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

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

В двух частях

Часть 1

Минск БГМУ 2025

УДК 615.1:54(076.5)-111
ББК 52.8+24я73
Л84

Рекомендовано Научно-методическим советом университета в качестве практикума 17.09.2025 г., протокол № 1

Рецензенты: канд. фармацевт. наук, зам. гл. технолога РУП «Белмедпрепараты» Л. В. Дьячкова; каф. фармацевтической технологии с курсом повышения квалификации и переподготовки Белорусского государственного медицинского университета

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Л84 Фармацевтическая химия = Pharmaceutical chemistry : практикум для студентов 3-го курса медицинского факультета иностранных учащихся, обучающихся по специальности «Фармация». В 2 ч. Ч. 1 / Р. И. Лукашов, С. Г. Хаминец, Н. И. Мандрик. – Минск : БГМУ, 2025. – 88 с.

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Включены методические рекомендации к лабораторным занятиям по фармацевтической химии. Содержатся контрольные вопросы по темам занятий, алгоритмы выполнения лабораторных работ, задания для самостоятельной работы студента, перечни литературы к каждому занятию.

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	Grade	Teacher's signature
1	Introduction to the academic discipline «Pharmaceutical chemistry». Methods and sources of obtaining medicines		
2	Ensuring the quality of pharmaceutical substances and medicines. General characteristics of pharmaceutical analysis. Pharmacopoeial analysis		
3	Stability, shelf life and modern approaches to degradation, neutralization and disposal of medicines		
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		
8	**Final lesson on the topics «General issues of pharmaceutical chemistry and methods used in pharmaceutical analysis»**		
9	Methods for identification of 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 testing of pharmaceutical substances		
12	Pharmacopoeial testing of pharmaceutical substances and electrochemical methods used in pharmaceutical analysis		
13	Impurities in pharmaceutical substances		
14	**Final lesson «Methods of pharmacopoeial analysis»**		
15	Pharmacopoeial water quality control. Statistical processing of chemical experiment results, validation of methods and principle of choosing a quantitative determination method		
16	Pharmacopoeial analysis of pharmaceutical substances of inorganic nature: s-elements		
17	**Final lesson «Basic approaches to pharmacopoeial analysis»**		

PREFACE

This manual is an example of a didactic approach to organizing a pharmaceutical chemistry laboratory lesson, as it optimizes work under the supervision of a teacher and increases the productivity of studying by 3rd year Faculty of Medicine for foreign students with English as the language of instruction in the specialty «Pharmacy».

Purpose of the manual: to facilitate and accelerate students' assimilation of material on pharmacopoeial quality control of medicines.

Manual specifies the topics of laboratory classes, as well as the requirements of the department and safety precautions.

Manual contains: the purpose of the lesson, requirements for the initial level of knowledge, test questions on the topics of the lesson, an algorithm for performing laboratory work, assignments for the student's independent work and lists of literature for each lesson. Using manual, students will reduce the time it takes to complete laboratory protocols, which will make it possible to pay more attention to studying theoretical material, and will also allow them to save notes regarding the implementation of the experiment, which is especially important when preparing for practical skills test.

At the end of the lesson, the teacher signs manual and conducts an exit test of the students' knowledge, on the basis of which a mark is given for the lesson.

Algorithm for conducting the class (total class time — 4 hours)

At the beginning of the lesson, questions that caused difficulty for students when preparing themselves for the topic of the lesson are discussed. This is followed by an oral discussion with students about test questions on the topic of the lesson. After the break, students are reviewed about the laboratory work content, and then they begin to complete it under the guidance of the teacher. After summing up the results of laboratory work, an exit test of knowledge follows. Summing up the lesson, the questions that caused difficulties for students are analyzed. At the end of the lesson, you need to check and sign manual and put marks in the journal. Also, at the end of the lesson, the teacher must provide solved problems for homework. If you have questions, you should ask your teacher. Only students who have signed manual and problem book are allowed to attend the final lesson.

LABORATORY LESSON TIMELINE

Marking of absentees, formulation of a plan for conducting a laboratory lesson, its goals and objectives, and significance for the professional activities of a pharmacist — 5 minutes.

Answers to students' questions that arose during preparation for the lesson — 5 minutes.

Discussion of questions on the topic of the lesson, oral survey — 90 minutes.

Break — 15 minutes.

Analysis of the algorithm for performing laboratory work, answers to questions on solving situational problems — 10 minutes.

Completion of laboratory work — 55 minutes.

Summarizing results of the laboratory lesson. Checking practical exercises, problem books, formula books with final knowledge control and putting marks in the electronic journal — 10 minutes.

REQUIREMENTS FOR STUDENTS BY THE DEPARTMENT PHARMACEUTICAL CHEMISTRY WITH THE COURSE OF ADDITIONAL TRAINING AND RETRAINING

Requirements for students by the department of pharmaceutical chemistry with the course of additional training and retraining:

1. Comply with safety rules in the classrooms of the department (safety instructions have been carried out), comply with the internal labor regulations of the educational institution «BSMU». Occupational health and safety rules are set out in Appendix 1 to the manual.

2. Come to laboratory classes on time, according to the schedule. Late students are not allowed to attend class.

3. During laboratory classes, students must have gowns, hats, shoe covers, manuals for laboratory work, and a problem books. Students without gowns, manuals and problem books are not allowed to attend class. Students must comply with the Moral and Ethical Code of students studying at the educational institution «Belarusian State Medical University», including the basic rules of the student's dress code.

4. While working in the classroom of the department, it is necessary to maintain discipline and order, the maintenance of which is the responsibility of the head of the group and the person on duty assigned by him.

5. It is prohibited to bring outerwear, food products, drinks, tobacco products into the department classrooms, as well as eat food, drink drinks, and smoke. Students store personal belongings during class in specially designated places.

6. If you have any questions regarding safety precautions, you should contact the laboratory assistant or teacher.

7. Treat the property of the department (inventory, teaching aids, books, instruments, etc.) with care and attention; it is prohibited to remove objects and various equipment from classrooms without permission from the University Administration.

8. Comply with the rules of medical ethics and deontology, generally accepted standards of ethics and morality.

FIRE SAFETY REQUIREMENTS

Every student should know where fire extinguishing equipment is located and be able to use it.

In the event of an explosion, fire or other emergency situations, it is necessary to disconnect electrical equipment from the power grid and inform the head of the structural unit.

During a fire, windows and doors must not be opened or glass broken. When leaving the room, you must close all doors and windows behind you, as the influx of fresh air contributes to the rapid spread of fire. If necessary, call the fire service by calling 101.

In order to prevent daily exposure to harmful substances, students who have contact with them are required to:

1. At the end of laboratory work and classes, wash your hands with soap.
2. Do not visit the dining room, buffet, conference room, library, etc. in overalls.
3. Store overalls separately from outerwear.

I am familiar with the requirements of the department _____ 202_____ (signature)

Lesson 1

INTRODUCTION TO THE ACADEMIC DISCIPLINE «PHARMACEUTICAL CHEMISTRY». METHODS AND SOURCES OF OBTAINING MEDICINES

Objective: familiarize students with the main sections and areas of research, the most important terms of pharmaceutical chemistry and its connections with other sciences; pharmaceutical substances and medicinal products types of names, methods of medicinal substances classifications used in pharmaceutical chemistry; main sources and methods of obtaining medicinal substances.

Requirements for the initial level of knowledge: repeat the basic terms and definitions in the field of medicines circulation in the Republic of Belarus and the Eurasian Economic Union; principles of chemicals classification; methods for producing chemicals used in medicine manufacture and pharmacy.

Problems for discussion:

1. Main sections of pharmaceutical chemistry, areas of research and connections with other sciences.

2. Basic terms used in pharmaceutical chemistry.

3. Rules for the selection and procedure for assigning names of medicines. International nonproprietary names (INN) of pharmaceutical substances. National nonproprietary names of pharmaceutical substances. Trade names of medicines. Synonyms of medicines. Analogues.

4. Classifications of medicinal substances used in pharmaceutical chemistry: classification of medicinal substances depending on the chemical structure, anatomical-therapeutic-chemical classification (ATC), nosological, pharmacotherapeutic classification, etc.

5. Main stages in the history of pharmaceutical chemistry. Development of pharmaceutical chemistry on the territory of the modern Republic of Belarus. Modern problems and prospects for the development of pharmaceutical chemistry.

6. Modern approaches to the production of pharmaceutical substances. Main methods and sources of obtaining medicines. Use of natural compounds as medicines. Plants, fungi, animals, microorganisms, minerals, etc. as sources of medicines. Extraction of medicinal substances from natural sources. Extraction of biologically active compounds from edible, toxic and other mushrooms. Obtaining medicinal substances by chemical modification of natural compounds and complete chemical synthesis.

7. Examples of pharmaceutical substances complete chemical synthesis (for example, sartans, steroids, antitumor medicines, etc.). Basic chemical transformations underlying total chemical synthesis. Initial chemicals for synthesis.

8. Application of biotechnological methods, incl. microorganisms and genetic engineering to obtain medicinal substances.

9. Metabolomics and proteomics in the production of modern medicines. Ex homine medicines.

10. Examples of medicinal products obtained by these methods.

Assignments for student independent work

1. Indicate sources and methods of obtaining following medicines: potassium chloride, boric acid, potassium permanganate, formaldehyde, chloral hydrate, camphor, glucose, lactose, glycine, salicylic acid, resorcinol, sodium sulfacetamide, rutin, ascorbic acid, bendazole, caffeine, folic acid, tocilizumab, insulin, cyanocobalamin, streptomycin, paclitaxel, irinotecan, tocopherol acetate and riboflavin.

2. Please indicate international nonproprietary, trade, national nonproprietary and other names among the following medicinal products:

Azelastine-Xantis, Allergodil, Azelastine, Dimisto,Momat Rino Advance;

Viagra®, Viasan-LF, Viasil, Vizarsin®, Vizarsin®, Ku-tab®, Vildegra®, Gent®, Dynamico, Maxigra, Revatio®, Rijamp®, Sildenafil-FPO®, Sealex®, Sildenafil, Sildenafil VERTEX, Sildenafil-Xanthis, Sildenafil Cardio, Sildenafil-SZ, Sildenafil, Renewal EFFEX®, Sildenafil Juvena;

Taxotere®, Tautax®, Docetaxel-anhydrous, Docetaxel-Phylaxis, Docetera, Novotax®, Docetaxel, Docetaxel Sandoz®, Docetaxel trihydrate-Long Sheng Pharma Limited, Docetaxel-Keloon-Kazpharm, Docetaxel trihydrate, Taxelen,Docetaxel-Pharm-Synthesis, DOCETAXEL-PROMOMED.

Tasks to be completed in class

1. Fill out the table.

	Anti-septic	**Biolo-gical**	**Biotech-nological**	**Immuno-logical**	**Orphan**	**Radio-pharmaceutical**	**Homeo-pathic**	**Original/ Generic**
Lantus			+					
Albumin-bio-pharma								
Mastodinon								
Iodopol								
Oscillococ-cinum								
Poltech MIBI								
Aldurasim								
Mukosanin								
Tuberculosis vaccine (BCG)								
Genferon								
Sildenafil-20 maxpharma								

2. Find and decipher the Anatomical Therapeutic Chemical Classification (ATC) code for the following pharmaceutical substances (PS): acyclovir, carvedilol, tetracycline, clozapine, melphalan, glyceryl trinitrate, ibuprofen, triamcinolone acetonide, ciprofloxacin and cholecalciferol.

List of literature

1. *Pharmaceutical* chemistry : textbook / ed. G. V. Ramenskaya. – Moscow: GEOTAR-Media, 2023. – 384 p.

2. *Tsurkan, O. O.* Pharmaceutical chemistry. Analysis of the Medicinal Substances according to Functional Groups: study guide / O. O. Tsurkan. – Kyiv : AUS Medicine Publishing, 2018. – 152 p.

3. Lecture and information material.

Lesson 2

ENSURING THE QUALITY OF PHARMACEUTICAL SUBSTANCES AND MEDICINES. GENERAL CHARACTERISTICS OF PHARMACEUTICAL ANALYSIS. PHARMACOPOEIAL ANALYSIS

Objective: introduce students to modern requirements for medicines; principles of quality assurance of pharmaceutical substances and medicines; the quality control system for medicines in the Republic of Belarus; types of regulatory documentation regulating the quality of pharmaceutical substances and medicines; with the basic principles of pharmacopoeial analysis.

Requirements for the initial level of knowledge: repeat regulatory legal framework in the field of medicines circulation in the Republic of Belarus and the Eurasian Economic Union.

Problems for discussion:

1. Modern requirements for medicines: safety, effectiveness, quality.
2. Regulatory legal acts regulating the quality control of medicines and the Republic of Belarus. System for ensuring the quality of medicines at all stages of circulation.
3. Good Practice Standards: Good Research Practice (GRP), Good Laboratory Practice (GLP), Good Clinical Practice (GCP), Good Manufacturing Practice (GMP), Good Pharmacy Practice (GPP), Good Storage Practice (GSP), Good Distribution Practice (GDP), Good Pharmacovigilance Practice (GVP), etc.
4. Structure of the quality control system for medicines in the Republic of Belarus.
5. The problem of counterfeit medicines. Prerequisites and countermeasures against counterfeiting of medicines.
6. Regulatory documentation regulating the quality of pharmaceutical substances and medicines. State Pharmacopoeia of the Republic of Belarus (SPh RB), regulatory documents on the quality of pharmaceutical substances and medicinal products. Regional (European Pharmacopoeia, Pharmacopoeia of the Eurasian Economic Union) and national pharmacopoeia (British Pharmacopoeia, US Pharmacopoeia, State Pharmacopoeia of the Russian Federation, State Pharmacopoeia of the Republic of Kazakhstan, etc.), International Pharmacopoeia of the World Health Organization.
7. Pharmaceutical analysis as an integral part of pharmaceutical chemistry and a section of applied analytical chemistry. Features and types of pharmaceutical analysis. Main groups of analytical chemistry methods used in pharmaceutical analysis. General and specific pharmacopoeial monographs. Pharmacopoeial terminology.
8. Basic principles of pharmacopoeial analysis. Unification and standardization of similar tests.
9. Difference between medicines and biologically active food additives, medical devices and other pharmaceutical products. Concept of diagnostic test systems, approaches to their development and quality control.
10. Principles of synthetic and biotechnological medicines quality control: similarities and differences.

Assignments for student independent work

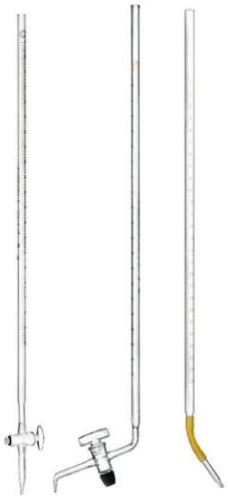
1. Identify glassware that could be used for pharmaceutical chemistry laboratory classes and indicate what it is intended for.

1 

2. 

3. 

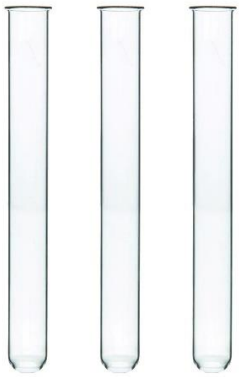
4. 

5. 

6. 

7. 

8. 

9. 

10. 

11. 

12. 

13. 

Tasks to be completed in class

1. Find information about the proposed medicines using the Unified Register of Registered Medicines of the Eurasian Economic Union.

Trade Name	**INN, grouping, chemical name**	**Dosage Form**	**Manufacturer**	**Type of medicinal medicine**
Suprastin®				
Angiorus				
Arifon® retard				
Adenuric® 80 mg				
Azelik				
Akriderm GHENTA				
Alkazol				
Aminazine®				
Aertal®				
Binnoferon alfa®				
VIOLETTA®, VENDIOL				
Vertigohel®				

2. Find information about the proposed medicines using the State Register of Medicines of the Republic of Belarus.

Tradename	**INN**	**Form release**	**Manufacturer**	**Applicant**	**Original / generic / biosimilar / innovative**
R-Mab					
Advagraf					
Angelique					
Brimogen					
Buprenorphine Sandoz					
Diavenon					
Gensulin N					
Oxyten					
Peptipak					
Detriol					
Enterogermina					
Dotagraph					

List of literature

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2. *Tsurkan, O. O.* Pharmaceutical chemistry. Analysis of the Medicinal Substances according to Functional Groups: study guide / O. O. Tsurkan. – Kyiv : AUS Medicine Publishing, 2018. – 152 p.

3. *Pharmaceutical* analysis: The study guide for students of higher schools / ed. by V. A. Georgiyants. – Kharkiv : NUPh Golden Pages, 2018. – 494 p.

4. Lecture and information material.

Lesson 3

STABILITY, SHELF LIFE AND MODERN APPROACHES TO DEGRADATION, NEUTRALIZATION AND DISPOSAL OF MEDICINES

Objective: familiarize students with the basic concepts related to the stability and shelf life of medicines; factors and processes affecting stability of pharmaceutical substances and medicines, requirements for their storage conditions; methods for testing stability of medicines; the main approaches to the degradation, neutralization and disposal of medicines.

Requirements for the initial level of knowledge: repeat the kinetics of chemical reactions; van't Hoff's rule.

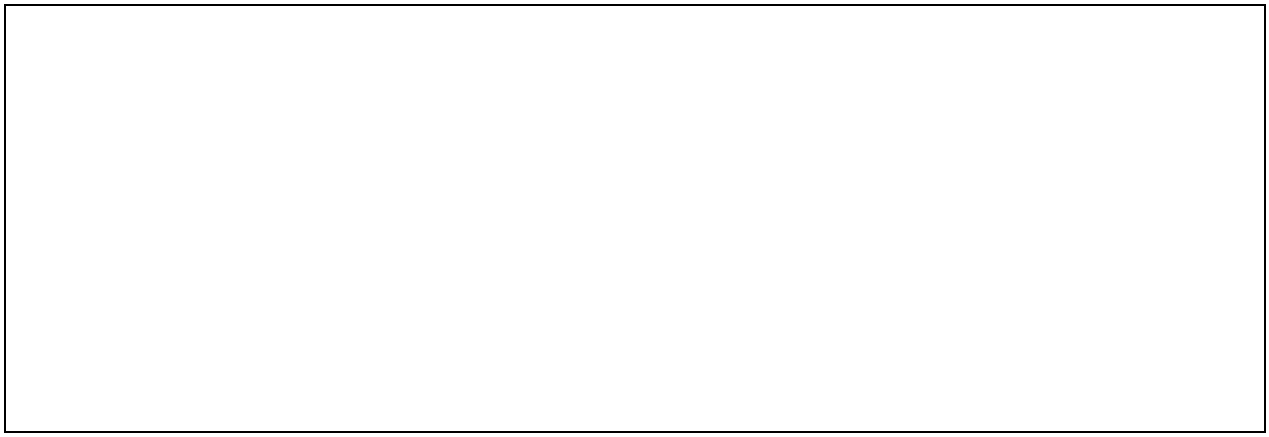
Problems for discussion:

1. Basic terms describing methodology for assessing stability and shelf life of medicines.
2. Environmental factors (physical, chemical, microbiological) affecting stability of medicines.
3. Types of chemical reactions leading to changes in the structure and properties of medicinal substances: oxidation, hydrolysis, polymerization, isomerization, etc.
4. Kinetic patterns of medicinal substances decomposition.
5. Methods for increasing stability of medicines. Stabilizers, preservatives, antioxidants, etc.
6. Methodology for assessing stability and determining shelf life of pharmaceutical substances and medicines. Long-term, accelerated and stress stability tests. Photostability studies. Predicting shelf life of medicines.
7. Calculation of medicinal products shelf life according to the markings on the packaging. Influence of packaging on stability of medicinal products. Requirements for storage containers and storage conditions for certain groups of pharmaceutical substances and medicinal products. Good storage practices. General and specific principles of medicines storage.
8. Concept of degradation, neutralization and disposal of medicines. Modern methods of medicine neutralization. Chemical disposal method as an option for pharmacophore degradation. Chemical reactions used to degrade medicines. Methods for monitoring completeness of medicines chemical degradation.
9. Examples of reagents used for the degradation of cytostatic and antimicrobial medicines.

Tasks to be completed in class

1. Using pharmacopoeial monograph of the State Pharmacopoeia of the Republic of Belarus (SPh RB) indicate storage group and storage conditions for the listed pharmaceutical substances: aluminum chloride hexahydrate, glutamic acid, levomenthol, formaldehyde 35% solution, bendazole hydrochloride, lidocaine hydrochloride, cholecalciferol, sunflower oil refined, theophylline-ethylenediamine hydrate, riboflavin.

2. Distribute proposed medicines into identical storage groups (storage on the same shelf), using ATC codes: analgin, rapimig, otrivin, fortix, nasobek, sumamigren, januvia, theotard, gastal, monocaps, dilasidome, nazol, glucophage, miconazole (cream), nitroglycerin, almagel neo, dopegit, etatsizin, ondansetron, lamisil, nystatin (ointment), amiodarone, digoxin, clonidine, tropisetron, griseofulvin, nasonex, singlelon, berodual, diadeon, glibenclamide-belmed.



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2. *Tsurkan, O. O.* Pharmaceutical chemistry. Analysis of the Medicinal Substances according to Functional Groups: study guide / O. O. Tsurkan. – Kyiv : AUS Medicine Publishing, 2018. – 152 p.

3. Lecture and information material.

Lesson 4

REAGENTS USED IN PHARMACOPOEIAL ANALYSIS. PROPERTIES OF PHARMACEUTICAL SUBSTANCES

Objective: familiarize students preparation of reagent solutions used in pharmacopoeial analysis; basic concepts related to the properties of pharmaceutical substances and methods of studying them; develop students' skills in reagents solutions used in pharmacopoeial analysis preparation; solubility of pharmaceutical substances determination; study of pharmaceutical substances by appearance and solubility.

Requirements for the initial level of knowledge: repeat concept of chemical substance crystal lattice; theories of acids and bases (Brønsted-Lowry, Lewis); quantitative description of acids and bases strength; general pharmacopoeial monographs of the State Pharmacopoeia of the Republic of Belarus.

Problems for discussion:

1. Section of the State Pharmacopoeia of the Republic of Belarus «Reagents». Preparation of reagent solutions, standard and buffer solutions.
2. Titrated solutions (standard solutions) used for titrimetric analysis. Standard substances for titrated solutions. Features of preparation and determination of titer (standardization). Correction factors.
3. Indicators. Features of indicators solutions used in pharmacopoeial analysis preparation.
4. Expiration dates and labeling of reagents.
5. Physical properties of pharmaceutical substances: state of aggregation, appearance, color, hygroscopicity, crystalline properties, polymorphism.
6. Solubility of pharmaceutical substances. Conventional terms denoting solubility.
7. Acid-base properties of pharmaceutical substances.

Assignments for student independent work

1. Fill out the table.

Titrant	Standardized by	Conditions for standardization	Equation of reactions	Indicator
Hydrochloric acid				
Sodium hydroxide				
Perchloric acid				
Sodium methylate				
Mercury (II) nitrate				
Sodium edetate				
Silver nitrate				
Mercury (I) nitrate				

End of the table

Titrant	Standardized by	Conditions for standardization	Equation of reactions	Indicator
Iodine				
Sodium thiosulfate				
Iodinchlorid				
Potassium iodate				
Potassium bromate				
Sodium nitrite				
Potassium permanganate				
Cerium (IV) sulfate				

Algorithm for performing laboratory work
«Preparation of reagent solutions for pharmacopoeial analysis.
Quality control of a pharmaceutical substance according to the section
"Description (Properties)"»

Goal of the work: develop students' skills for preparing reagents used in pharmacopoeial analysis and assessing properties of pharmaceutical substances.

1. Preparation of reagent solutions for pharmacopoeial analysis

Ammonium chloride solution (50 ml)

5.35 g of ammonium chloride R (NH_4Cl) are dissolved in water R and diluted to 50 ml with the same solvent.

Potassium dichromate solution (50 ml)

5.3 g of potassium dichromate R ($K_2Cr_2O_7$) are dissolved in water R and diluted to 50 ml with the same solvent.

Potassium ferricyanide solution (50 ml)

Wash 2.5 g of potassium ferricyanide R ($K_3[Fe(CN)_6]$) with a small amount of water R, dissolve in water R and dilute to a volume of 50 ml with the same solvent. Solution is prepared immediately before use.

Potassium ferrocyanide solution (50 ml)

2.65 g of potassium ferrocyanide R ($K_4[Fe(CN)_6]\times 3H_2O$) are dissolved in water R and diluted to 50 ml with the same solvent.

Potassium thiocyanate solution (50 ml)

4.85 g of potassium thiocyanate R (KSCN) are dissolved in water R and diluted to 50 ml with the same solvent.

***Barium chloride solution R1* (50 ml)**

3.05 g of barium chloride R ($BaCl_2$) are dissolved in water R and diluted to 50 ml with the same solvent.

Potassium permanganate solution (50 ml)

1.50 g of potassium permanganate R ($KMnO_4$) is dissolved in water R and diluted to 50 ml with the same solvent

***Silver nitrate solution R1* (50 ml)**

2.125 g of silver nitrate R ($AgNO_3$) are dissolved in water R and diluted to 50 ml with the same solvent.

Copper (II) sulfate solution (50 ml)

6.25 g of copper (II) sulfate R ($CuSO_4 \times 5H_2O$) are dissolved in water R and diluted to 50 ml with the same solvent.

Hydrazine sulfate solution (50 ml)

Dissolve 0.50 g of hydrazine sulfate R in water R and dilute with water R to a volume of 50.0 ml. Solution is kept for 4–6 hours.

Yellow solution (50 ml)

2.30 g of iron (III) chloride R are placed in a volumetric flask with a capacity of 50.0 ml, dissolved in 45 ml of a mixture of hydrochloric acid R — water R (25:975, v/v) and adjusted to a volume of 50.0 ml with the same solvent. 1 ml of solution should contain $FeCl_3\times 6H_2O$ 45.0 mg.

Red solution (50 ml)

3.00 g of cobalt chloride R is placed in a 50.0 ml volumetric flask, dissolved in 45 ml of a mixture of hydrochloric acid R — water R (25:975, v/v) and diluted to a volume of 50.0 ml with the same solvent. 1 ml of solution should contain $CoCl_2\times 6H_2O$ 59.5 mg.

Blue solution (50 ml)

3.15 g of copper sulfate R is placed in a 50.0 ml volumetric flask, dissolved in 45 ml of a mixture of hydrochloric acid R - water R (25:975, v/v) and adjusted to a volume of 50.0 ml with the same solvent. 1 ml of solution should contain $CuSO_4\times 5H_2O$ 62.4 mg.

2. Assess appearance and solubility (description (properties)) of the pharmaceutical substance in water. Make a conclusion about the compliance of the test sample with the State Pharmacopoeia of the Republic of Belarus.

List of substances

1. Sodium chloride
2. Magnesium sulfate heptahydrate
3. Corn starch
4. Sodium citrate
5. Potassium permanganate
6. Lactose monohydrate
7. Glycine
8. Potassium chloride
9. Sucrose
10. Caffeine
11. Iodine
12. Riboflavin
13. Sulfanilamide

SOLUBILITY

To carry out the test, use no more than 111 mg of the test sample (for each solvent) and no more than 30 ml of each solvent.

Dissolution process

Shake vigorously for 1 minute and maintain at a temperature of (25.0 ± 0.5) °C for 15 minutes. If the test sample is not completely dissolved, repeat shaking for 1 minute and maintain at a temperature of (25.0 ± 0.5) °C for 15 minutes.

Methodology

100 mg of finely ground test sample is placed in a test tube (inner diameter — 16 mm, length ─ 160 mm) with a stopper, 0.1 ml of solvent is added and the dissolution process is carried out as described above. If the test sample has completely dissolved, it is considered very soluble.

If the test sample is not completely dissolved, add 0.9 ml of solvent and carry out the dissolution process as described above. If the test sample has completely dissolved, it is considered readily soluble.

If the test sample is not completely dissolved, add 2.0 ml of solvent and carry out the dissolution process. If the test sample has completely dissolved, it is considered soluble.

If the test sample is not completely dissolved, add 7.0 ml of solvent and carry out the dissolution process as described above. If the test sample has completely dissolved, it is considered moderately soluble.

If the test sample is not completely dissolved, 10 mg of finely ground test sample is placed in a stoppered tube, 10.0 ml of solvent is added and the dissolution process is carried out as described above. If the test sample has completely dissolved, it is considered slightly soluble.

If the test sample is not completely dissolved, 1 mg of finely ground test sample is placed in a stoppered tube, 10.0 ml of solvent is added and the dissolution process is carried out as described above. If the test sample has completely dissolved, it is considered to be very slightly soluble.

Description (properties): *Appearance:* *Solubility:* *Conclusion:*

List of literature

1. *Pharmaceutical* chemistry : textbook / ed. G. V. Ramenskaya. – Moscow : GEOTAR-Media, 2023. – 384 p.

2. *Tsurkan, O. O.* Pharmaceutical chemistry. Analysis of the Medicinal Substances according to Functional Groups: study guide / O. O. Tsurkan. – Kyiv : AUS Medicine Publishing, 2018. – 152 p.

3. *Pharmaceutical* analysis : The study guide for students of higher schools / ed. by V. A. Georgiyants. – Kharkiv : NUPh Golden Pages, 2018. – 494 p.

4. *European* Pharmacopeia / European Directorate for the quality of medicines and healthcare. 10th edition, Supplement 10.0. Vol. 1. Council of Europe, Strasbourg, 2019. – 4312 p.

5. Lecture and information material.

Lesson 5

TITRIMETRIC METHODS USED IN PHARMACEUTICAL ANALYSIS. GRAVIMETRY

Objective: familiarize students with the principles of basic chemical methods of analysis and areas of their application in pharmaceutical analysis; develop in students' skills of pharmaceutical substances quantitative determination using titrimetric methods of analysis.

Requirements for the initial level of knowledge: repeat chemical equilibrium in analytical chemistry; gravimetric method of analysis; titrimetric methods of analysis.

Problems for discussion:

1. Chemical methods of analysis. Gravimetric method of analysis.

2. Titrimetric methods of analysis. Acid-base titration in aqueous, aqueous-organic and non-aqueous media. Determination of nitrogen in organic compounds. Titrants, analytes, determination of titration end point, implementation features and application in pharmaceutical analysis.

3. Methods of redox titration (iodometry, chloriodometry, iodometry, nitrimetry (determination of amine nitrogen in compounds that contain a primary aromatic amino group), permanganatometry, cerimetry, dichromatometry). Titrants, analytes, determination of titration end point, implementation features and application in pharmaceutical analysis.

4. Methods of complexometric titration (complexometry). Pharmacopoeial conditions for complexometric titration. Titrants, analytes, determination of titration end point, implementation features and application in pharmaceutical analysis.

5. Methods of precipitation titration (argentometry). Titrants, analytes, determination of titration end point, implementation features and application in pharmaceutical analysis.

Assignments for student independent work

1. Fill out the table.

Type of titration	**Titrant**	**Method for determining titration end point**	**Chemical reaction**	**Special titration conditions (temperature, speed, catalysts, pH, etc.)**	**Examples of pharmaceutical substances from the SPh of the Republic of Belarus**
Acidimetric in aqueous media					
Acidimetric in aqueous-organic medium					
Acidimetric in non-aqueous medium					
Alkalimetric in aqueous media					
Alkalimetric in aqueous-organic medium					
Alkalimetric in non-aqueous medium					
Nitritometric					
Bromatometric, bromometric					

End of the table

Type of titration	**Titrant**	**Method for determining titration end point**	**Chemical reaction**	**Special titration conditions (temperature, speed, catalysts, pH, etc.)**	**Examples of pharmaceutical substances from the SPh of the Republic of Belarus**
Iodatometric					
Iodometric					
Chloriodometric					
Permanganometric					
Dichromatometric					
Cerimetric					
Argentometric					
Complexometric					

Algorithm for performing laboratory work «Quality control of potassium iodide and benzoic acids according to the section "Quantitative determination"»

Goal of the work: develop in students skills for quantitative determination of potassium iodide and benzoic acid using titrimetric methods of analysis.

1. Quality control of potassium iodide according to the section «QUANTITATIVE DETERMINATION» of the SPh of the Republic of Belarus.

Dissolve 1,500 g of the test sample in water R and dilute to a volume of 100.0 ml with the same solvent. To 20.0 ml of the resulting solution add 40 ml of hydrochloric acid R and titrate with 0.05 M potassium iodate solution until the color changes from red to yellow. Add 5 ml of chloroform R and continue titration, vigorously shaking, until the chloroform layer becomes discolored.

1 ml of 0.05 M potassium iodate solution corresponds to 16.60 mg KI.

According to the SPh of the Republic of Belarus content of potassium iodide in the substance must be no less than 99.0% and no more than 100.5% (in terms of dry matter).

Reaction equations:

Formulas and calculations:

Conclusion:

2. Quality control of benzoic acid according to the section «QUANTITATIVE DETERMINATION» of the SPh of the Republic of Belarus.

0.200 g of the test sample is dissolved in 20 ml of 96% alcohol R and titrated with 0.1 M sodium hydroxide solution until the color of the solution changes from yellow to violet-red, using 0.1 ml of phenol red solution R as an indicator.

A correction factor for the alkali solution (based on HCl) is preliminarily established.

1 ml of 0.1 M sodium hydroxide solution corresponds to 12.21 mg of $C_7H_6O_2$.

According to the SPh of the Republic of Belarus content of benzoic acid in the substance must be no less than 99.0% and no more than 100.5%.

Reaction equation:

Formulas and calculations:

Conclusion:

List of literature

1. *Pharmaceutical* chemistry : textbook / ed. G. V. Ramenskaya. – Moscow : GEOTAR-Media, 2023. – 384 p.

2. *Tsurkan, O. O.* Pharmaceutical chemistry. Analysis of the Medicinal Substances according to Functional Groups: study guide / O. O. Tsurkan. – Kyiv : AUS Medicine Publishing, 2018. – 152 p.

3. *Pharmaceutical* analysis: The study guide for students of higher schools / ed. by V. A. Georgiyants. – Kharkiv : NUPh Golden Pages, 2018. – 494 p.

4. *European* Pharmacopeia / European Directorate for the quality of medicines and healthcare. 10th edition, Supplement 10.0. Vol. 1. Council of Europe, Strasbourg, 2019. – 4312 p.

5. Lecture and information material.

Lesson 6

SPECTROMETRIC AND THERMAL METHODS USED IN PHARMACEUTICAL ANALYSIS

Objective: familiarize students with the principles of basic spectrometric and thermal methods of analysis and areas of their application in pharmaceutical analysis; develop in students' skills of medicines quantitative determination by means of spectrometric methods of analysis.

Requirements for the initial level of knowledge: repeat nature and properties of electromagnetic radiation; classification of spectrometric methods of analysis; value of temperature as a measure of molecules kinetic energy; nature of thermal radiation and its characteristics.

Problems for discussion:

1. Spectrometric methods of analysis. Absorption methods (atomic absorption spectrometry, molecular absorption spectrometry in the ultraviolet and visible regions, infrared spectrometry, nuclear magnetic resonance spectrometry). Principle of the method, equipment used and application in pharmaceutical analysis.

2. Emission spectrometric methods of analysis (atomic emission spectrometry, fluorimetry, X-ray fluorescence spectrometry). Principle of the method, equipment used and application in pharmaceutical analysis.

3. Spectrometric methods based on the scattering of electromagnetic radiation (Raman spectrometry, giant Raman spectrometry, nephelometry, turbidimetry). Principle of the method, equipment used and application in pharmaceutical analysis.

4. Refractometry. Chiroptical methods of analysis (polarimetry, circular dichroism spectrometry). Principle of the method, equipment used and application in pharmaceutical analysis.

5. Thermal methods of analysis (thermogravimetry, differential thermal analysis, differential scanning calorimetry).

Assignments for student independent work

1. Fill out the table.

Method	**Principle of the method**	**Device structure**	**Wavelength range used**	**Application in pharm. analysis**	**Examples of pharmaceutical substances**
Atomic absorption spectrometry					
Molecular absorption spectrometry in the ultraviolet region					
Molecular absorption spectrometry in the visible region					
Infrared spectrometry					
Atomic emission spectrometry					
Fluorimetry					
Raman spectrometry					
Nephelometry					

End of the table

Method	Principle of the method	Device structure	Wavelength range used	Application in pharm. analysis	Examples of pharmaceutical substances
Turbidimetry					
Refractometry					
Polarimetry					

Algorithm for performing laboratory work
«Spectrophotometric determination of chloramphenicol in capsules and quality control of magnesium sulfate solution according to the section "Quantitative determination"»

Goal of the work: develop in students skills for quantitative determination of chloramphenicol in capsules and magnesium sulfate using spectrometric methods of analysis.

1. Spectrophotometric determination of chloramphenicol in capsules.

An exact weighing of the capsule contents is dissolved in water R and brought to a volume of 100.0 ml with the same solvent. Filtered 2.00 ml of the resulting solution (filtrate) is diluted with water R to a volume of 100.0 ml. Optical density of the resulting solution relative to water R is measured at a maximum at 278 nm. Content of $C_{11}H_{12}CI_2N_2O_5$ is calculated taking into account the specific absorption index of 297. Content of chloramphenicol in one capsule should not differ from the declared one by more than ±10%.

Formulas and calculations:

Conclusion:

2. Quality control of magnesium sulfate solution 5% according to the section «QUANTITATIVE DETERMINATION» of the SPh of the Republic of Belarus.

Composition of the medicinal product:

Magnesium sulfate heptahydrate – 5.0 g

Purified water – up to 100 ml

Refractive index is determined. Refractive index factor for the solution under study is F = 0.00095.

According to the SPh of the Republic of Belarus permissible deviation from the prescribed mass is ±4%.

Formulas and calculations: *Conclusion:*

List of literature

1. *Pharmaceutical* chemistry : textbook / ed. G. V. Ramenskaya. – Moscow : GEOTAR-Media, 2023. – 384 p.

2. *Tsurkan, O. O.* Pharmaceutical chemistry. Analysis of the Medicinal Substances according to Functional Groups: study guide / O. O. Tsurkan. – Kyiv : AUS Medicine Publishing, 2018. – 152 p.

3. *Pharmaceutical* analysis : The study guide for students of higher schools / ed. by V. A. Georgiyants. – Kharkiv : NUPh Golden Pages, 2018. – 494 p.

4. *European* Pharmacopeia / European Directorate for the quality of medicines and healthcare. 10th edition, Supplement 10.0. Vol. 1. Council of Europe, Strasbourg, 2019. – 4312 p.

5. Lecture and information material.

Lesson 7

CHROMATOGRAPHIC AND BIOLOGICAL METHODS USED IN PHARMACEUTICAL ANALYSIS

Objective: familiarize students with the principles of basic chromatographic and biological methods of analysis and scope of their application in pharmaceutical analysis; develop students' skills for identifying pharmaceutical substances using chromatographic analysis methods.

Requirements for the initial level of knowledge: repeat theoretical foundations of chromatographic methods of analysis; chromatographic parameters used for identification and quantitation; basics of antigen-antibody interaction; concept of haptens; methods for detecting immunochemical reactions; determination of antibiotic activity.

Problems for discussion:

1. Chromatographic separation methods.

2. Gas chromatography. Principle of the method, equipment (materials) used and application in pharmaceutical analysis.

3. Liquid chromatography (thin layer (TLC) and paper chromatography, high performance liquid chromatography (liquid chromatography), size exclusion chromatography, ion exchange chromatography). Supercritical fluid chromatography. Principle of the method, equipment (materials) used and application in pharmaceutical analysis.

4. Electrophoresis. Capillary electrophoresis. Principle of the method, equipment (materials) used and application in pharmaceutical analysis.

5. Mass spectrometry. Combination of mass spectrometry with chromatographic methods. Principle of the method, equipment (materials) used and application in pharmaceutical analysis.

6. Biological methods of analysis. Protein-binding analysis methods (immunochemical and receptor).

7. Microbiological determination of antibiotic activity (diffusion method, turbidimetry method).

Assignments for student independent work

1. Fill out the table.

Type	**Principle of separation (indicating MPh and IPh)**	**Main components of the device**	**Possible detectors**	**Application in pharmacopoeial analysis**
Gas chromatography				
High performance liquid chromatography				
Thin layer chromatography				
Paper chromatography				
Size exclusion chromatography				
Ion exchange chromatography, incl. ion pair				
Supercritical fluid chromatography				
Electrophoresis				
Capillary electrophoresis				

Algorithm for performing laboratory work
«Quality control of rutoside trihydrate according
to the section "Authenticity": TLC»

Goal of the work: develop students' skills in assessing authenticity of rutoside trihydrate using TLC.

Test solution: crush 1 tablet of ascorutin (rutascorbine), dissolve in ethanol R and bring to a volume of 20.0 ml with the same solvent, filter.

Reference solution: 25 mg of pharmacopoeial reference standard (PRS) of rutoside trihydrate is dissolved in ethanol R and diluted to a volume of 10.0 ml with the same solvent.

Plate: TLC plate with a layer of silica gel GP.

Mobile phase: butanol R – anhydrous acetic acid R – water R – methyl ethyl ketone R – ethyl acetate R (5:10:10:30:50, v/v/v/v/v).

Sample volume applied: 10 µl.

Mobile phase front: at least 10 cm from the start line.

Drying: on air.

Development: plate is sprayed with a mixture of 7.5 ml of a solution of 10 g/l potassium ferricyanide R ($K_3[Fe(CN)_6]$) and 2.5 ml of a solution of iron (III) chloride R1 and viewed for 10 minutes.

Results: on the chromatogram of the test solution a main spot is detected, corresponding in location, color and size to the main spot on the chromatogram of the reference solution.

Type of chromatographic plates (draw):   *Conclusion:*

List of literature

1. *Pharmaceutical* chemistry : textbook / ed. G. V. Ramenskaya. – Moscow : GEOTAR-Media, 2023. – 384 p.
2. *Tsurkan, O. O.* Pharmaceutical chemistry. Analysis of the Medicinal Substances according to Functional Groups: study guide / O. O. Tsurkan. – Kyiv : AUS Medicine Publishing, 2018. – 152 p.
3. *Pharmaceutical* analysis: The study guide for students of higher schools / ed. by V. A. Georgiyants. – Kharkiv : NUPh Golden Pages, 2018. – 494 p.
4. *European* Pharmacopeia / European Directorate for the quality of medicines and healthcare. 10th edition, Supplement 10.0. Vol. 1. Council of Europe, Strasbourg, 2019. – 4312 p.
5. Lecture and information material.

Lesson 8

FINAL LESSON ON THE TOPIC «GENERAL ISSUES OF PHARMACEUTICAL CHEMISTRY AND METHODS USED IN PHARMACEUTICAL ANALYSIS»

Objective: monitoring students' knowledge on topics 1–7.
Test questions:

Block 1. General issues of pharmaceutical chemistry

1. Terminology used in pharmaceutical chemistry: medicine, medicine, pharmaceutical substance, excipient, dosage form, antiseptic medicine, homeopathic medicine, original medicine, generic medicine, biological medicine, immunological medicinal product, radiopharmaceutical medicinal product, etc.

2. Rules for choosing names of medicines. Names of pharmaceutical substances: chemical name, INN, national name. Trade names of medicines.

3. Classifications of medicinal substances used in pharmaceutical chemistry: chemical classification, ATC classification.

4. Sources and methods of obtaining medicines: extracting of medicines from natural sources, chemical modification of natural compounds.

5. Sources and methods of obtaining medicines: obtaining medicines by complete chemical synthesis, use of biotechnological and microbiological methods to obtain medicines.

6. Modern requirements for medicines: safety, effectiveness, quality. System for ensuring quality of medicines at all stages of creation and use. Good Practice Standards: Good Research Practice (GRP), Good Laboratory Practice (GLP), Good Clinical Practice (GCP), Good Manufacturing Practice (GMP), Good Distribution Practice (GDP), Good Pharmacy Practice (GPP), Good Storage Practice (GSP), good pharmacovigilance practice (GVP), etc.

7. Structure of quality control system for medicines in the Republic of Belarus. Counterfeiting of medicines.

8. Regulatory documentation regulating the quality of pharmaceutical substances and medicines. State Pharmacopoeia of the Republic of Belarus: structure, pharmacopoeial monographs. Basic principles of pharmacopoeial analysis. Pharmacopoeia of the EAEU.

9. Stability of medicines, its types. Factors affecting stability: physical, microbiological, chemical. Methods for increasing stability: physical, chemical (stabilizers), antimicrobial (preservatives).

10. Stability tests (decision of the UEC Board of 2018 No. 69 with amendments and additions): long-term, accelerated, stress, intermediate. Expiration date (Law of the Republic of Belarus dated 2006 No. 161-Z as amended and supplemented), expiration date (decision of the UEC Board dated 2018 No. 69 as amended and supplemented).

11. Classification of pharmaceutical substances and medicines according to storage conditions. Examples of individual groups according to storage conditions.

12. Pharmaceutical analysis: definition, features, types (pharmacopoeial, step-by-step quality control in industrial manufacture, express analysis of extemporaneous dosage forms, biopharmaceutical analysis).

13. Classification of reagents. Preparation of reagent solutions, standard and buffer solutions. Expiration dates and labeling of reagents. Indicators. Features of indicators solutions used in pharmacopoeial analysis preparation.

14. Physical properties of substances: state of aggregation, appearance, color, hygroscopicity, crystallinity, polymorphism.

15. Solubility of pharmaceutical substances. Conventional terms denoting solubility. Method for determining solubility. Acid-base properties of medicinal substances (basic theories of acids and bases). Henderson-Hasselbach equation.

Block 2. Analytical methods used in pharmaceutical chemistry

1. Gravimetric method of analysis. Essence of the method. Stages of gravimetric analysis. Application in pharmaceutical analysis.

2. Titrimetric methods of analysis: classification (by type of chemical reaction, by titration method). Titrated solutions, their standardization (establishment of correction factor: k).

3. Determination of nitrogen in organic compounds (Kjeldahl method).

4. Acid-base titration in aqueous media. Essence of the method (titrant, equations for the reactions occurring, establishing the titration end point (TEP) (indicators, etc.), execution conditions). Application in pharmaceutical analysis.

5. Acid-base titration in aqueous-organic media. Essence of the method. Application in pharmaceutical analysis.

6. Acid-base titration in non-aqueous media. Essence of the method. Application in pharmaceutical analysis.

7. Complexometric titration: complexometry. Essence of the method. Application in pharmaceutical analysis.

8. Precipitation titration: argentometry. Essence of the method. Application in pharmaceutical analysis.

9. Redox titration: iodine(o)metry, chloriodometry, iodatemetry, bromatometry. Essence of methods. Application in pharmaceutical analysis.

10. Redox titration: nitritometry, permanganatometry, dichromatometry, cerimetry. Essence of methods. Application in pharmaceutical analysis.

11. Spectrometric methods: general characteristics and classification.

12. Atomic absorption spectrometry. Basic principles. Device structure. Application in pharmaceutical analysis.

13. Molecular absorption spectrometry in the ultraviolet and visible regions. Basic principles. Devices structure, their differences. Application in pharmaceutical analysis.

14. Infrared spectrometry. Basic principles. Device structure. Application in pharmaceutical analysis.

15. Nuclear magnetic resonance spectrometry. Basic principles. Device structure. Application in pharmaceutical analysis.

16. Atomic emission spectrometry. Basic principles. Device structure. Application in pharmaceutical analysis.

17. Fluorimetry. Basic principles. Device structure. Application in pharmaceutical analysis.

18. Spectrometric methods based on scattering of electromagnetic radiation (Raman spectrometry, nephelometry, turbidimetry). Basic principles. Device structure. Application in pharmaceutical analysis.

19. Refractometry. Basic principles. Device structure. Application in pharmaceutical analysis.

20. Chiroptical methods of analysis (polarimetry, circular dichroism spectrometry). Basic principles. Device design. Application in pharmaceutical analysis.

21. Chromatographic methods of analysis. General characteristics and classification.

22. Gas chromatography. Basic principles. Classification. Gas chromatograph device. Detectors. Application in pharmaceutical analysis.

23. TLC. Basic principles. Methods of obtaining. Basic chromatographic parameters. Application in pharmaceutical analysis.

24. HPLC. Basic principles. Liquid chromatograph device. Detectors. Application in pharmaceutical analysis.

25. Types of liquid chromatography (size exclusion chromatography, ion exchange chromatography). Supercritical fluid chromatography. Basic principles. Application in pharmaceutical analysis.

26. Electrophoresis. Capillary electrophoresis. Basic principles. Classification. Application in pharmaceutical analysis.

27. Mass spectrometry. Basic principles and stages. Basic ionization methods. Application in pharmaceutical analysis. Combination of mass spectrometry with chromatographic methods.

28. Thermal methods of analysis: thermogravimetry, differential thermal analysis, differential scanning calorimetry. Basic principles. Application in pharmaceutical analysis.

29. Protein-binding methods of analysis: immunochemical methods. Basic principles. Classification. Application in pharmaceutical analysis.

30. Protein-binding methods of analysis: immunofluorescence and receptor methods. Basic principles. Classification. Application in pharmaceutical analysis.

31. Biological methods of analysis: determination of antibiotic activity. General principles. Methodology. Application in pharmaceutical analysis.

List of literature

See the literature lists for lessons 1–7.

Lesson 9

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

Objective: familiarize students with the essence of the chemical processes occurring during the pharmacopoeial identification of inorganic cations and anions, as well as conditions for carrying out identification reactions; develop students' skills in identification (authentication) of inorganic cations and anions in accordance with the requirements of the pharmacopeical monograph of the State Pharmacopoeia of the Republic of Belarus.

Requirements for the initial level of knowledge: repeat chemical methods for detecting inorganic substances; systematic and fractional analysis.

Problems for discussion:

1. General characteristics of identification methods used in pharmacopoeial analysis (identification). First and second identification.

2. Chemical identification methods. Pharmacopeical monograph of the State Pharmacopoeia of the Republic of Belarus «Reactions of authenticity (identification) to ions and functional groups». Partial identification reactions.

3. Identification reactions of inorganic cations: aluminum, ammonium salts, ammonium salts and salts of volatile bases, bismuth, iron, potassium, calcium, magnesium, sodium, mercury, lead, silver, antimony, zinc.

4. Identification reactions of inorganic anions: bromides, iodides, carbonates and bicarbonates, arsenic (arsenites and arsenates), nitrates, nitrites, silicates, sulfates, sulfites, phosphates, chlorides.

Assignments for student independent work

1. Fill out the table.

Ion	Reagent	Features of the event	Analytical effect	Equation of the reaction
Al^{3+}				
NH^{4+}				
Ammo-nium salts and volatile base salts				
Bi^{3+}				
Fe^{2+}				
Fe^{3+}				
K^{+}				
Ca^{2+}				
Mg^{2+}				
As(III)				
As(V)				
Na^{+}				
Hg^{2+}				
Pb^{2+}				

End of the table

Ion	Reagent	Features of the event	Analytical effect	Equation of the reaction
Ag^{+}				
Sb^{3+}				
Sb^{5+}				
Zn^{2+}				
Br^{-}				
I^{-}				
Cl^{-}				
CO_3^{2-}				
NO^{3-}				
NO^{2-}				
SiO_3^{2-}				
SO_4^{2-}				
SO_3^{2-}				
PO_4^{3-}				

Algorithm for performing laboratory work
«Pharmacopeical identification of inorganic cations and anions using chemical reactions»

Goal of the work: develop students' skills in identifying inorganic cations and anions using chemical reactions.

Work order

Cation identification reactions

Aluminum (Al^{3+})

About 15 mg of the test sample is dissolved in 2 ml of water. To the resulting solution or the solution specified in the pharmacopeical monograph add 0.5 ml of diluted hydrochloric acid R and about 0.5 ml of thioacetamide reagent R; no precipitate is formed. Then a diluted sodium hydroxide solution R is added dropwise, a gel-like white precipitate is formed, which dissolves with the subsequent addition of a diluted sodium hydroxide solution R. Ammonium chloride solution S is gradually added to the resulting solution, a gel-like white precipitate is again formed.

Reaction equations indicating the analytical effect:
Conclusion:

Ammonium salts and volatile base salts

About 20 mg of the test sample is dissolved in 2 ml of water R. To the resulting solution or to 2 ml of the solution specified in the pharmacopeical monograph add 2 ml of diluted sodium hydroxide solution R. When the solution is heated, ammonia vapors are released, which are detected by the smell and alkaline reaction (blue color of litmus paper).

Reaction equations indicating the analytical effect:
Conclusion:

Bismuth (Bi^{3+})

a) 0.5 g of the test sample is dissolved in 10 ml of diluted hydrochloric acid R. The resulting solution or 10 ml of the solution specified in the pharmacopeical monograph is boiled for 1 minute, cooled and, if necessary, filtered. Add 20 ml of water to 1 ml of the resulting solution; a white or light yellow precipitate is formed, color of which changes to brown after adding 0.05 ml to 0.1 ml of sodium sulfide solution R.

b) About 45 mg of the test sample is dissolved in 10 ml of diluted nitric acid R. The resulting solution or 10 ml of the solution specified in the pharmacopeical monograph is boiled for 1 minute, cooled and, if necessary, filtered. To 5 ml of the resulting solution add 2 ml of a solution of 100 g/l thiourea R; a yellowish-orange color appears or an orange precipitate forms. Then add 4 ml of a solution of 25 g/l sodium fluoride R; the solution does not discolor within 30 minutes.

c) A weighed sample of the test sample containing about 50 mg of bismuth ion is shaken with 5 ml of diluted sulfuric acid R and filtered. Add 2 drops of potassium iodide solution R1 to the filtrate; a black precipitate is formed, soluble in excess of the reagent to form yellowish-orange solutions.

Reaction equations indicating the analytical effect:

Conclusion:

Iron (Fe^{2+}) and (Fe^{3+})

a) A sample of the test sample containing about 10 mg of iron ion (Fe^{2+}) is dissolved in 1 ml of water R. To the resulting solution or to 1 ml of the solution specified in the pharmacopeical monograph, add 1 ml of potassium ferricyanide solution R; a blue precipitate is formed, which does not dissolve when diluted hydrochloric acid R is added.

b) A weighed sample of the test sample containing about 1 mg of iron ion (Fe^{3+}) is dissolved in 30 ml of water R. To the resulting solution or to 3 ml of the solution specified in the pharmacopeical monograph, add 1 ml of diluted hydrochloric acid S and 1 ml of potassium thiocyanate solution R; a red color appears. Take two portions of the resulting solution, 1 ml each. Add 5 ml of isoamyl alcohol R or 5 ml of ether R to one portion, shake and leave until separation; the organic layer turns pink.

c) Test sample containing at least 1 mg of iron ion (Fe^{3+}) is dissolved in 1 ml of water R. To the resulting solution or to 1 ml of the solution specified in the pharmacopeical monograph, add 1 ml of potassium ferrocyanide solution R; a blue precipitate is formed, which does not dissolve when adding 5 ml of diluted hydrochloric acid R.

Reaction equations indicating the analytical effect:

Analytical effect:

Conclusion:

Potassium (K^+)

a) 0.1 g of the test sample is dissolved in 2 ml of water R. To the resulting solution or to 2 ml of the solution specified in the pharmacopeical monograph, add 1 ml of sodium carbonate solution R and heat; no precipitate forms. Add 0.05 ml of sodium sulfide solution R to the hot solution; no precipitate forms. The solution is cooled in ice water, 2 ml of a solution of 150 g/l tartaric acid R is added and left to settle; a white crystalline precipitate is formed.

b) About 40 mg of the test sample is dissolved in 1 ml of water R. To the resulting solution or to 1 ml of the solution specified in the pharmacopeical monograph, add 1 ml of diluted acetic acid R and 1 ml of a freshly prepared solution of 100 g/l sodium cobaltinitrite R; A yellow or orange-yellow precipitate immediately forms.

c) Potassium salt added to a colorless flame turns it violet or, when viewed through blue glass, purple-red.

Reaction equations indicating the analytical effect:

Conclusion:

Calcium (Ca^{2+})

a) About 20 mg or the amount of the test sample specified in the pharmacopeical monograph is dissolved in 5 ml of acetic acid R. To the resulting solution add 0.5 ml of a solution of potassium ferrocyanide R (potassium hexacyanoferrate (II)); the solution remains clear. About 50 mg of ammonium chloride is added to the solution; a white crystalline precipitate is formed.

b) To 1 ml of a solution containing the test sample in an amount of 2-20 mg of calcium ion (Ca^{2+}), add 1 ml of a solution of 40 g/l ammonium oxalate R; a white precipitate is formed, insoluble in dilute acetic acid R and ammonia solution R, soluble in dilute mineral acids.

c) Calcium salt, moistened with hydrochloric acid and added to a colorless flame, colors it orange-red.

Reaction equations indicating the analytical effect:

Conclusion:

Magnesium (Mg^{2+})

About 15 mg of the test sample is dissolved in 2 ml of water R. To the resulting solution or to 2 ml of the solution specified in the pharmacopeical monograph add 1 ml of diluted ammonia solution R1; a white precipitate is formed, which dissolves when 1 ml of ammonium chloride solution R is added. 1 ml of disodium hydrogen phosphate solution R is added to the resulting solution; a white crystalline precipitate is formed.

Reaction equations indicating the analytical effect:

Conclusion:

Sodium (Na^+)

a) 0.1 g of the test sample is dissolved in 2 ml of water R. To the resulting solution or to 2 ml of the solution specified in the pharmacopeical monograph, add 2 ml of 150 g/l potassium carbonate R and heat to boiling; no precipitate forms. Add 4 ml of potassium pyroantimonate solution R to the solution and heat to boiling, then cool in ice water and, if necessary, rub the inner walls of the test tube with a glass rod; a dense white precipitate forms.

c) Sodium salt, moistened with hydrochloric acid R and added to a colorless flame, turns it yellow.

Reaction equations indicating the analytical effect:

Conclusion:

Lead (Pb^{2+})

a) 0.1 g of the test sample is dissolved in 1 ml of acetic acid R. To the resulting solution or to 1 ml of the solution specified in the pharmacopeical monograph, add 2 ml of potassium chromate solution R; a yellow precipitate is formed, which dissolves when 2 ml of concentrated sodium hydroxide solution R is added.

b) 50 mg of the test sample is dissolved in 1 ml of acetic acid R. To the resulting solution or to 1 ml of the solution specified in the pharmacopeical monograph, add 10 ml of water and 0.2 ml of potassium iodide solution R, a yellow precipitate is formed. The mixture is boiled for 1–2 minutes; the precipitate dissolves. The solution is allowed to cool; a precipitate forms again in the form of shiny yellow flakes.

Reaction equations indicating the analytical effect:

Conclusion:

Silver (Ag^+)

a) About 10 mg of the test sample is dissolved in 10 ml of water R. To the resulting solution or to 10 ml of the solution specified in the pharmacopeical monograph, add 0.3 ml of hydrochloric acid R1, a white cheesy precipitate is formed, which dissolves with the addition of 3 ml of diluted ammonia solution R1.

c) To 1 ml of a solution of the test sample, equivalent to 5 mg of silver ion, add a solution of diluted ammonia R1 until the precipitate that initially forms dissolves, then add 2-3 drops of a solution of formaldehyde R and heat; A shiny coating of metallic silver forms on the walls of the test tube.

Reaction equations indicating the analytical effect:

Conclusion:

Zinc (Zn^{2+})

a) 0.1 g of the test sample is dissolved in 5 ml of water R. To the resulting solution or to 5 ml of the solution specified in the pharmacopeical monograph, add 0.2 ml of concentrated sodium hydroxide solution R; a white precipitate forms. Then add another 2 ml of concentrated sodium hydroxide solution R; the precipitate dissolves. To the resulting solution add 10 ml of ammonium chloride solution R; the solution remains clear. Add 0.1 ml of sodium sulfide solution R to the solution; A white flocculent precipitate forms.

b) To 2 ml of a solution containing the test sample in an amount of 5–20 mg of zinc ion (Zn^{2+}), add 0.5 ml of potassium ferrocyanide solution R; A white precipitate is formed, insoluble in diluted hydrochloric acid S.

Reaction equations indicating the analytical effect:

Conclusion:

Anion identification reactions

Bromides (Br^-)

a) A weighed portion of the test sample containing about 3 mg of bromide anion (Br^-) is dissolved in 2 ml of water R. The resulting solution or 2 ml of the solution specified in the pharmacopeical monograph is acidified with diluted nitric acid R, and 0.4 ml of silver nitrate solution is added R1, mix and settle; A light yellow cheesy precipitate is formed. The precipitate is separated by centrifugation and washed with three portions of water R, 1 ml each. These operations are carried out quickly in a place protected from bright light, and it is allowed that the liquid above the sediment

is not completely transparent. The resulting precipitate is suspended in 2 ml of water and 1.5 ml of ammonia solution R is added; the precipitate slowly dissolves.

c) To 1 ml of a solution containing the test sample in an amount equivalent to about 2–30 mg of bromide ion (Br^-), add 1 ml of diluted hydrochloric acid S, 0.5 ml of a freshly prepared solution of 50 g/l chloramine R, 1 ml chloroform R and shake; the chloroform layer becomes yellow-brown in color.

Reaction equations indicating the analytical effect:

Conclusion:

Iodides (I^-)

a) A weighed portion of the test sample containing about 4 mg of iodide ion (I^-) is dissolved in 2 ml of water R. The resulting solution or 2 ml of the solution specified in the pharmacopeical monograph is acidified with diluted nitric acid R, and about 0.4 ml of the solution is added silver nitrate R1, mix and settle until a light yellow cheesy sediment forms. The precipitate is separated by centrifugation and washed with 3 portions of water R 1 ml each. This operation is carried out quickly in a place protected from bright light; it is allowed that the liquid above the sediment is not completely transparent. The precipitate is suspended in 2 ml of water and 1.5 ml of ammonia solution R is added; the precipitate does not dissolve.

b) To 2 ml of a solution of the test sample containing about 5 mg of iodide ion (I^-) in 1 ml, or to 0.2 ml of the solution specified in the pharmacopeical monograph, add 0.5 ml of dilute sulfuric acid R, 0.1 ml of potassium dichromate solution R, 2 ml of water R, 2 ml of chloroform R, shake for several seconds and leave until separation; the chloroform layer acquires a violet or red-violet color.

c) When 0.1 g of the test sample is heated with 1 ml of sulfuric acid R, violet iodine vapor is released.

Reaction equations indicating the analytical effect:

Conclusion:

Carbonates (CO_3^{2-}) (we do not perform reaction(s))

b) Dissolve 0.2 g of the test sample in 2 ml of water R. To the resulting solution add 0.5 ml of a saturated solution of magnesium sulfate R; a white precipitate is formed (difference from bicarbonate, solutions, which form a precipitate only when boiled).

c) Dissolve 0.2 g of the test sample in 2 ml of water R. Add 0.05 ml of phenolphthalein solution R to the resulting solution; a red color appears (unlike hydrocarbonates, solutions of which remain colorless).

Reaction equations indicating the analytical effect:

Conclusion:

Nitrates (NO_3^-)

b) A solution containing the test sample in an amount of about 2 mg of nitrate ion (NO_3^-) does not discolor a solution of 1 g/l potassium permanganate R, acidified with dilute sulfuric acid (different from nitrites).

Reaction equations:

Conclusion:

Nitrites (NO_2^-)

a) Several crystals of antipyrine (phenazone) are dissolved in a porcelain cup in 0.1 ml of diluted hydrochloric acid R, 0.1 ml of a solution containing about 1 mg of nitrite ion (NO_2^-) is added; a green color appears (different from nitrates).

b) To a weighed portion of the test sample equivalent to 30 mg of nitrite ion add 1 ml of diluted sulfuric acid R; yellow-brown vapors are released (different from nitrates).

Reaction equations indicating the analytical effect:

Conclusion:

Sulfates (SO_4^{2-})

a) About 45 mg of the test sample is dissolved in 5 ml of water R. To the resulting solution or to 5 ml of the solution specified in the pharmacopeical monograph, add 1 ml of diluted hydrochloric acid S and 1 ml of barium chloride solution R1; a white precipitate forms.

To the suspension obtained as a result of reaction a, add 0.1 ml of 0.05 M iodine solution; The yellow color of iodine does not disappear (unlike sulfites and dithionites), but becomes discolored when a solution of tin chloride R is added dropwise (unlike iodates). The mixture is boiled; the precipitate is not colored (unlike selenates and tungstates).

Reaction equations indicating the analytical effect: *Conclusion:*

Sulfites (SO_3^{2-})

a) To 2 ml of a solution containing the test sample in the amount of 10–30 mg of sulfite ion (SO_3^{2-}), add 2 ml of diluted hydrochloric acid R and shake; sulfur dioxide is gradually released, detected by a characteristic pungent odor.

b) To the solution containing sulfite ion (SO_3^{2-}) indicated in the pharmacopeical monograph, add 0.1 ml of 0.5 M iodine solution; the reagent becomes discolored.

Reaction equations indicating the analytical effect: *Conclusion:*

Phosphates (orthophosphates) (PO_4^{3-})

a) To 5 ml of the solution specified in the pharmacopeical monograph, neutralized if necessary, add 5 ml of silver nitrate solution R1; a yellow precipitate is formed, color of which does not change when boiled and which dissolves when ammonia solution is added.

c) To 1 ml of a solution of the test sample containing 10–30 mg of phosphate ion in diluted nitric acid R, add 2 ml of ammonium molybdate solution R and heat; A yellow crystalline precipitate is formed dissolving in a solution of diluted ammonia R1.

d) To 1 ml of a solution of the test sample containing 10–30 mg of phosphate ion, add 1 ml of ammonium chloride solution R, 1 ml of diluted ammonia solution R1 and 0.5 ml of a solution of 100 g/l magnesium sulfate R; forming a white crystalline precipitate, soluble in dilute mineral acids.

Reaction equations indicating the analytical effect:

Conclusion:

Chlorides (Cl^-)

a) A weighed portion of the test sample containing about 2 mg of chloride ion (Cl^-) is dissolved in 2 ml of water R. The resulting solution or 2 ml of the solution specified in the pharmacopeical monograph is acidified with diluted nitric acid R, and 0.4 ml of silver solution is added nitrate R1, mix and settle; a white cheesy precipitate is formed, which is centrifuged and washed with three portions of water, 1 ml each. This operation is carried out quickly in a place protected from bright light, and it is allowed that the liquid above the sediment is not completely transparent. The precipitate is suspended in 2 ml of water R and 1.5 ml of ammonia solution R is added; the precipitate dissolves quickly; the presence of several large particles that dissolve slowly is allowed.

b) A weighed sample of the test sample containing about 15 mg of chloride or the amount specified in the pharmacopeical monograph is placed in a test tube, 0.2 g of potassium dichromate R and 1 ml of sulfuric acid R are added. Filter paper soaked with 0.1 ml diphenylcarbazide solution R; the paper turns purple-red.

Reaction equations indicating the analytical effect:

Conclusion:

List of literature

1. *Pharmaceutical* chemistry : textbook / ed. G. V. Ramenskaya. – Moscow : GEOTAR-Media, 2023. – 384 p.

2. *Tsurkan, O. O.* Pharmaceutical chemistry. Analysis of the Medicinal Substances according to Functional Groups: study guide / O. O. Tsurkan. – Kyiv : AUS Medicine Publishing, 2018. – 152 p.

3. *Pharmaceutical* analysis : The study guide for students of higher schools / ed. by V. A. Georgiyants. – Kharkiv : NUPh Golden Pages, 2018. – 494 p.

4. *European* Pharmacopeia / European Directorate for the quality of medicines and healthcare. 10th edition, Supplement 10.0. Vol. 1. Council of Europe, Strasbourg, 2019. – 4312 p.

5. Lecture and information material.

Lesson 10

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

Objective: acquaint students with the essence of chemical processes occurring during pharmacopoeial identification of organic substances and conditions for carrying out identification reactions; principles of pharmaceutical substances and medicines identification using instrumental methods; develop students' skills in identification of organic anions and functional groups in accordance with the requirements of the general pharmacopeical monograph of the State Pharmacopoeia of the Republic of Belarus and organic substances using instrumental methods.

Requirements for the initial level of knowledge: repeat chemical methods of detecting organic substances; classification of spectrometric methods of analysis; theoretical foundations of chromatographic methods of analysis; chromatographic parameters used for identification

Problems for discussion:

1. General pharmacopeical monograph of the State Pharmacopoeia of the Republic of Belarus «Reactions of authenticity (identification) to ions and functional groups». Partial identification reactions.
2. Identification reactions of organic anions: acetates, benzoates, lactates, salicylates, tartrates, citrates.
3. Reactions for identifying functional groups: acetyl, primary aromatic amines, esters. Identification reactions for alkaloids, barbiturates (except for N-substituted ones), xanthines.
4. Application of instrumental methods for identification. Spectrometric identification methods. Chromatographic identification methods. Identification methods based on the determination of physical constants.

Assignments for student independent work

1. Fill out the table.

	Reagent	**Features of reaction**	**Analytical effect**	**Equation of the reaction**
Alkaloids				
Primary aromatic amines				
Acetates				
Acetyl				
Barbiturates N1-unsubstituted				
Benzoates				
Xanthines				
Lactates				
Salicylates				
Tartrates				
Citrates				
Esters				

Algorithm for performing laboratory work
«Pharmacopoeial identification of organic ions
and functional groups using chemical reactions,
organic substances using instrumental methods»

Goal of the work: develop students' skills in identifying organic ions and functional groups using chemical reactions and organic substances using instrumental methods.

Work order

Identification reactions of organic ions and functional groups according to the State Pharmacopoeia of the Republic of Belarus

Alkaloids

A few milligrams or the amount of the test sample specified in the pharmacopeical monograph is dissolved in 5 ml of water R, diluted hydrochloric acid R is added until the solution is acidic (2.2.4), then 1 ml of potassium iodobismuthate solution R (Dragendorff reagent); an orange or orange-red precipitate immediately forms.

Reaction equations indicating the analytical effect:
Conclusion:

Primary aromatic amines

The test solution specified in the pharmacopeical monograph is acidified with diluted hydrochloric acid R # (or 0.05 g of the test sample is dissolved in dilute hydrochloric acid R) # and add 0.2 ml of sodium nitrite solution R. After 1-2 minutes, add 1 ml of solution β-naphthol R; an intense orange or red color appears and, as a rule, a precipitate of the same color is formed.

Reaction equations indicating the analytical effect:
Conclusion:

Acetates

a) The test sample is heated with an equal amount of oxalic acid R; acetic acid is released, detectable by smell and acidic reaction (2.2.4).

#c) To 2 ml of a neutral solution of the test sample containing 20-60 mg of acetate ion ($CH3COO^-$) add 0.2 ml of a solution of 30 g/l iron (III) chloride R; a red-brown color appears, disappearing with the addition of diluted mineral acids.

#d) 2 ml of a solution of the test sample containing 20-60 mg (CH_3COO^-), heated with an equal amount of concentrated sulfuric acid R and 0.5 ml of 96% alcohol R; Ethyl acetate is formed, detectable by smell.

Reaction equations indicating the analytical effect:

Conclusion:

Barbiturates (except N-substituted)

About 5 mg of the test sample is dissolved in 3 ml of methanol R, 0.1 ml of a solution containing 100 g/l cobalt nitrate R and 100 g/l calcium chloride S is added, mixed and added with shaking 0.1 ml of sodium hydroxide solution diluted R. A violet-blue color appears and a precipitate forms.

Reaction equations indicating the analytical effect:

Conclusion:

Benzoates

a) To 1 ml of the solution specified in the pharmacopeical monograph add 0.5 ml of iron (III) chloride solution R1; a pinkish-yellow precipitate is formed, soluble in ether R.

b) 0.2 g of the test sample, if necessary prepared as indicated in the pharmacopeical monograph, is placed in a test tube, moistened with 0.2 ml or 0.3 ml of sulfuric acid R and the bottom of the test tube is carefully heated; a white coating appears on the inner walls of the test tube.

c) 0.5 g of the test sample is dissolved in 10 ml of water S. To the resulting solution or to 10 ml of the solution specified in the pharmacopeical monograph, add 0.5 ml of hydrochloric acid R. A precipitate is formed, which, after recrystallization from warm water R and drying under vacuum (2.2.32) has a melting point (2.2.14) from 120 °C to 124 °C.

Reaction equations indicating the analytical effect:

Conclusion:

Xanthines

To a few milligrams or as indicated in a pharmacopeical monograph, add 0.1 ml of concentrated hydrogen peroxide solution R, 0.3 ml of diluted hydrochloric acid R and evaporate in a water bath until a dry yellowish-red residue is obtained. To the residue add 0.1 ml of diluted ammonia R2; the color of the sediment changes to violet-red.

Reaction equations indicating the analytical effect: *Conclusion:*

Lactates

A weighed sample of the test sample, equivalent to 5 mg of lactic acid, is dissolved in 5 ml of water R. To the resulting solution or 5 ml of the solution specified in the pharmacopeical monograph, add 1 ml of bromine water R, 0.5 ml of dilute sulfuric acid S and heat in a water bath, stirring occasionally with a glass rod until the solution becomes discolored. Add 4 g of ammonium sulfate R to the solution and mix. Add dropwise, without stirring, 0.2 ml of a solution of 100 g/l sodium nitroprusside R in diluted sulfuric acid R, carefully add, also without stirring, 1 ml of concentrated ammonia solution R and leave for 30 minutes; a dark green ring forms at the interface of the two liquids.

Reaction equations indicating the analytical effect: *Conclusion:*

Salicylates

a) To 1 ml of the solution specified in the pharmacopeical monograph, add 0.5 ml of iron (III) chloride solution R1; a violet color appears, which does not disappear after adding 0.1 ml of acetic acid R, but disappears with the addition of diluted hydrochloric acid R; this results in the formation of a white crystalline precipitate of salicylic acid.

#b) 0.5 g of the test sample is dissolved in 10 ml of water R. To the resulting solution or to 10 ml of the solution specified in the pharmacopeical monograph, add 0.5 ml of hydrochloric acid R. The resulting precipitate after recrystallization from hot water R and drying under vacuum (2.2.32) has a melting point (2.2.14) from 156 °C to 161 °C.

Reaction equations indicating the analytical effect:

Conclusion:

Tartrates

a) About 15 mg of the test sample is dissolved in 5 ml of water R. To the resulting solution or to 5 ml of the solution specified in the pharmacopeical monograph add 0.05 ml of a solution of 10 g/l iron (II) sulfate R and 0.05 ml of the solution diluted hydrogen peroxide R; An unstable yellow color appears. After the solution has become discolored, a diluted solution of sodium hydroxide S is added dropwise; an intense blue color appears.

b) To 0.1 ml of a solution of the test sample containing about 15 mg/ml tartaric acid, or to 0.1 ml of the solution specified in the pharmacopeical monograph add 0.1 ml of a solution of 100 g/l potassium bromide R, 0.1 ml of a solution of 20 g/l resorcinol R, 3 ml of sulfuric acid R and heated in a water bath for 5 minutes to 10 minutes; a dark blue color appears. The solution is cooled and poured into water R; the color of the solution changes to red.

Reaction equations indicating the analytical effect:

Conclusion:

Citrates

a) A weighed sample of the test sample containing about 50 mg of citric acid is dissolved in 5 ml of water R. To the resulting solution or to 5 ml of the solution specified in the pharmacopeical monograph add 0.5 ml of sulfuric acid R and 1 ml of potassium permanganate solution R. The solution is heated until discolored, add 0.5 ml of a solution of 100 g/l sodium nitroprusside S in diluted sulfuric acid R, 4 g of sulfamic acid R. A concentrated ammonia solution R is added to the mixture until the medium is alkaline, adding it drop by drop until the acid is completely dissolved sulfamic. The addition of an excess of concentrated ammonia solution R leads to the appearance of a violet color, turning into violet-blue.

#b) To 1 ml of a neutral solution of the test sample containing 2–10 mg of citrate ion add 1 ml of a solution of 200 g/l calcium chloride R; the solution remains clear; When the solution is boiled, a white precipitate is formed, soluble in diluted hydrochloric acid R.

Reaction equations indicating the analytical effect:

Conclusion:

Esters

To 30 mg or to the amount of the test sample specified in the pharmacopeical monograph add 0.5 ml of a solution of 70 g/l hydroxylamine hydrochloride R in methanol R, 0.5 ml of a solution of 100 g/l potassium hydroxide R in 96% alcohol R, heat to boiling and cool. The resulting solution is acidified with diluted hydrochloric acid R, add 0.2 ml of a solution of iron (III) chloride R1, diluted 10 times; a bluish-red or red color appears.

Reaction equations indicating the analytical effect:

Conclusion:

Analysis of medicinal substances

Quinine(R)-(6-Methoxyquinolin-4-yl)[(2S,4S,5R)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl]methanol hydrochloride (1:1), dihydrate

20 mg of the substance is dissolved in 20 ml of water R. To 5 ml of the resulting solution add 3 drops of diluted sulfuric acid S; blue fluorescence should be observed.

Observations:

Conclusion:

Bendazole hydrochloride (dibazole) 2-Benzyl-1H-benzimidazole hydrochloride

Dissolve 20 mg of the substance in 5 ml of water R, add 0.15 ml of diluted hydrochloric acid S, 0.15 ml of 0.1 M iodine solution and shake; a reddish-silver precipitate should form.

Reaction equations indicating the analytical effect:

Conclusion:

Caffeine1,3,7-Trimethyl-1H-purine-2,6(3H,7H)-dione

To 0.5 ml of solution for injection add 0.05 ml of iodized potassium iodide solution R. The solution remains clear. Add 0.1 ml of diluted hydrochloric acid S to the resulting solution. A brown precipitate is formed. Neutralize with diluted sodium hydroxide solution R. The precipitate dissolves.

Reaction equations indicating the analytical effect:

Conclusion:

Amino acids (glutamic acid, aspartic acid, arginine, glycine, etc.)

20 mg of the substance is dissolved when heated in 1 ml of water R, 1 ml of a freshly prepared solution of ninhydrin S is added and heated; a blue-violet color should appear.

Reaction equations indicating the analytical effect:

Conclusion:

Quality control of atenolol according to the section «AUTHENTICITY (IDENTIFICATION)» according to the State Pharmacopoeia of the Republic of Belarus

b) Ultraviolet absorption spectrophotometry

Test is carried out in accordance with the State Pharmacopoeia of the Republic of Belarus 2.2.25, volume 1.

Test solution. 0.010 g of the test sample of the substance is dissolved in ethanol R and brought to a volume of 10.0 ml with the same solvent. 1.0 ml of the resulting solution is diluted with ethanol R to a volume of 100 ml.

Wavelength range: from 230 to 350 nm.

Absorption maxima: at 275 nm and at 282 nm.

According to the State Pharmacopoeia of the Republic of Belarus, the ratio of optical densities should be in the range:

A275/A282 – from 1.15 to 1.20.

Absorption maxima: *Calculation of optical density ratio:* *Conclusion:*

Quality control of levomenthol according to the section «AUTHENTICITY (IDENTIFICATION)» according to the State Pharmacopoeia of the Republic of Belarus

a) Specific optical rotation

Dissolve 1.00 g of the test sample in 96% alcohol R and dilute to a volume of 10.0 ml with the same solvent. The angle of optical rotation is measured and the specific optical rotation is calculated.

According to the State Pharmacopoeia of the Republic of Belarus, the specific optical rotation should be in the range from -48 to -51.

Formulas and calculations: *Conclusion:*

List of literature

1. *Pharmaceutical* chemistry : textbook / ed. G. V. Ramenskaya. – Moscow : GEOTAR-Media, 2023. – 384 p.

2. *Tsurkan, O. O.* Pharmaceutical chemistry. Analysis of the Medicinal Substances according to Functional Groups: study guide / O. O. Tsurkan. – Kyiv : AUS Medicine Publishing, 2018. – 152 p.

3. *Pharmaceutical* analysis : The study guide for students of higher schools / ed. by V. A. Georgiyants. – Kharkiv : NUPh Golden Pages, 2018. – 494 p.

4. *European* Pharmacopeia / European Directorate for the quality of medicines and healthcare. 10th edition, Supplement 10.0. Vol. 1. Council of Europe, Strasbourg, 2019. – 4312 p.

5. Lecture and information material.

Lesson 11
PHARMACOPOEIAL TESTS OF PHARMACEUTICAL SUBSTANCES

Objective: familiarize students with the principles of determining melting, solidification and dropping points, temperature limits of distillation and boiling point, density of liquids and solids, viscosity of liquids and their use in pharmacopoeial analysis; develop students' skills to determination of the pharmaceutical substances melting point using capillary method, density of liquids using a pycnometer and viscosity using capillary viscometry.

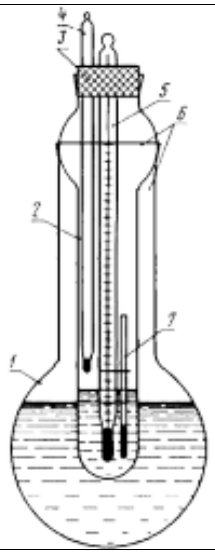
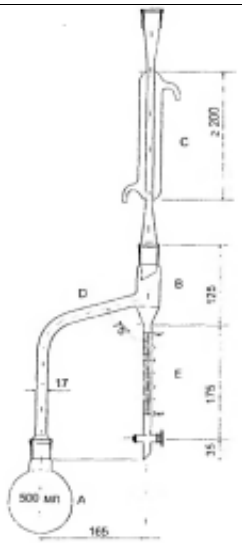
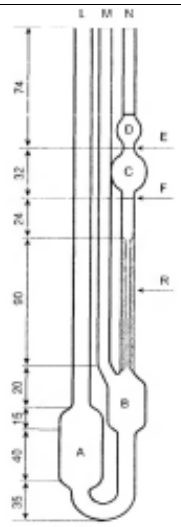
Requirements for the initial level of knowledge: review the basics of thermodynamics; fundamentals of hydrodynamics.

Problems for discussion:

1. Melting temperature. Determination methods: capillary method, open capillary method, instant melting method. Application in pharmacopoeial analysis.
2. Dripping temperature. Method of determination. Application in pharmacopoeial analysis.
3. Solidification temperature. Method of determination. Application in pharmacopoeial analysis.
4. Distillation temperature limits and boiling point. Method of determination. Application in pharmacopoeial analysis.
5. Density of liquids. Types of density: density (ρ), relative density (d). Determination of liquids density by means of hydrometer, pycnometer and density meter. Features of determining solid fats and wax density. Application of density in pharmacopoeial analysis.
6. Determination of solids density. Types of density: true density, particle density, volumetric density. Principles of determination. Application in pharmacopoeial analysis.
7. Viscosity of liquids. Types of viscosity: dynamic, kinematic, relative, specific, reduced, characteristic, structural. Determination of viscosity by capillary and rotational viscometry, as well as using a falling ball viscometer. Application of viscosity in pharmacopoeial analysis.
8. Determination of specific rotation and refractive index.

Assignments for student independent work

1. Find out the device, label the main elements.

		
1 - 2 – 3 – 4 - 5 - 6 – 7 –	A – B – C – D – E –	A – B – C – D – E – F – L – M – N – R –

Algorithm for performing laboratory work
«Determination of salicylic acid melting point. Determination of sulfuric acid relative density. Determination of the dynamic viscosity of a chondroitin for injections solution using capillary viscometry method. Quality control of ethyl alcohol 96% according to the section «Tests»: determination of relative density»

Goal of the work: develop students' skills in determining melting point of salicylic acid, relative density of sulfuric acid and alcohol 96%, dynamic viscosity of a chondroitin sulfate solution for injection.

1. Determination of salicylic acid melting point.

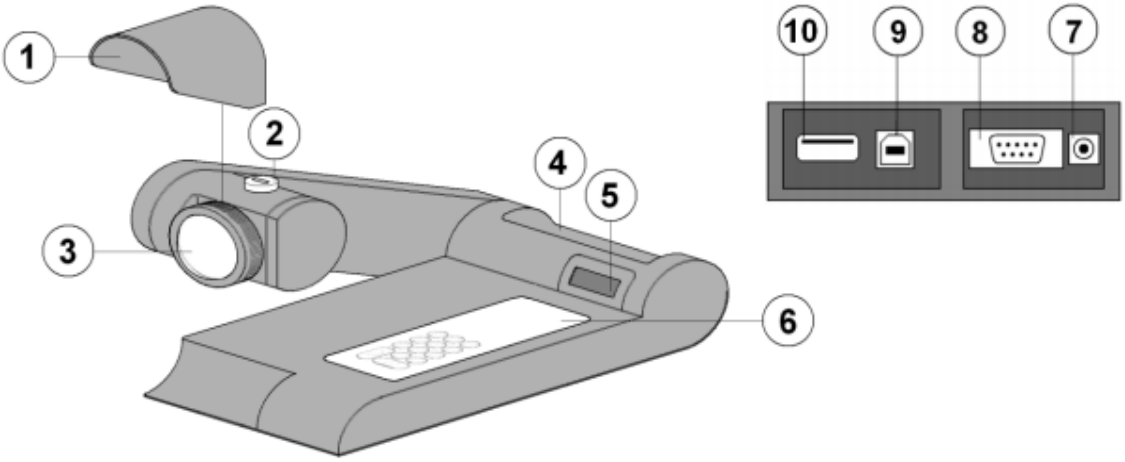
According to the State Pharmacopoeia of the Republic of Belarus melting point is determined for bendazole hydrochloride, solid fat, cocoa butter, coconut oil, aqueous lanolin, soybean oil, cetyl alcohol, cytostearyl alcohol when controlling quality of substances according to the «TEST» section.

To obtain the practical skill of determining melting point by the capillary method in this laboratory work pharmaceutical substance of salicylic acid will be used (for which the determination of the melting point is used in quality control according to the «AUTHENTICITY» section).

To complete the laboratory work, you must read section 2.2.14. Melting point — capillary method (volume 1, p. 55).

To determine melting point by the capillary method it is necessary to fill the capillary with the test sample until a compacted column with a height of 4 mm to 6 mm is obtained. The necessary compaction of the substance when filling a capillary tube can be achieved by throwing it several times, sealed end down, into a glass tube at least 1 m long placed vertically on a hard surface.

Device structure:



1. Lens hood
2. Hole for capillaries
3. Lens
4. Capillary tube holder
5. Display
6. Control Panel
7. Network connection
8. Printer connector
9. USB connector

Next, you need to measure melting temperature according to the given algorithm:

1. Connect the device to power grid.
2. Press ENTER (large arrow button).
3. Set temperature to approximately 10°C below the expected melting point.
4. Press ENTER.
5. Set heating mode (speed of temperature rise):

– from 0.5 to 1 °C/min when determining melting point below 100 °C;
– from 1 to 1.5 °C/min when determining melting temperature from 100 °C to 150 °C;
– from 1.5 to 2 °C/min when determining melting point above 150 °C;
– from 2.5 to 3.5 °C/min for substances that are unstable when heated.

6. Next, press ENTER 2 times. Temperature will rise to the one set in step 3, wait for the sound signal.
7. Next, press ENTER 2 times.

At least two determinations are made. The average value is taken as melting temperature. Discrepancy between determinations should not exceed 1 °C.

According to the State Pharmacopoeia of the Republic of Belarus melting point of salicylic acid should be in the range of 158 °C up to 161 °C.

Values: *Conclusion:*

2. Determination of relative density of sulfuric acid

Relative density of sulfuric acid should be between 1.83 and 1.85.

#Method 3. Used in case of determining density of liquids with an accuracy of 0.01 g/cm^3.

Test liquid is placed in a cylinder, and at a liquid temperature of 20 °C, a clean, dry hydrometer is carefully lowered into it, scale of which allows you to determine the expected density value. The hydrometer is not released from the hands until it becomes obvious that it is floating; in this case it is necessary to ensure that the hydrometer does not touch walls and bottom of the cylinder. Density reading is carried out 3–4 minutes after immersing the hydrometer according to the division on the scale corresponding to the lower meniscus of the liquid (in the case of determining dark-colored liquids reading is made along the upper meniscus). When counting, eye should be at the level of the meniscus. Determining density of highly volatile substances with a hydrometer is not allowed.

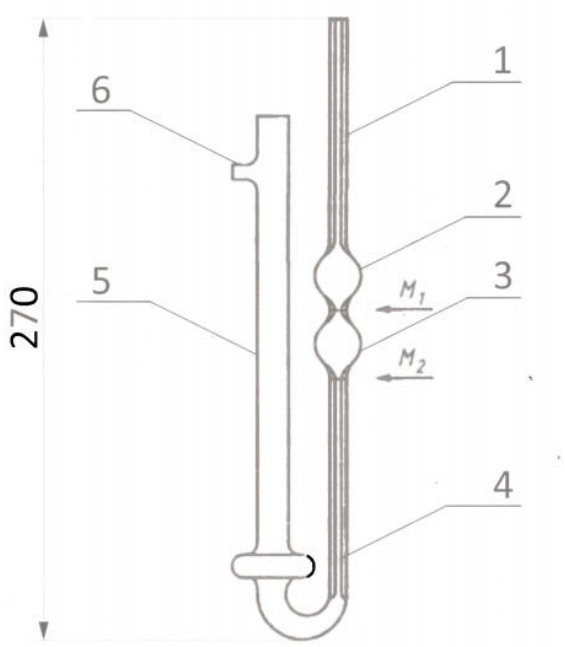
Please note that concentrated acid is used for the experiment, when working with which you must strictly follow safety precautions. After the test pre-rinse the hydrometer in a glass of water and then carefully wash it under running water.

Values: *Conclusion:*

3. Determination of chondroitin sulfate solution for injection dynamic viscosity using the capillary viscometry method

Determine flow time, carry out three tests and calculate dynamic viscosity.

To measure flow time of the liquid a bulb is placed on the outlet tube 6. Next, holding tube 5 with your finger and turning viscometer over lower tube 1 into a glass of liquid and suck it in (press the rubber bulb and gradually release it) above the M_2 mark (until the bend of the tube), making sure that no air bubbles form in the liquid. Viscometer is then removed from the vessel and quickly turned over to its normal position. Remove your finger from tube 5, close tube 1 with your finger. Fix viscometer on a tripod. Connect elbow 1 to the atmosphere and determine the time of outflow — lowering of the liquid meniscus from mark M_1 to mark M_2.



Viscosity is calculated using the formula based on the average (from three experiments) fluid flow time:

$$\eta = k \cdot \rho \cdot t,$$

where k is viscometer constant, mm^2/s^2 (for Mk4 = 0.82; for Mk2 = 0.01100); ρ – density of the test liquid obtained by method 1 (described below), mg/mm^3; t – liquid flow time, s.

Calculations:

4. Quality control of ethyl alcohol 96% according to the «TESTS» section

Determination of relative density

Relative density of ethyl alcohol 96% should be from 0.805 to 0.812.

#Method 1. Used in case of determining density of liquids with an accuracy of 0.001 g/cm^3.

A clean, dry pycnometer is weighed, filled with water R using a dry funnel just above the mark, closed with a stopper and thermostated for 20 minutes at a temperature of 20+0.1 °C. At this temperature water level in the pycnometer is brought to the mark by quickly removing excess water using a pipette or a strip of filter paper wrapped in a tube. Pycnometer is again closed with a stopper and thermostated for another 10 minutes checking position of the meniscus in relation to the mark. Then pycnometer is removed from the thermostat, inner surface of the pycnometer neck, as well as entire outside of pycnometer is wiped with filter paper, kept under the glass of the scale for 10 minutes and weighed with the accuracy indicated above. Pycnometer is emptied of water, dried by rinsing with 96% alcohol R and ether R (drying pycnometer by heating is not allowed), remainder of the ether is removed by blowing air, pycnometer is filled with the test liquid and then the same operations are carried out as with water R.

Relative density is calculated using the formula:

$$d^{2020} = 1.00180 \cdot \rho 20$$

Density ρ20 (g/cm^3) is calculated using the formula:

$$\frac{(m_2 - m) \cdot 0{,}99703}{m_1 - m} + 0{,}0012,$$

where m is the mass of the empty pycnometer, g;

m_1 - mass of pycnometer with water R, g;

m_2 is the mass of the pycnometer with the test liquid, g;

0.99703 - value of water density at 20 °C, g/cm^3 (taking into account air density);

0.0012 - air density value at 20 °C, g/cm^3 and barometric pressure 101.3 kPa (760 mm Hg).

Calculations:

Conclusion:

List of literature

1. *Pharmaceutical* chemistry : textbook / ed. G. V. Ramenskaya. – Moscow : GEOTAR-Media, 2023. – 384 p.

2. *Tsurkan, O. O.* Pharmaceutical chemistry. Analysis of the Medicinal Substances according to Functional Groups: study guide / O. O. Tsurkan. – Kyiv : AUS Medicine Publishing, 2018. – 152 p.

3. *Pharmaceutical* analysis: The study guide for students of higher schools / ed. by V. A. Georgiyants. – Kharkiv : NUPh Golden Pages, 2018. – 494 p.

4. *European* Pharmacopeia / European Directorate for the quality of medicines and healthcare. 10th edition, Supplement 10.0. Vol. 1. Council of Europe, Strasbourg, 2019. – 4312 p.

5. Lecture and information material.

Lesson 12

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

Objective: Introduce students to the principles of liquids transparency and turbidity, degree of liquids coloration, volatiles and water, weight loss on drying, sulphate and total ash and the application of test data in pharmaceutical analysis; basic concepts related to electrochemical methods of analysis; develop students' skills in determination of turbidity degree, transparency and color of liquids, potentiometric determination of pH.

Requirements for the initial level of knowledge: repeat concept of electric charge; electric current and its parameters; electrical circuit; Ohm's and Joule-Lenz's laws; theoretical foundations of pH measurement; theoretical foundations of Karl Fischer titration.

Problems for discussion:

1. Determination of liquids transparency and degree of turbidity. Application in pharmacopoeial analysis.
2. Determination of liquids coloration degree. Application in pharmacopoeial analysis.
3. Potentiometric determination of pH. Application in pharmacopoeial analysis.
4. Determination of volatile substances and water. Methods for determining water: distillation method, semi-micromethod, microdetermination. Application in pharmacopoeial analysis.
5. Determination of weight loss upon drying. Application in pharmacopoeial analysis.
6. Determination of total and sulfate ash. Application in pharmacopoeial analysis.
7. Basic concepts related to electrochemical methods of analysis: electrochemical cell, electrode, electrolyte. Classification of electrodes. Operating modes of an electrochemical cell: galvanic cell, electrolytic cell.
8. General characteristics and classification of electrochemical methods of analysis.
9. Conductometry (direct conductometry and conductometric titration). Basic principles. Application in pharmaceutical analysis.
10. Potentiometry (ionometry and potentiometric titration). Basic principles. Application in pharmaceutical analysis. Ion selective electrodes.
11. Voltammetry (direct voltammetry and amperometric titration). Basic principles. Voltammogram. Application in pharmaceutical analysis.

Algorithm for performing laboratory work
«Determination of turbidity degree, transparency and color of solutions.
Quality control of disodium edetate according to the section "Tests": pH»

Goal of the work: develop students' skills in determining degree of turbidity, transparency and color of solutions; potentiometric determination of pH.

1. Determination of solutions transparency.

From the State Pharmacopoeia of the Republic of Belarus 2.2.1, volume 1: Determination of liquids transparency and degree of turbidity

Visual method. To determine liquids transparency and degree of turbidity identical test tubes made of colorless, transparent and neutral glass with a flat bottom, which have an internal diameter of 15 mm to 25 mm, are used. A 40 mm thick layer of the test liquid is compared with a 40 mm layer of a freshly prepared standard. Comparison of solutions is carried out in diffuse daylight 5 minutes after preparing standard viewing objects along the vertical axis of the test tube against a black background.

Liquids are considered transparent if their transparency does not differ from water R or the solution used to prepare the liquid, or which do not exceed intensity of the reference suspension I turbidity.

Preparation of the main opalescent suspension

15.0 ml of the original opalescent suspension is brought to a volume of 1000.0 ml with water R. Shelf life of the main opalescent suspension is 24 hours.

Preparation of standards

The standards are prepared in accordance with the table.

	I	II	III	IV
Basic opalescent suspension, ml	5.0	10.0	30.0	50.0
Water R, ml	95.0	90.0	70.0	50.0

The main opalescent suspension and water R are mixed and shaken before use.

Execution order

1. It is necessary to look at the State Pharmacopoeia of the Republic of Belarus in a pharmacopeical monograph on glycine and hydrated aluminum oxide requirements for the transparency of the solution S.
2. Prepare solution S according to the method specified in the pharmacopeical monograph for two samples.
3. If necessary, prepare a standard solution according to the above procedure.
4. Determine transparency using the above method.

Observations:

Conclusion:

2. Determination of the solutions color.

Test samples of pharmaceutical substances:

1. Sodium benzoate
2. Sodium bicarbonate
3. Papaverine hydrochloride
4. Resorcinol
5. Sodium sulfacetamide
6. Aluminum chloride hexahydrate
7. Galactose

8. Glycine
9. Drotaverine hydrochloride
10. Sodium salicylate
11. Nicotinamide
12. Aluminum oxide hydrated

Execution order

1. It is necessary to look at the State Pharmacopoeia of the Republic of Belarus in a pharmacopeical monograph for the issued sample of the requirements for the color of solution S.
2. Prepare the necessary reference solutions (reduce the volumes by 10 times).
3. Determine required indicator.

Determination of liquids coloration degree in the brown-yellow-red series, they are carried out visually by comparison with the corresponding standards (comparison solutions) using one of the two methods described below.

A solution is considered colorless if it can withstand comparison with water S or solvent, or is no more intensely colored than standard B9.

Degree of test solution coloration should not exceed degree of corresponding standard coloration, and the color of the test solution should be as close as possible to the color of the corresponding standard.

METHOD I

2.0 ml of the test liquid is compared with 2.0 ml of water R, solvent or standard (see standard tables) described in the pharmacopeical monograph, using identical test tubes of colorless, transparent, neutral glass with an outer diameter of 12 mm. Color comparison is carried out in diffuse daylight, viewing objects horizontally (perpendicular to the axis of the tubes) on a white matte background. According to method I the coloring of liquids is usually compared with standards [B, BY, Y, GY, R] 1-3.

METHOD II

A 400 mm layer of the test liquid is compared with a 400 mm layer of water R, solvent or standard (see standard tables) specified in the pharmacopeical monograph, using identical flat-bottomed, clear, neutral glass tubes having an internal diameter of 15 mm to 25 mm. Color comparison is carried out in diffuse daylight, viewing objects along the vertical axis of the tubes on a white background. According to method II, the coloring of liquids is usually compared with standards [B, BY, Y, GY, R] 4-9.

STANDARDS

Stock solutions

Yellow solution.

46 g of iron (III) chloride R are dissolved in 900 ml of a mixture of hydrochloric acid R — water R (25:975, v/v) and diluted to a volume of 1000.0 ml with the same solvent. Determine concentration of the resulting solution and dilute solution with the same solvent so that the content of $FeCl_3$ $6H_2O$ is 1 ml is 45.0 mg. Solution is stored in a place protected from light.

Red solution.

60 g of cobalt chloride R are dissolved in 900 ml of a mixture of hydrochloric acid R — water R (25:975, v/v) and diluted to a volume of 1000.0 ml with the same solvent. Determine the concentration of the resulting solution and dilute the solution with the same solvent so that the content of $CoCI_2$ $6H_2O$ is 1 ml is 59.5 mg.

Blue solution.

63 g of copper sulfate R are dissolved in 900 ml of a mixture of hydrochloric acid R — water R (25:975, v/v) and diluted to a volume of 1000.0 ml with the same solvent. Determine the concentration of the resulting solution and dilute the solution with the same solvent so that the content of $CuSO_4 \cdot 5H_2O$ is 1 ml is equal to 62.4 mg.

Basic solutions

Five initial solutions are prepared using three original solutions as indicated in Table 2.2.2.-1 (SPh RB).

Basic solution	Volume, ml			
	Yellow solution	Red solution	Blue solution	Hydrochloric acid solution (10 g/l HCl)
B (brown)	3.0	3.0	2.4	1.6
BY (brown-yellow)	2.4	1.0	0.4	6.2
Y (yellow)	2.4	0.6	0.0	7.0
GY (greenish-yellow)	9.6	0.2	0.2	0.0
R(red)	1.0	2.0	0.0	7.0

Standards for methods I and II

Standards are prepared using five initial solutions as indicated in the tables.

Standard solutions B

Reference	Volume, ml	
	Original solution B	Hydrochloric acid solution (10 g/l HCl)
B1	75.0	25.0
B2	50.0	50.0
B3	37.5	62.5
B4	25.0	75.0
B5	12.5	87.5
B6	5.0	95.0
B7	2.5	97.5
B8	1.5	98.5
B9	1.0	99.0

Standard solutions BY

Reference	Volume, ml	
	Original solution BY	Hydrochloric acid solution (10 g/l HCl)
BY1	100.0	0.0
BY2	75.0	25.0
BY3	50.0	50.0
BY4	25.0	75.0
BY5	12.5	87.5
BY6	5.0	95.0
BY7	2.5	97.5

Standard solutions Y

Reference	Volume, ml	
	Original solution Y	**Hydrochloric acid solution (10 g/l HCl)**
Y1	100.0	0.0
Y2	75.0	25.0
Y3	50.0	50.0
Y4	25.0	75.0
Y5	12.5	87.5
Y6	5.0	95.0
Y7	2.5	97.5

Standard solutions GY

Reference	Volume, ml	
	Original solution GY	**Hydrochloric acid solution (10 g/l HCl)**
GY1	25.0	75.0
GY2	15.0	85.0
GY3	8.5	91.5
GY4	5.0	95.0
GY5	3.0	97.0
GY6	1.5	98.5
GY7	0.75	99.25

Standard solutions R

Reference	Volume, ml	
	Original solution R	**Hydrochloric acid solution (10 g/l HCl)**
R1	100.0	0.0
R2	75.0	25.0
R3	50.0	50.0
R4	37.5	62.5
R5	25.0	75.0
R6	12.5	87.5
R7	5.0	95.0

Storage

Standards for determining the liquids coloration degree according to method I are stored in a place protected from light in sealed test tubes made of colorless, transparent, neutral glass with an outer diameter of 12 mm.

Standards for determining the liquids coloration degree using method II are prepared from basic solutions immediately before use.

Shelf life of primary and basic solutions when stored in a place protected from light in glass containers with a ground-in stopper is 1 year.

Observations: *Conclusion:*

3. Quality control of disodium edetate according to the «TESTS» section.

pH (2.2.3). From 4.0 to 5.5. Measure the pH of solution S.

Solution S. 5.0 g of the test sample (take 2.0 g) is dissolved in water free of carbon dioxide, S and brought to a volume of 100 ml (adjusted to 40 ml) with the same solvent.

Values: *Conclusion:*

List of literature

1. *Pharmaceutical* chemistry : textbook / ed. G. V. Ramenskaya. – Moscow : GEOTAR-Media, 2023. – 384 p.

2. *Tsurkan, O. O.* Pharmaceutical chemistry. Analysis of the Medicinal Substances according to Functional Groups: study guide / O. O. Tsurkan. – Kyiv : AUS Medicine Publishing, 2018. – 152 p.

3. Pharmaceutical analysis: The study guide for students of higher schools / ed. by V. A. Georgiyants. – Kharkiv : NUPh Golden Pages, 2018. – 494 p.

4. *European* Pharmacopeia / European Directorate for the quality of medicines and healthcare. 10th edition, Supplement 10.0. Vol. 1. Council of Europe, Strasbourg, 2019. – 4312 p.

5. Lecture and information material.

Lesson 13
IMPURITIES IN PHARMACEUTICAL SUBSTANCES

Objective: introduce students to basic concepts related to impurities; classification and possible routes of impurities entering pharmaceutical substances; methods for determining impurities; principles and conditions for testing for the maximum impurities content in pharmaceutical substances; principles of identification and control of the residual organic solvents content, determination of pharmaceutical substances microbiological purity; develop students' skills in carrying out tests for the impurities maximum content in pharmaceutical substances.

Requirements for the initial level of knowledge: repeat classification of organic solvents; composition of nutrient media for aerobic bacteria and fungi growth; methods for determining the number of aerobic bacteria and fungi; concept of sterility; sterilization methods.

Problems for discussion:

1. Concept of impurities in pharmaceutical substances. Types of impurities: identifiable impurity, unidentifiable impurity, specified impurity, unspecified impurity, potential impurity, associated impurities. Classification of impurities depending on their chemical nature.
2. Sources of impurities. Classification of impurities depending on toxicity. Genotoxic impurities and methods for their determination. Examples of genotoxic impurities.
3. General characteristics of pharmacopoeial methods for determining impurities. General and specific methods for determining impurities. Reference and non-reference methods for determining impurities. Standardization of impurity content.
4. Pharmacopoeial monograph of the State Pharmacopoeia of the Republic of Belarus «Tests for the maximum impurities content». Tests for the maximum impurities content of ammonium salts, arsenic, calcium, chlorides, fluorides, magnesium, magnesium and alkaline earth metals, heavy metals, iron, phosphates, potassium, sulfates, aluminum.
5. Examples of impurities formed at different stages of pharmaceutical substances and medicines circulation. Impurities of synthesis, storage and production. Examples of impurities.
6. Determination of associated impurities.
7. Identification of residual solvents and control of their quantity.
8. Determination of pharmaceutical substances and medicines microbiological purity.

Assignments for student independent work

1. Fill out the table.

Impurity	**Reaction equation**	**Analytical effect**	**Principle of considering results of impurity determination***
Ammonium salts			
Arsenic			
Calcium			
Chlorides			
Fluorides			
Magnesium			
Magnesium and alkaline earth metals			
Heavy metals			
Iron			
Phosphates			
Potassium			
Sulfates			
Aluminum			
Free formaldehyde			

* Principle of considering the result of determining an impurity (titration, comparison with color/opalescence/fluorescence of a standard, etc.).

Algorithm for performing laboratory work «Tests for maximum impurity content»

Goal of the work: develop students' skills in conducting tests for the maximum content of impurities in substances for pharmaceutical use in accordance with the requirements of the State Pharmacopoeia of the Republic of Belarus.

Execution order

During laboratory work it is necessary to monitor the indicated impurities in the issued samples of substances and draw a conclusion about the compliance of the issued pharmaceutical substances with the requirements of the State Pharmacopoeia of the Republic of Belarus.

Excerpts from pharmacopoeial monographs

Sodium bicarbonate

Solution S. Dissolve 5.0 g of the test sample in 90 ml of carbon dioxide-free water R and dilute to a volume of 100.0 ml with the same solvent.

Chlorides (2.4.4). No more than 0.0150% (150 ppm). To 7 ml of solution S add 2 ml of nitric acid R and dilute with water R to a volume of 15 ml.

Calcium (2.4.3). No more than 0.0100% (100 ppm). To a suspension of 1.0 g of the test sample and 10 ml of distilled water R add hydrochloric acid R until the medium is neutral and dilute with distilled water R to a volume of 15 ml.

Ammonium salts (2.4.1). No more than 0.0020% (20 ppm). 10 ml of solution S is diluted with water R to a volume of 15 ml. Standard is prepared using a mixture of 5 ml water R and 10 ml ammonium standard solution (1 ppm NH_4) R.

Sodium chloride

Solution S. Dissolve 20.0 g of the test sample in carbon dioxide-free water R prepared from distilled water R and dilute to a volume of 100.0 ml with the same solvent.

Magnesium and alkaline earth metals (2.4.7). No more than 0.0100% (100 ppm) relative to Ca. 10.0 g of the test sample shall pass the test for magnesium and alkaline earth metals. Use 0.150 g of indicator mixture of black mordant 11 R. Volume of 0.01 M sodium edetate solution used for titration should not exceed 2.5 ml.

Sulfates (2.4.13). No more than 0.0200% (200 ppm). 7.5 ml of solution S is diluted with distilled water R to a volume of 30 ml. 15 ml of the resulting solution must pass the sulfate test.

Heavy metals (2.4.8, method A). No more than 0.0005% (5 ppm). 12 ml of solution S must pass heavy metal test. Standard is prepared using lead standard solution (1 ppm Pb) R.

Excerpts from General Pharmacopoeial monograph 2.4 «Tests for the maximum content of impurities»

Calcium

Distilled water R should be used in the preparation of all solutions used in this test.

Before starting work it is necessary to complete the preparation of the reference alcohol solution of calcium (100 ppm Ca^{2+}) R: immediately before use the resulting solution must be diluted with 96% alcohol R 10 times.

Then, 1 ml of ammonium oxalate solution R is added to 0.2 ml of a standard solution of calcium alcohol (100 ppm Ca^{2+}) R. After 1 min, add a mixture of 1 ml of diluted acetic acid R and 15 ml of a solution containing the amount of the test sample specified in the pharmacopeical monograph, and shake.

In parallel with the same amounts of reagents and under the same conditions prepare a standard using a mixture of 1 ml of diluted acetic acid R, 10 ml of a standard aqueous calcium solution (10 ppm Ca^{2+}) R and 5 ml of distilled water R.

After 15 minutes opalescence of the test solution should not exceed opalescence of the standard.

Reaction equation and observations:

Result:

Chlorides

Before starting work it is necessary to complete the preparation of the standard solution of chloride (5 ppm Cl^-) R: immediately before use the resulting solution must be diluted with water R 100 times.

To 15 ml of the solution specified in the pharmacopeical monograph add 1 ml of diluted nitric acid R and pour mixture into a test tube containing 1 ml of silver nitrate solution R2.

In parallel with the same amounts of reagents and under the same conditions prepare a standard using, instead of 15 ml of the test solution, 10 ml of a standard solution of chloride (5 ppm Cl^-) R and 5 ml of water R.

The test tubes are placed in a place protected from light. After 5 minutes the tubes are viewed horizontally (perpendicular to the axis of the tubes) against a black background. Opalescence of the test solution should not exceed the opalescence of the standard.

Reaction equation and observations:

Result:

Magnesium and alkaline earth metals

To 200 ml of water R add 0.1 g of hydroxylamine hydrochloride R, 10 ml of ammonia buffer solution pH 10.0 R, 1 ml of 0.1 M zinc sulfate solution and about 15 mg of indicator mixture of black mordant 11 R. Heat to a temperature of about 40 ° C. The resulting solution is titrated with 0.01 M sodium edetate solution until the color of the solution changes from violet to blue. To the resulting solution add the amount of the test sample specified in the pharmacopeical monograph, dissolved in 100 ml of water R, or use the solution specified in the pharmacopeical monograph. If color of the solution turns purple, titrate again until the color of the solution turns blue. Volume of 0.01 M sodium edetate solution used for the second titration should not exceed volume of titrant specified in the pharmacopeical monograph.

Reaction equations and observations:

Result:

Sulfates

Distilled water R should be used in the preparation of all solutions used in this test.

Before starting work it is necessary to complete the preparation of the standard solution of sulfate (10 ppm SO_4^{2-}) P1: immediately before use the resulting solution must be diluted with alcohol (30%, v/v) P 100 times.

To 4.5 ml of a standard solution of sulfate (10 ppm SO_4^{2-}) R1 add 3 ml of a solution of 250 g/l barium chloride R. Shake and hold for 1 minute. To 2.5 ml of the resulting solution add 15 ml of the test solution prepared as indicated in the pharmacopeical monograph, and 0.5 ml of acetic acid R.

In parallel with the same amounts of reagents and under the same conditions, prepare a standard using 15 ml of a standard solution of sulfate (10 ppm SO_4) R instead of the test solution.

After 5 minutes opalescence of the test solution should not exceed opalescence of the standard.

Reaction equation and observations: *Result:*

Ammonium salts

Before starting work, it is necessary to complete the preparation of the ammonium reference solution (1 ppm NH_4^+) R: immediately before use the resulting solution must be diluted with water R 2.5 times.

METHOD A

Quantity of the test sample specified in the pharmacopeical monograph is placed in a test tube, dissolved in 14 ml of water R, if necessary, made alkaline with diluted sodium hydroxide solution R and diluted with water R to a volume of 15 ml. Add 0.3 ml of alkaline potassium tetraiodomercurate solution R. The test tube is closed.

As a standard use a solution obtained by adding 5 ml of water R and 0.3 ml of alkaline potassium tetraiodomercurate solution R to 10 ml of ammonium standard solution (1 ppm NH_4^+) R. The test tube is closed.

After 5 minutes yellow color of the test solution should be no more intense than the color of the standard.

Reaction equation and observations: *Result:*

Heavy metals

All methods described below require use thioacetamide reagent R. It is permissible to use sodium sulfide solution R1 (0.1 ml) instead of thioacetamide reagent R. If the test procedure prescribed in a pharmacopeical monograph was developed using thioacetamide reagent R, but sodium sulfide solution R1 is used instead, then for methods A, B and H, it is necessary to introduce a test solution prepared from the same amount of the test sample that is used in the preparation of the test solution to which is added the same volume of a standard lead solution as in the preparation of the

reference solution. Test is considered invalid if color of the test solution is less intense than the color of the reference solution.

Before starting work it is necessary to complete the preparation of the lead standard solution (1 ppm Pb^{2+}) P:

The resulting standard solution of lead (0.1% Pb^{2+}) R must be diluted with water R 10 times — you will get a standard solution of lead (100 ppm Pb^{2+}) R. This solution must also be diluted with water R 10 times — you will get a standard solution of lead (10 ppm Pb^{2+}) R. This solution must be diluted with water R 10 times — you will get a standard solution of lead (1 ppm Pb^{2+}) R.

METHOD A

Test solution. 12 ml of the aqueous solution of the test sample specified in the pharmacopeical monograph.

Reference solution (standard). A mixture of 10 ml of a standard solution of lead (1 ppm Pb^{2+}) R or a standard solution of lead (2 ppm Pb^{2+}) R, specified in a pharmacopeical monograph, and 2 ml of an aqueous solution of the test sample specified in a pharmacopeical monograph.

Control solution. A mixture of 10 ml of water R and 2 ml of the aqueous solution of the test sample specified in the pharmacopeical monograph. To each solution add 2 ml of buffer solution pH 3.5 R and mix. The resulting solutions are added to 1.2 ml portions of thioacetamide reagent R and immediately mixed. Comparison of solutions is carried out after 2 minutes.

System suitability: Reference solution is light brown in color compared to the control solution.

Result: Color of the test solution should be no more intense than color of the reference solution. If the test result cannot be clearly assessed, filter the solutions through a suitable membrane filter (nominal pore size 0.45 μm). Syringe plunger pressure should be moderate and constant to ensure slow and even filtration. Colors of membrane filters obtained in experiments with different solutions are compared.

Reaction equations and observations: *Result:*

Conclusion on sodium bicarbonate:

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_____

Conclusion on sodium chloride:

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List of literature

1.*Pharmaceutical* chemistry : textbook / ed. G. V. Ramenskaya. – Moscow: GEOTAR-Media, 2023. – 384 p.

2.*Tsurkan, O. O.* Pharmaceutical chemistry. Analysis of the Medicinal Substances according to Functional Groups: study guide / O. O. Tsurkan. – Kyiv : AUS Medicine Publishing, 2018. – 152 p.

3.*Pharmaceutical* analysis: The study guide for students of higher schools / ed. by V. A. Georgiyants. – Kharkiv : NUPh Golden Pages, 2018. – 494 p.

4.*European* Pharmacopeia / European Directorate for the quality of medicines and healthcare. 10th edition, Supplement 10.0. Vol. 1. Council of Europe, Strasbourg, 2019. – 4312 p.

5.Lecture and information material.

Lesson 14
FINAL LESSON «METHODS OF PHARMACOPOEIAL ANALYSIS»

Objective: monitoring students' knowledge on lesson topics 9–13.

Test questions:

Block 1. Reactions for identification and detection of impurities

1. Identification reactions to inorganic cations: aluminum, calcium, magnesium, zinc.
2. Identification reactions to inorganic cations: ammonium salts, ammonium salts and salts of volatile bases, potassium, sodium.
3. Identification reactions to inorganic cations: lead, silver, antimony.
4. Identification reactions to inorganic cations: bismuth, iron, arsenic, mercury.
5. Identification reactions to inorganic anions: bromides, iodides, chlorides, silicates.
6. Identification reactions to inorganic anions: carbonates and bicarbonates, nitrates, nitrites.
7. Identification reactions to inorganic anions: sulfates, sulfites, phosphates.
8. Identification reactions to organic substances: acetates, acetyl, benzoates, salicylates.
9. Identification reactions to organic substances: alkaloids, primary aromatic amines.
10. Identification reactions to organic substances: barbiturates, tartrates.
11. Identification reactions to organic substances: xanthines, tartrates.
12. Identification reactions to organic substances: lactates, citrates, esters.
13. General and specific methods for detecting impurities. Tests for the maximum content of impurities: ammonium salts (A, D), arsenic (A, B).
14. General and specific methods for detecting impurities. Tests for the maximum content of impurities: calcium, chlorides, fluorides, sulfates.
15. General and specific methods for detecting impurities. Tests for maximum impurity content: magnesium, magnesium and alkaline earth metals, phosphates, potassium.
16. General and specific methods for detecting impurities. Tests for maximum impurity content: heavy metals, iron, aluminum.

Block 2. Pharmacopoeial tests

1. Determination of melting point (capillary method, open capillary method, instant melting method). Device design.
2. Determination of solidification temperature, dripping point, temperature limits of distillation and boiling point. Device design.
3. Determination of density. Types of density. Devices for determining density.
4. Determination of liquids viscosity. Types of viscosity. Instruments for determining viscosity.
5. Nature of foreign substances in medicines. Impurities: definition, classification (is the structure known, is the maximum permissible level established, by nature, by relative toxicity). Qualification of impurities. Determination of associated impurities.
6. Sources of impurities. Methods for determining impurities: chemical, instrumental. Determination methods: standard, non-standard. Aimes test.
7. Determination of liquids transparency and degree of turbidity. Preparation of standards.
8. Determination of liquids coloring degree. Preparation of standards.
9. Determination of volatile substances and water: micro- and semi-micro method according to Fischer, distillation method, electrolytic hygrometer.
10. Determination of volatile substances and water: loss in mass upon drying. Determination of total ash and sulphate ash.
11. Residual solvents: general concept, classification, toxicity, definition.
12. Determination of microbiological purity of non-sterile products. General principles. Eligibility. Criteria. Test methodology. Application in pharmaceutical analysis.

13. Electrochemical methods of analysis. General characteristics and classification. Basic concepts (electrochemical cell, electrodes, electrolytes).

14. Conductometry (direct conductometry and conductometric titration). Basic principles. Application in pharmaceutical analysis.

15. Potentiometry (ionometry and potentiometric titration). Basic principles. Application in pharmaceutical analysis. Potentiometric determination of pH. Ion selective electrodes.

16. Voltammetry (direct voltammetry and amperometric titration). Basic principles. Voltammogram. Application in pharmaceutical analysis.

List of literature

See the literature lists for lessons 9–13.

Lesson 15

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

Objective: familiarize students with the methods of production, properties, quality control and storage conditions of water various types included in the State Pharmacopoeia of the Republic of Belarus; develop students' skills in performing pharmacopoeial quality control of purified water; with the basic principles of analytical methods validation; teach students statistical processing of chemical experiment results and justify choice of a quantitative determination method.

Requirements for the initial level of knowledge: review the basics of direct conductometry; impurities determination of chlorides, sulfates, reducing substances, ammonium salts in pharmaceutical substances; repeat approximate algorithm for statistical data processing; fundamentals of titrimetric, spectrometric, chromatographic and electrochemical methods of analysis.

Problems for discussion:

1. Types of water in accordance with the State Pharmacopoeia of the Republic of Belarus. Pharmacopoeial water quality control.
2. Purified water («in bulk» and in containers). Production, properties, testing, storage.
3. Highly purified water. Production, properties, testing, storage.
4. Water for injections («in bulk» and sterile). Production, properties, testing, storage.
5. Electrical conductivity. Determination of water specific electrical conductivity.
6. Determination of total organic carbon content in water for pharmaceutical use.
7. Microbiological criteria for test results of various types of water.
8. Water quality control in a pharmacy.
9. Pharmacopoeial requirements for statistical processing and validation. Statistical processing of chemical experiment results.
10. Validation of analytical methods used in pharmaceutical analysis. Basic validation characteristics of methods and tests.
11. Prerequisites for choosing a method for the quantitative determination of a medicine depending on its chemical structure and the object of analysis.
12. Features of pharmaceutical substances, dosage forms and impurities analysis.
13. Application of titrimetric, spectrometric, chromatographic and other methods for quantitative analysis.
14. Calculation of substance content based on the analytical signal value.

Assignments for student independent work

1. Fill out the table indicating standards if needed and presence/absence.

		Highly purified water	Purified water		Water for injections	
			in bulk	in containers	in bulk	sterile
Production	Microbiological purity					
	Total organic carbon					
	Electrical conductivity					
Tests	Nitrates					
	Aluminum					
	Bacterial endotoxins					
	Heavy metals					
	Acidity or alkalinity					
	Reducing agents					
	Chlorides					
	Sulfates					
	Ammonium salts					
	Calcium and magnesium					
	Residue after evaporation					
	Microbiological purity					
	Electrical conductivity					
	Mechanical inclusions					
	Sterility					

2. Suggest a quantitative determination method for: a) pharmaceutical substance drotaverine hydrochloride, b) the medicine streptomycin sulfate. Give reasons for your answer.

3. Fill out the table for compliance between validation characteristics and test types.

	Identification	Quantitative testing for impurities	Limit tests for impurities	Quantitation
Specificity				
Correctness				
Precision				
Detection limit				
Limit of quantitation				
Linearity				
Range of application				
Sustainability				

Algorithm for performing laboratory work
«Pharmacopoeial quality control of purified water in containers»

Goal of the work: develop students' skills in monitoring the quality of purified water in containers in accordance with the State Pharmacopoeia of the Republic of Belarus.

Execution order

Nitrates. No more than 0.00002% (0.2 ppm).

Place 5 ml of the test sample in a test tube immersed in an ice bath, add 0.4 ml of a solution of 100 g/l potassium chloride R, 0.1 ml of a solution of diphenylamine R and drop by drop with stirring 5 ml of nitrogen-free sulfuric acid R. Test tube is placed in a water bath heated to a temperature of 50 °C. After 15 minutes blue color of the test solution should be no more intense than color of the standard prepared in parallel using a mixture of 4.5 ml of nitrate-free water R and 0.5 ml of a nitrate standard solution (2 ppm NO_3^-) R.

ATTENTION!!! It is necessary to complete the preparation of a standard solution of nitrate (100 ppm NO_3^-), from which a standard solution of nitrate (10 ppm NO_3^-) R and then a standard solution of nitrate (2 ppm NO_3^-) R are prepared in accordance with the State Pharmacopoeia of the Republic of Belarus.

Nitrate reference solution (100 ppm NO_3^-). 5002100.

A sample of potassium nitrate R corresponding to 0.815 g of KNO_3 is dissolved in water R and brought to a volume of 500.0 ml with the same solvent.

Immediately before use the resulting solution is diluted with water R 10 times.

Nitrate reference solution (10 ppm NO_3^-). 5002101.

Immediately before use nitrate reference solution (100 ppm NO_3^-) **diluted with water R 10 times.**

Nitrate reference solution (2 ppm NO_3^-). 5002102.

Immediately before use nitrate reference solution (10 ppm NO_3^-) **diluted with water R 5 times.**

Reaction equation:

Analytical effect:

Result:

Electrical conductivity

Carry out in off-line or in-line mode under the following conditions.

EQUIPMENT

Measuring chamber:

– electrodes must be made of appropriate material, for example stainless steel;

– chamber constant: chamber constant is usually certified by the manufacturer and then tested at specified intervals using a certified standard solution having a conductivity of less than 1500 μS/cm, or relative to a chamber with a certified chamber constant value; chamber constant is considered confirmed if the found value is within 2% of the certified value; if there is a discrepancy, it is necessary to re-calibrate.

Conductivity meter: accuracy 0.1 μS/cm or better.

Calibration system (measuring chamber and conductivity meter):

– relative to one or more relevant certified standard solutions;

– accuracy: within 3% of the measured electrical conductivity plus 0.1 μS/cm.

Conductivity meter calibration: calibrate for each measurement range used after disconnecting the chamber and using certified precision resistors or similar devices with an uncertainty of no more than 0.1% of the certified value.

If the in-line measuring chamber cannot be dismantled, the calibration system can be carried out relative to a calibrated measuring device with the measuring chamber located close to the calibrated chamber in the water flow.

Temperature measurement: deviation ±2 °C.

METHODOLOGY

Measure electrical conductivity without temperature compensation while simultaneously recording temperature. Temperature compensated measurements can be carried out after appropriate validation. The test water satisfies the requirements if the measured electrical conductivity at the measured temperature does not exceed the value specified in table 0008.-2 (SPh RB).

If the temperature value is not indicated in table 0008.-2, then the maximum possible electrical conductivity is calculated by interpolation between the next lowest and next highest table values.

Required values of electrical conductivity at a certain temperature

Temperature (°C)	**Electrical conductivity ($\mu S \cdot cm^{-1}$)**
0	2.4
10	3.6
20	4.3
25	5.1
30	5.4
40	6.5
50	7.1
60	8.1
70	9.1
75	9.7
80	9.7
90	9.7
100	10.2

Values:

Result:

Acidity or alkalinity

To 10 ml of the test sample, freshly boiled in a borosilicate glass flask and cooled, add 0.05 ml of a solution of methyl red R. The solution should not turn red. To 10 ml of the test sample add 0.1 ml of bromothymol blue solution R1. The solution should not turn blue.

Observations:

Result:

Reducing agents

To 100 ml of the test sample add 10 ml of diluted sulfuric acid R, 0.1 ml of 0.02 M potassium permanganate solution and boil for 5 minutes. The solution should retain a faint pink color.

Reaction equation:

Analytical effect:

Result:

Chlorides

To 10 ml of the test sample add 1 ml of diluted nitric acid R and 0.2 ml of silver nitrate solution R2. There should be no visible changes in the solution within 15 minutes.

Reaction equation:

Analytical effect:

Result:

Sulfates

To 10 ml of the test sample add 0.1 ml of diluted hydrochloric acid R and 0.1 ml of barium chloride solution R1. There should be no visible changes in the solution within 1 hour.

Reaction equation:

Analytical effect:

Result:

Ammonium salts. No more than 0.00002% (0.2 ppm)

To 20 ml of the test sample add 1 ml of alkaline potassium tetraiodomercurate solution R. After 5 minutes examine the solution along the vertical axis of the test tube. Color of the resulting solution should be no more intense than color of the standard prepared in parallel by adding 1 ml of alkaline potassium tetraiodomercurate solution R to a mixture of 4 ml of ammonium standard solution (1 ppm NH_4^+) R and 16 ml of ammonia-free water R.

ATTENTION!!! It is necessary to complete the preparation of the standard ammonium solution 2.5 ppm NH_4^+ from which the standard ammonium solution (1 ppm NH_4^+) P is prepared, and prepare the necessary standard solution in accordance with the State Pharmacopoeia of the Republic of Belarus.

Ammonium reference solution (2.5 ppm NH_4^+). 5000301

A weighed portion of ammonium chloride R, corresponding to 0.741 NH_4Cl, is dissolved in water R and brought to a volume of 1000.0 ml with the same solvent.

Immediately before use the resulting solution is diluted 100 times with water R.

Ammonium reference solution (1 ppm NH_4^+). 5000302.

Immediately before use the ammonium standard solution (2.5 ppm NH_4^+) P is diluted 2.5 times with water R.

Reaction equation: *Observations:* *Result:*

Calcium and magnesium

To 100 ml of the test sample add 2 ml of ammonia buffer solution pH 10.0 R, 50 mg of black mordant 11 indicator mixture R and 0.5 ml of 0.01 M sodium edetate solution. A blue color appears.

Reaction equation: *Analytical effect:* *Result:*

Conclusion on the analyzed water sample:

_____

_____

Comparative analysis of water samples, mark using +/- signs according to compliance of the water samples to the tested parameters:

Index	Sample 1	Sample 2	Sample 3	Sample 4
Electrical conductivity				
Nitrates				
Acidity or alkalinity				
Reducing agents				
Chlorides				
Sulfates				
Ammonium salts				
Calcium and magnesium				

List of literature

1. *Pharmaceutical* chemistry : textbook / ed. G. V. Ramenskaya. – Moscow: GEOTAR-Media, 2023. – 384 p.

2. *Tsurkan, O. O.* Pharmaceutical chemistry. Analysis of the Medicinal Substances according to Functional Groups: study guide / O. O. Tsurkan. – Kyiv : AUS Medicine Publishing, 2018. – 152 p.

3. *Pharmaceutical* analysis: The study guide for students of higher schools / ed. by V. A. Georgiyants. – Kharkiv : NUPh Golden Pages, 2018. – 494 p.

4. *European* Pharmacopeia / European Directorate for the quality of medicines and healthcare. 10th edition, Supplement 10.0. Vol. 1. Council of Europe, Strasbourg, 2019. – 4312 p.

5. Lecture and information material.

Lesson 16

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

Objective: introduce students to methods of preparation, structural formulas, properties, quality control, chemical basis of pharmacological action and storage conditions of pharmaceutical substances derived from s-elements; develop students' skills in pharmacopoeial quality control of pharmaceutical substances — s-elements derivatives.

Requirements for the initial level of knowledge: repeat features of s-elements — chemical elements of groups IA and IIA in the Periodic Table; general characteristics, physical and chemical properties of s-elements.

Problems for discussion:

1. Methods of preparation, structural formula, properties, quality control, chemical basis of pharmacological action and storage conditions of s-elements derivatives: barium sulfate, magnesium oxide light and heavy, magnesium hydroxide, magnesium sulfate heptahydrate, anhydrous calcium chloride, hexahydrate and dihydrate.

2. Organic and inorganic salts of magnesium (pidolate, lactate, stearate, gluconate, aspartate, acetate, light and heavy carbonate, sulfate, chloride, citrate, etc.) and calcium (nitrate, glycerophosphate, carbonate, lactate, stearate, chloride, etc.). Chelated forms of magnesium. Influence of anion nature on the bioavailability of the cation.

Situational tasks

1. Specify which magnesium compounds (light oxide, heavy oxide, hydroxide, light carbonate, heavy carbonate, etc.) are best suited in antacids? Explain your answer.

2. A customer came to the pharmacy with a request to sell a medicine to eliminate magnesium deficiency. Insomnia, night cramps, nervous exhaustion are observed. What magnesium preparations can be selected? Explain the answer based on your knowledge of the bioavailability of magnesium salts.

3. A pharmaceutical substance of calcium stearate was obtained in the laboratory for analysis. A quantitative determination of calcium and the composition of fatty acids was carried out. 1.5 ml of the titrant solution was used for titration when determining calcium. When determining the composition of fatty acids, the areas of the chromatographic peaks belonging to palmitic and stearic acids of the test solution were 13,000 and 5,560, respectively, and the corresponding parameters for the comparison solution were 12,500 and 4,900. Draw a conclusion about the quality of the analyzed sample.

4. When determining loss in mass during drying of anhydrous magnesium citrate, the following data were obtained: mass of the empty weighing bottle — 10.850 g; mass of the weighing bottle after drying — 10.878 g. pH of the solution is 7.4. Degree of turbidity of the solution does not exceed standard II and color does not exceed standard Y5. Draw a conclusion about quality of the analyzed sample.

Algorithm for performing laboratory work
«Quality control of pharmaceutical substances magnesium sulfate heptahydrate and calcium chloride dihydrate»

Goal of the work: develop students' quality control skills of magnesium sulfate heptahydrate and calcium chloride dihydrate.

1. Quality control of the pharmaceutical substance magnesium sulfate heptahydrate
1.1. IDENTIFICATION

A. Test sample gives reaction to sulfates.

a) About 45 mg of the test sample is dissolved in 5 ml of water R. To the resulting solution add 1 ml of diluted hydrochloric acid R and 1 ml of barium chloride solution R1; a white precipitate forms.

Reaction equation:

Analytical effect:

Result:

b) To the suspension obtained as a result of reaction (a) add 0.1 ml of 0.05 M iodine solution; yellow color of iodine does not disappear (unlike sulfites and dithionites), but becomes discolored when a solution of tin chloride R is added dropwise (unlike iodates). Mixture is boiled; precipitate is not colored (unlike selenates and tungstates).

Reaction equations:

Analytical effect:

Result:

B. Test sample gives reaction to magnesium.

About 15 mg of the test sample is dissolved in 2 ml of water R. To the resulting solution add 1 ml of diluted ammonia solution R1; a white precipitate is formed, which dissolves when 1 ml of ammonium chloride solution R is added. 1 ml of disodium hydrogen phosphate solution R is added to the resulting solution; a white crystalline precipitate is formed.

Reaction equations: *Analytical effect:* *Result:*

1.2. QUANTITATION

Dissolve 0.250 g of the test sample in 100 ml of water R, add 10 ml of ammonia buffer solution pH 10.0 R and carry out complexometric titration of magnesium (2.5.11). Add about 50 mg of indicator mixture of black mordant 11 R (eriochrome black T). The solution is heated to a temperature of about 40 °C and titrated at this temperature with 0.1 M sodium edetate solution until the violet color changes to blue.

1 ml of 0.1 M sodium edetate solution corresponds to 12.04 mg of $MgSO_4$.

Weight loss during drying is 48.0–52.0 %, i. e. it is necessary to take into account content of crystalline water.

Reaction equations: *Formulas and calculations:* *Result:*

Conclusion on magnesium sulfate heptahydrate:

_____

_____

2. Quality control of pharmaceutical substance calcium chloride dihydrate

SOLUTION S. 15.0 g of the test sample is dissolved in carbon dioxide-free water R prepared from distilled water R and diluted to a volume of 100 ml with the same solvent.

2.1. IDENTIFICATION

A. Solution S gives reaction (a) to chlorides.

a) 2 ml of the solution specified in the pharmacopeical monograph is acidified with diluted nitric acid R, add 0.4 ml of silver nitrate solution R1, mix and settle; a white cheesy precipitate is formed, which is centrifuged and washed with three portions of water R, 1 ml each. This operation is carried out quickly in a place protected from bright light, and it is allowed that the liquid above the sediment is not completely transparent. The precipitate is suspended in 2 ml of water R and 1.5 ml of ammonia solution R is added; the precipitate dissolves quickly; the presence of several large particles that dissolve slowly is allowed.

Reaction equations: *Analytical effect:* *Result:*

B. Test sample gives reaction (a) and (b) to calcium.

b) To 5 ml of the solution specified in the pharmacopeical monograph, add 0.5 ml of potassium ferrocyanide solution R; the solution remains clear. About 50 mg of ammonium chloride R is added to the solution; a white crystalline precipitate is formed.

Reaction equation: *Analytical effect:* *Result:*

Conclusion on calcium chloride dihydrate:

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List of literature

1. *Pharmaceutical* chemistry : textbook / ed. G. V. Ramenskaya. – Moscow: GEOTAR-Media, 2023. – 384 p.

2. *Tsurkan, O. O.* Pharmaceutical chemistry. Analysis of the Medicinal Substances according to Functional Groups: study guide / O. O. Tsurkan. – Kyiv : AUS Medicine Publishing, 2018. – 152 p.

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5. Lecture and information material.

Lesson 17

FINAL LESSON «BASIC APPROACHES TO PHARMACOPOEIAL ANALYSIS»

Objective: control of students' knowledge in pharmaceutical chemistry for the 5th semester of study

Credit for the 5th semester in pharmaceutical chemistry is carried out in the form of practical skills test.

List of practical skills for the test:

1. Alkalimetric titration of benzoic acid.
2. Determination of salicylic acid melting point.
3. Refractometric determination of magnesium sulfate 5% solution.
4. Determination of sodium edetate pH.
5. Spectrophotometric determination of chloramphenicol in capsules.
6. Calculation of the results of spectrophotometric, titrimetric, polarimetric and refractometric determination, their interpretation and conclusion on the compliance of the medicinal product with the requirements of regulatory documentation.

List of literature

1. *Pharmaceutical* chemistry : textbook / ed. G. V. Ramenskaya. – Moscow: GEOTAR-Media, 2023. – 384 p.
2. *Tsurkan, O. O.* Pharmaceutical chemistry. Analysis of the Medicinal Substances according to Functional Groups: study guide / O. O. Tsurkan. – Kyiv : AUS Medicine Publishing, 2018. – 152 p.
3. Pharmaceutical analysis: The study guide for students of higher schools / ed. by V. A. Georgiyants. – Kharkiv : NUPh Golden Pages, 2018. – 494 p.
4. *European* Pharmacopeia / European Directorate for the quality of medicines and healthcare – 10th ed., Supplement 10.0. Vol. 1. Council of Europe. – Strasbourg, 2019. – 4312 p.
5. Lecture and information material.

Appendix 1

GENERAL RULES FOR LABORATORY WORK

Each student working in the laboratory is given a place that he must keep neat and clean. When performing work, do not clutter workplace with unnecessary objects. At the end of classes, all students are required to clean up their workplace: carefully inspect and check that electricity, water, appliances and equipment are turned off, remove flammable garbage, wash glassware, hand over reagents to a laboratory assistant. After this hand over the workplace to the laboratory attendants, who in turn hand over the laboratory to the teacher.

When performing laboratory work, the following rules must be strictly followed:

1. Before classes the student needs to get acquainted with the course of the experiments, understand the goals and objectives of the work, think about each action. One can start performing experiments only after the student has submitted a preliminary report (title, brief description of the course of the experiment, reactions) and passed an interview. Admission to work in the form of a signature from the teacher is noted in the student's work log.

2. When performing experiments, it is necessary to know the basic properties of the substances used and obtained, their effect on the body, the rules for working with them, and based on this, take all measures for the safety of the work.

3. It is prohibited to conduct experiments in dirty containers, as well as to use substances from bottles without labels or with illegible inscriptions for experiments.

4. Do not pour excess reagent from the test tube back into the reagent flask. Dry salts are collected with a clean spatula or spoon.

5. Stoppers from different bottles should not be confused. To keep the inside of the cork clean the cork is placed on the table with its outer surface.

6. You cannot take public reagents to your workplace.

7. After the experiments the remaining metals are not thrown into the sink, but collected in a jar. Expensive reagents (for example, residual silver salts) are collected in specially designated containers. Do not pour residual solvents, flammable substances, reaction mixtures, solutions of acids, alkalis and other harmful substances into the sink. They must be collected in special containers ("waste organic matter", "waste acids", "waste alkalis").

8. It is forbidden to clog sinks and drains in cabinets with sand, paper, broken glassware and other solid waste, which leads to failure of the sewer system. All solid waste should be disposed of in the trash.

9. When performing work, use reagents, electricity and water carefully. Do not leave electrical appliances or burning alcohol lamps on unnecessarily. Upon completion of work, you must immediately turn off electrical appliances and put out the alcohol lamps.

10. Performing laboratory work and each individual experiment requires strict adherence to all instructions. Experiment must be performed carefully, accurately and without haste.

11. Students are strictly prohibited from conducting any experiments that are not related to current work or changing order of the experiment without permission of the teacher. It should be remembered that every experiment, even one that seems outwardly simple, can turn out to be dangerous if carried out thoughtlessly.

SAFETY REGULATIONS

1. It is strictly forbidden to work alone in the laboratory, because even a small undetected malfunction in equipment or an error in performing an experiment can lead to serious consequences.

2. During all work silence, cleanliness and order in the workplace must be maintained. It must be remembered that carelessness, inattention, as well as insufficient familiarity with the properties of substances and operation of devices can lead to an accident.

3. Avoid direct contact of skin, eyes and respiratory tract with reagents. Wear a lab coat and cap at all times during class.

4. All work with toxic and strong-smelling substances, concentrated solutions of acids, alkalis, as well as evaporation of their solutions should be carried out only in a fume hood. During operation cabinet doors should be lowered to 18-20 cm from its working surface.

5. Grinding solids that produce caustic dust (alkalis, lime, iodine, etc.), diluting concentrated acids and alkalis, preparing a chrome mixture, etc. should be carried out in porcelain dishes and in a fume hood, protecting your eyes with goggles and your hands with gloves. When diluting concentrated acids, especially sulfuric acid, carefully pour the acid into water.

6. Do not work with flammable liquids near heating devices. It is prohibited to heat volatile flammable liquids and substances (ethers, gasolines, alcohols, acetone, etc.) over an open flame. To do this you must use a water or oil bath.

7. Handling an alcohol lamp. Before use alcohol lamp must be filled with ethanol (no more than 2/3 of the volume of the alcohol lamp), disk tightly covers opening of the alcohol lamp reservoir, wick in the tube should not fit too tightly, but also not fall out of the tube. When not in use, alcohol lamp must be closed with a cap. Alcohol lamp is lit only from a burning match. You cannot light it from another alcohol lamp or from a lighter. You should never blow on a burning alcohol lamp. Simmer it covering it with a cap. Heating on an alcohol lamp is carried out as follows: first, warm up the test tube with the contents for 15–20 seconds, then proceed directly to heating the contents of the test tube. When heating, do not touch the bottom of the test tube to the wick. An alcohol lamp can only heat dishes made of thin (chemical) glass.

8. Test tubes should be filled with reagents to ½–¼ volume. When heated, the test tubes are fixed either in a tripod claw or in a test tube holder closer to the hole. Opening of the test tube must be directed away from yourself and others to avoid the release of substances from the test tube.

9. When getting acquainted with the smell of a substance, you should not bend over a vessel with liquid and inhale deeply. To do this you need to direct a stream of air from the opening of the vessel towards yourself with your hand and take a light breath through your nose.

10. Liquid should be drawn into pipettes using a special dispenser or rubber bulb. Do not draw liquids into pipettes with your mouth! Upper hole of the pipette is closed with the index finger. Liquid is measured by holding the pipette so that the mark corresponds to the lower edge of the meniscus and is at eye level. Keep the pipette vertical. After liquid has flowed out tip of the pipette is touched to the glass vessel. Do not blow out any liquid remaining in the pipette.

11. Particular care must be taken when assembling glass installations. At the same time you cannot clamp glass products into the legs of tripods without an appropriate soft pad. Handle thin-walled glassware, thermometers and refrigerators with particular care.

12. You cannot heat any sealed apparatus or vessels, except those specifically designed for this purpose. Do not heat liquids in thick-walled or measuring containers (they may burst).

13. When pouring reagents, do not lean over the opening of the vessel to avoid splashes on your face and clothes.

14. It is prohibited to taste reagents in the laboratory, as well as to eat or drink.

15. You cannot place foreign objects (bags, hats, etc.) on laboratory tables, or hang outerwear in the laboratory.

16. Any incident in the laboratory, no matter how minor, must be reported to the teacher or laboratory assistant.

17. You must not leave substances in unlabeled containers; you must not use reagents from jars without labels or with questionable labels.

FIRE SAFETY RULES

1. Handle heating devices with care. It is prohibited to work with faulty equipment and devices. It is strictly forbidden to use electrical appliances with exposed wires or damaged insulation for connection. If an electric stove's spiral burns out, disconnect the stove from the power supply.

2. When conducting experiments in which spontaneous combustion may occur, it is necessary to have an asbestos blanket, sand, scoop, etc. on hand.

3. In case of ignition of flammable substances quickly turn off ventilation of the fume hood, extinguish alcohol lamp, turn off power to electric heating devices, remove vessels with flammable substances and extinguish the fire:

a) cover burning liquids with asbestos, and then, if necessary, cover them with sand, but do not fill them with water;

b) if a person’s clothing catches fire, it is necessary to cover him with an asbestos blanket;

c) extinguish small local fires using a carbon dioxide fire extinguisher; in case of heavy smoke use a gas mask.

SAFETY RULES WHEN WORKING WITH ACIDS AND ALKALI

1. Concentrated acids and alkalis should be stored in a fume hood in a durable container on a tray. Large bottles of concentrated acids and ammonia are kept in baskets.

2. All work with concentrated acids and alkalis must be carried out in a fume hood.

3. Dilution of acids should be carried out in thin-walled glass or porcelain containers, and acid should be added to water in small portions. You cannot add water to concentrated acid, since in this case a large amount of heat is released. Water as a less dense substance boils on the surface of the acid, and liquid can be thrown out of the vessel. Be sure to pour acids through a funnel, protecting your eyes with safety glasses.

4. Remains of acids and alkalis are poured into a special container.

SAFETY REGULATIONS WHEN WORKING WITH PHENOL

Phenol (hydroxybenzene, carbolic acid) is colorless crystals that turn pink in the light. Phenol is a poison that paralyzes nerves. Dust, solutions and phenol vapors irritate mucous membranes of the respiratory tract, eyes, and skin.

1. Phenol should be stored in a dark glass container with a tightly ground stopper in a fume hood.

2. All work with phenol should be carried out in a fume hood wearing rubber gloves.

FEATURES OF THE WORK WITH SOME ORGANIC SOLVENTS

Organic solvents serve as a medium for many reactions. Solvents used must be pure, analytical grade. (pure for analysis) or "reagent grade". (chemically pure). Organic solvents are liquid products belonging to various classes of organic compounds - hydrocarbons, ethers and esters, alcohols, etc.

1. Aliphatic hydrocarbons (pentane, hexane, heptane, isooctane, octane, petroleum ether) are flammable liquids. Pentane, hexane and petroleum ether are especially dangerous in terms of fire. They have a low flash point and form explosive mixtures with air. Vapors of aliphatic hydrocarbons have a mild narcotic effect and are hazardous to health in high concentrations.

2. Aromatic hydrocarbons are colorless liquids with a characteristic odor. Benzene, toluene and xylene are flammable. Benzene is one of the most hazardous solvents. It enters body mainly through inhalation of vapors, but can also penetrate through intact skin. Acts as a strong poison. The most pronounced changes are in the hematopoietic system, and the consequences of benzene poisoning sometimes appear after several years. Toluene and xylene act similarly to benzene, but due to their lower volatility, they are less hazardous to work with.

3. Chlorine derivatives of hydrocarbons have a higher dissolving ability compared to hydrocarbons, but contain more impurities. Dichloroethane is a flammable liquid, while methylene chloride, chloroform and carbon tetrachloride are non-flammable. Chlorinated hydrocarbons should be stored in dark glass jars without access to air since they decompose in light and when exposed to oxygen. Vapors of chlorinated hydrocarbons have a narcotic effect. Particularly strong poisons are carbon tetrachloride and dichloroethane which cause damage to the liver, kidneys and other organs when their vapors are inhaled. Able to be absorbed through the skin.

4. Ethers (diethyl ether, tetrahydrofuran, dioxane) are flammable liquids. Diethyl ether is especially dangerous in terms of fire safety: it has very high volatility at room temperature, its vapors are heavier than air and can spread over the surface of the workbench forming explosive mixtures with air. Before working with ethers, you should always check them for the presence of peroxides, and if detected, carry out additional purification. Ether vapors have a strong narcotic effect.

5. Esters (ethyl acetate, butyl acetate) are flammable liquids. Their vapors in high concentrations have a narcotic effect.

6. Alcohols are the most common solvents in laboratory practice and are classified as flammable liquids. Alcohols are strong medicines, and isopropyl and propyl alcohols are poisonous mainly when taken orally. Methanol is one of the most dangerous poisons among organic solvents in terms of its effect on the body. If 5-10 ml of methanol enters the stomach it can cause blindness, and a dose of 30-50 ml is fatal. Visual disturbances also occur when inhaling methanol vapors and when absorbing it through the skin.

7. Acetone belongs to the class of ketones and is a highly volatile solvent. It is extremely dangerous in terms of fire safety. Vapors form explosive mixtures with air. When working with acetone, special precautions should be taken: do not allow vapors to enter the atmosphere, do not use open fire as a heating source. In terms of its effect on the body acetone is a strong medicine that affects the nervous system. Inhalation of vapors over a long period of time or in high concentrations is dangerous.

8. Acetic acid belongs to the class of carboxylic acids and is a flammable liquid. Has a strong irritating effect. Solutions with acid concentrations above 30% cause skin burns.

9. Acid amides (dimethylformamide, dimethylacetamide) are flammable liquids. Inhalation of amide vapors is harmful to health, but due to their low volatility dangerous concentrations are reached only when evaporated from large surfaces or when heated. Able to penetrate intact skin.

FIRST AID MEASURES IN CASE OF ACCIDENTS

1. In case of cuts, remove glass fragments from the wound with tweezers washed with alcohol, lubricate the edges of the wound with an alcohol solution of iodine and, placing a sterile bandage on the wound, bandage it.

2. In case of wounds with severe bleeding, the bleeding should be stopped by bandaging above the wound site (thick-walled rubber tourniquet), bandaged the victim must be taken to a medical center.

3. For first-degree thermal burns (redness, swelling), the affected area is treated with a 2% solution of potassium permanganate or a 5% alcohol solution of tannin, lubricate the affected area with ointment or burn gel and apply a bandage. For second- and third-degree burns (blisters, ulcers), only disinfectant lotions made from a solution of potassium permanganate are permissible, after which you must consult a doctor.

4. In case of chemical burns, it is necessary, first of all, to remove the substances that caused the burns from the skin, and then treat them accordingly:

a) in case of burns with acids or alkalis, wash the burned area with a strong stream of water, and then neutralize the acid with a 1-2% solution of sodium bicarbonate, and the alkali with a 1-2% solution of acetic or boric acid;

b) for burns with bromine, treat the affected area with a 10-20% solution of sodium thiosulfate, wash it off with plenty of water and then apply a gauze swab moistened with a 5% urea solution; You can wash the affected area with ethyl alcohol and lubricate the affected area with glycerin;

c) for burns with liquid phenol, rub the whitened area of skin with glycerin until the normal color is restored, rinse with water and apply a gauze swab moistened with glycerin;

d) if aggressive organic substances come into contact with the skin, the affected area is washed with 96% ethyl alcohol and then lubricated with ointment or gel for burns.

5. In case of chemical burns of the eyes with acid or alkali, it is necessary to rinse the eyes abundantly with water for 3-5 minutes, and then with a 1-2% solution of sodium bicarbonate (if acid has got in) or 2% solution of boric acid (if alkali has got in).

6. In case of inhalation injuries (poisoning by laboratory gases), the victim must be immediately taken out into fresh air, freed from constricting clothing, placed in absolute rest, placed on his back, wrapped warmly and called a doctor. In case of phenol vapor poisoning, it is strictly forbidden to drink milk.

7. In case of electric shock, you must immediately turn off power supply using a switch. A victim who is under current should not be touched with unprotected hands (without rubber gloves). If the victim loses consciousness, it is necessary to immediately apply artificial respiration after turning off the current.

8. In case of poisoning, severe burns and electric shock, you should immediately consult a doctor.

Учебное издание

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ФАРМАЦЕВТИЧЕСКАЯ ХИМИЯ

PHARMACEUTICAL CHEMISTRY

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

На английском языке

В двух частях

Часть 1

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