20 ml of diluted hydrochloric acid R and diluted with water R to a volume of 100.0 ml. Then 20.0 ml of the prepared solution was placed in a conical flask with a capacity of 500 ml and volume of the solution was adjusted to 300 ml with water. 10 ml of an ammonia buffer solution pH 10 and about 50 mg of an indicator mixture of eriochrome black T were added. Solution was heated to a temperature of about 40 °C and titrated at this temperature with a 0.1000 M solution of sodium edetate until purple color of the solution changed to blue. As a result of the analysis, it was established that the mass fraction of magnesium oxide is 99.0 % in terms of the calcined substance. Weight loss on calcination is 7.00 %. Calculate volume of titrant consumed by pharmacist.

3. Pharmacist-analyst carried out quality control of barium sulfate PhS according to the indicator «Quantitative determination» using the gravimetric method. 600.0 mg of the test sample was mixed with anhydrous sodium carbonate. Mixture was treated with water and hydrochloric acid. An acetate buffer solution, a solution of potassium dichromate and urea were added to the resulting solution. Precipitate of barium chromate was separated from the solution, washed with a solution of potassium dichromate, dried at a temperature of 105 °C and, after cooling, its mass was measured. Write the equations for the reactions that take place. Calculate the mass fraction of barium sulfate (M = 233.40 g/mol) in the sample if the mass of barium chromate precipitate (M = 253.33 g/mol) turns out to be 0.6485 g.

4. Pharmacist-analyst carried out quality control of the PhS magnesium sulfate heptahydrate (M anhydrous substance = 120.4 g/mol) according to the indicator «Quantitative determination» in accordance with the methodology from the SPh RB. 452.0 mg of the test sample was dissolved in 100 ml of water R and volume of the solution was adjusted to 300 ml with the same solvent. 10 ml of an ammonia buffer solution pH 10 and about 50 mg of an indicator mixture of eriochrome black T were added. Solution was heated to a temperature of about 40 °C and titrated at this temperature with a 0.1000 M solution of sodium edetate until purple color of the solution changed to blue. 18.7 ml of titrant was used for titration. Write the equation for the reaction that take place. Calculate the mass fraction of magnesium sulfate heptahydrate in the test sample in terms of dry matter (mass loss on drying is 50.0 %) with a preliminary calculation of titer. According to the requirements of the SPh RB content of magnesium sulfate must be no less than 99% and no more than 100.5 %. Make a conclusion about the compliance of the test sample with the requirements of regulatory documentation.

5. Pharmacist-analyst carried out quality control of the PhS calcium chloride hexahydrate according to the indicator «Quantitative determination» in accordance with the methodology from the SPh RB. 0.2050 g of the test sample was dissolved in 100 ml of water R and diluted with the same solvent to a volume of 300 ml. Add 6.0 ml of concentrated sodium hydroxide solution R and 15 mg of calcone carboxylic acid indicator mixture R. Titrate with 0.1 M sodium edetate solution (k = 0.9925) until violet color changes to deep blue. 9.40 ml of titrant was used for titration. Write the equation for the reaction that take place. Calculate the mass of calcium chloride hexahydrate in the sample, taking into account that 1 ml of 0.1 M sodium edetate solution corresponds to 21.91 mg of calcium chloride hexahydrate.

ANSWERS TO PROBLEMS

Reagents used in pharmacopoeial analysis. Properties of pharmaceutical substances

1. 1.026.
2. 0.9949.
3. 0.446 g.
4. 8.94 % (hygroscopic).
5. 9.9 ml/g (easily soluble).

Titrimetric methods used in pharmaceutical analysis. Gravimetry

1. 99.7 %.
2. 99.4 %.
3. 99.9 %.
4. 30.0 %.
5. 99.6 %.

Spectrometric and thermal methods used in pharmaceutical analysis

1. 98.5 %.
2. 56.3 g.
3. 99.8 g.
4. –42.0.
5. 99.1 %.

Chromatographic and biological methods used in pharmaceutical analysis

1. 99.4 %.
2. R = 2.4; for isopropanol N = 272, H = 3.68 mm, W = 46.67 %; for n-propanol N = 417, H = 2.40 mm, W = 53.33 %.
3. 0.551.
4. 99.4 %. Compliant.
5. 98.8 %. Compliant.

Methods for identification of inorganic cations and anions used in pharmacopoeial analysis

1. IO_3^-
2. Br^-
3. Al^{3+}
4. NH_4^+
5. Ca^{2+}

Methods for identifying organic ions and functional groups used in pharmacopoeial analysis. Instrumental identification methods

1. 900. Compliant.
2. +31.1. Compliant.
3. 2.83. Does not compliant.
4. Salicylate.
5. Citrate.

Pharmacopoeial tests of pharmaceutical substances

1. 1.8×10^{-5} m^2/s.
2. 5.6 mPa × s.
3. 0.918.
4. 1.068.
5. from –1.88 to –1.94.

Pharmacopoeial tests of pharmaceutical substances and electrochemical methods used in pharmaceutical analysis

1. 0.09 %. Compliant.
2. 0.79 %. Does not compliant.
3. 11.9 %. Compliant.
4. 45.9 %. Compliant.
5. 1.66 %. Compliant.

Pharmacopoeial analysis of pharmaceutical substances of inorganic nature: s-elements

1. 99.5 %. Compliant.
2. 13.7 ml.
3. 99.58 %.
4. 99.6 %. Compliant.
5. 204.4 mg.

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PHARMACEUTICAL CHEMISTRY

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На английском языке

В двух частях

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