MINISTRY OF HEALTH PROTECTION OF UKRAINE

ODESSA NATIONAL MEDICAL UNIVERSITY

Faculty Pharmaceutical

(faculty name)

Department Pharmaceutical chemistry and drug technology

(name of department)

I APPROVE

Vice-rector for scientific and pedagogical work

_____ Eduard BURYACHKIVSKY

" 01 " September 20 23

METHODOLOGICAL DEVELOPMENT
TO THE LECTURE AND FROM THE ACADEMIC DISCIPLINE

Faculty, course Pharmaceutical, course 4

Academic discipline Drug technology

(name of academic discipline)

Approved:

Meeting of the Department of Pharmaceutical Chemistry and Drug Technology

Odessa National Medical University

Protocol No. 1 dated August 28 , 2023 .

Head Head of the department _____ Volodymyr HELMBOLDT

(signature) (First name, last name)

Developers:

Assoc. Zamkovaya A.V.

Lecture No. 1

Topic: " Requirements for sterile products. Determination of the main indicators of the quality of ampoule glass. Industrial production of injection solutions" - 2 hours.

Relevance of the topic: Drug technology (industrial technology of drugs) is one of the fundamental technological sciences. It consists of several key aspects that are important for modern medicine and patients: Effectiveness and safety - Modern technologies make it possible to produce drugs with high efficiency and safety for patients. Exact dosage, quality control and the absence of impurities make medicines more effective and safer. Innovations in medicine: New technologies allow the creation of innovative drugs that can be more targeted and effective drug therapy. For example, drugs designed to precisely affect specific cells or genes provide more effective treatments. Minimization of side effects: Technologies make it possible to develop medicinal formulas that minimize side effects and negative effects on the body. This provides a more comfortable and safe treatment for patients. Fast production and delivery process: The use of modern technologies allows to speed up the production process of medicines, which is especially important in the conditions of a rapidly changing medical environment, such as the spread of diseases or epidemics. Individual approach to treatment: Technologies make it possible to develop medicines that take into account the individual characteristics of the patient, which leads to a personalized approach to treatment and increases its effectiveness. Cost-effectiveness and availability Improved manufacturing technologies can reduce production costs, making drugs more accessible to a wide range of patients, providing cost-effectiveness in healthcare.

Thus, the use of modern technologies for the production of medicines is an important factor for improving the effectiveness of treatment, patient safety and the general state of public health.

Goal: To study the general technological scheme of the production of injection solutions, injection solutions of their substances require special cleaning, familiarize yourself with the proper production rules. To learn the methods of stabilization of

injection solutions, to be able to obtain injection solutions with various medicinal and auxiliary substances, to carry out step-by-step control and to be able to standardize the finished product in accordance with the requirements of regulatory and technical documentation, to be able to draw up technological production schemes

Basic concepts: LF for injections - a group of LF introduced into the body using a syringe with a violation of the integrity of the skin or mucous membranes. HF XI: sterile aqueous and non-aqueous solutions, suspensions, emulsions and dry solids (powders and tablets) that are dissolved with sterile water immediately before administration are included in injectable LF. Injection solutions V ≥ 100 ml - infusion

Requirements for injectable solutions.

The main requirements for injectable drugs are sterility, pyrogenicity and the absence of mechanical inclusions. According to the requirements of GF XI - "there must be no mechanical impurities." Requirements of others Countries have a limited number of particles invisible to the naked eye, because in these countries there are devices that allow monitoring of such particles.

Sterility is the complete absence of living microorganisms and their spores.

Pyrogenic - products of vital activity and decay of microorganisms, dead microbial cells. According to the chemical composition, it is a lipopolysaccharide-type Navy from M.M. up to 8 · 106. When a solution containing pyrogens is introduced, it is characterized by increased body temperature, and sometimes a drop in blood pressure, chills, vomiting, diarrhea. This is the thermolability of a substance that is destroyed at a temperature of 250 ºC within 30 minutes. In the production of injectable drugs, pyrogens are removed by various physicochemical methods - by passing the solution through columns with activated carbon, cellulose, and membrane ultrafilters.

Ampoule glass is a substance for making ampoules; should not change the properties of solutions for injections, be chemically and thermally stable, transparent, clean and easy to melt. Boron and aluminum oxides are added to the ampoule glass to increase its chemical resistance . The thermal stability of ampoule glass increases when magnesium oxide is added to its composition. Domestic enterprises use neutral ampoule glass HC-1, HC-3 and alkaline, boron-free ampoule glass AB-1 (for oil solutions) to manufacture ampoules.

Plan and organizational structure of the lecture:

No p.p.	The main stages of the lecture and their content.	Goals in levels of abstraction.	Type of lecture, lecture equipment.	Time allocation.
1	2	3	4	5
I 1.	***Preparatory stage*** Determination of educational goals.		The lecture is combined	1%
2.	Providing positive motivation.			2%
	The main stage Presentation of lecture material.			90%
II 3.	Plan: 1. Concept of stability of medicines. The basic principle of stabilization. .	I	Slides	
	2. Factors affecting the stability of injection solutions.	II		
	3. Theories of oxidation-reduction processes by A.N. Bach and I.O. Engler.	III		
	4. The theory of branched chains by N. N. Semenov.		List of references, questions, assignments.	

	5. Chemical methods of stabilization. 6. Stabilizers used in the production of injection solutions. 7. Influence of surfactants on the kinetics of chemical reactions. 8. Physical methods of stabilization. 9. Gas protection of injection solutions. 10. Effect of glass quality on the stability of substances. 11. Characteristics of the group of substances that require chemical stabilization. 12. Mechanisms of action of stabilizers: 12.1. Stabilization of solutions of salts of weak bases and strong acids. 12.2. Stabilization of solutions of salts of strong bases and weak acids. 12.3. Stabilization of glucose solutions for			

	injections. 13. Stabilization of solutions of easily oxidizing substances. 13.1. Mechanisms of action of direct antioxidants. 13.2. Mechanisms of action of indirect antioxidants. 13.3. Use of IUD for stabilization of injection solutions. 14. The effect of pH and the presence of heavy metals on the rate of oxidation reactions. 15. Methods of removing oxygen from solvents used in the manufacture of injection solutions. 16. Use of preservatives. 17. Technological methods of stabilization of ampoule solutions			
III	***The final stage***			
4.	Summary of the lecture, general conclusions.			2%
5.	Lecturer's answers to possible questions.			3%
	Tasks for self-training of			2%

6.	students.			

Structural and logical scheme of the content of the lecture

1. Concept of stability of medicines. The basic principle of stabilization.

2. Factors affecting the stability of injection solutions.

3. Theories of oxidation-reduction processes by A.N. Bach and I.O. Engler.

4. The theory of branched chains by N. N. Semenov.

5. Chemical methods of stabilization.

6. Stabilizers used in the production of injection solutions.

7. Influence of surfactants on the kinetics of chemical reactions.

8. Physical methods of stabilization.

9. Gas protection of injection solutions.

10. Effect of glass quality on the stability of substances.

11. Characteristics of the group of substances that require chemical stabilization.

12. Mechanisms of action of stabilizers:

13. Stabilization of solutions of easily oxidizing substances.

14. The effect of pH and the presence of heavy metals on the rate of oxidation reactions.

15. Methods of removing oxygen from solvents used in the manufacture of injection solutions.

16. Use of preservatives.

17. Technological methods of stabilization of ampoule solutions

Content of lecture material (lecture text)

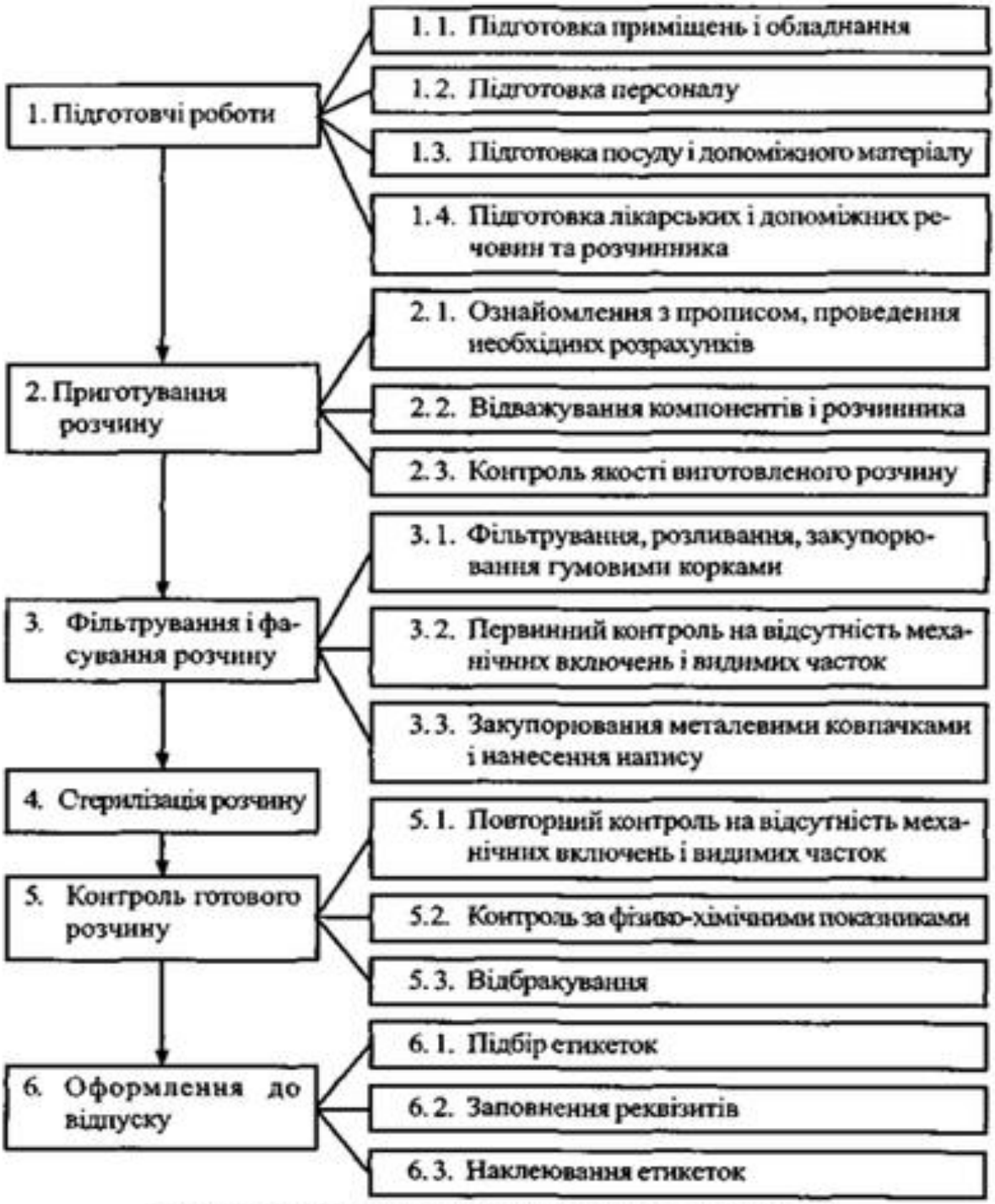


Схема 7.2. Етапи виробничого процесу серійного виготовлення стерильних розчинів

Medicinal products for parenteral use are sterile preparations intended for administration by injection, infusion, implantation into the body of a person or animal. These include solutions, emulsions, suspensions, powders and tablets for obtaining solutions and implants, lyophilized drugs that are administered parenterally (subcutaneously, intramuscularly, intravenously, intraarterially, in various cavities).

Glassware for injection solutions is made of medical glass (neutral or silicate), which are a solid solution (alloy) of silicates, metal oxides and some salts.

Requirements for glass for ampoules

1. Transparency - for visual and optical control for the absence of mechanical inclusions2. Colorlessness - allows you to detect, in addition to mechanical inclusions, a change in the color of the solution3. Low melting point - necessary for high-quality sealing of ampoules at a relatively low temperature to prevent heating of the solution4. Thermal stability the ability of glass products not to be destroyed by sharp temperature fluctuations5. Chemical resistance - guarantees the preservation of medicinal substances and other components of the drug, reflects the ability of glass to leach6. Mechanical strength - resistance to loads during the processing of ampoules during production, transportation, and storage

Indicators of the quality of ampoule glass and ampoules

1. Water resistance
2. Alkalinity
3. Residual voltage
4. Thermal stability
5. Chemical resistance
6. Light-shielding properties (for SNS-1 glass)
7. Visual control of ampoules
8. Radial beating of the ampoule stem relative to the body
9. Deviation from the circumference of ampoules
10. Determining the depth of rarefaction (for ampoules of vacuum filling)
11. Hydrolytic stability
12. For ampoules with a colored break ring, the strength of the break is determined.

Determination of thermal stability of glass ampoules

The thermal stability of glass is its ability not to be destroyed by sharp fluctuations in temperature over 100 °C. Ampoules are considered chemically resistant if at least 98% of the ampoules remain intact after the test.

Determination of the chemical stability of ampoule glass using solutions of indicators (after the color change of acid-base indicators - methyl red and phenolphthalein) and using a pH meter

After determining the quality of the glass, the ampoules are subjected to external and internal washing. External washing is more often carried out by showering or combined with internal washing. The following methods are used for internal washing: syringe, vacuum

After washing the ampoules, they are transferred to drying or sterilization in the shortest possible way and quickly enough to prevent contamination, depending on the conditions of ampoulation. Washed, dried or sterilized ampoules and vials are transferred to the ampoule stage.

Preparation of ampoules for filling

1. Opening of ampoules
2. Determination of ampoule quality
3. Washing
4. Drying
5. Sterilization

Technology of solutions for injections

The production process begins with auxiliary work on production preparation, which includes the following operations:

– sanitary preparation of industrial premises;

– preparation of sterile ventilation air;

- preparation of technological equipment and inventory;

- preparation of technological clothing;

- personnel training.

One of the main stages of the technological process is the preparation of injection solutions for filling vessels. The stage of preparation of the solution includes the following operations: dissolution of substances, isotonization, stabilization, introduction of preservatives, filtration. Depending on the properties of medicinal substances, some operations may be excluded.

Preparation of aqueous or non-aqueous solutions for injections is carried out by the mass-volume method. In cases where the density of the solvent is significantly different from the density of water, the weight method is used. Dissolution of slowly or sparingly soluble medicinal substances is carried out by heating and stirring.

The purified (filtered) solution is transferred to the ampoule filling stage, which includes operations of filling and sealing ampoules.

Filling ampoules with solutions is carried out in three ways: vacuum, vapor condensation and syringe.

Ampoules with solutions can be sealed in two main ways: melting or pulling capillaries.

Bottles with injection forms are closed using corks of special types of rubber and additionally "rolled" with metal caps.

Filled and sealed vessels are subjected to sterilization. Currently, there are three groups of sterilization methods:

1. Mechanical (sterile filtration using depth and membrane filters).

2. Chemical (gas sterilization, addition of antimicrobial preservatives).

3. Physical (thermal, radiation, ultrasonic, and other types of sterilization).

After a positive conclusion about the quality of the finished product according to all NTD indicators, the ampoules are marked and packed on automatic lines in secondary and transport packaging.

Stabilization

Some medicinal substances are unstable during production or storage, cannot withstand the conditions of thermal sterilization, etc. therefore, they can undergo various chemical transformations in solution. At the same time, such chemical reactions as hydrolysis, redox and photochemical processes, isomerization, etc. take place. Many reactions are initiated under the influence of light, air oxygen, elevated temperature during sterilization, changes in the pH value of the solution, chemical impurities in the raw materials, etc.

The stability of injection solutions, first of all, depends on the quality of the original solvents and medicinal substances, class, brand of glass of ampoules and vials, presence of oxygen in water and solutions, pH of solutions, temperature and time of

sterilization, presence of heavy metal ions, production conditions and storage of drugs and others.

Stabilization of solutions is carried out by physical and chemical methods. The following requirements apply to physical methods: separate ampoulation of medicinal substance and solvent, selection of ampoules from chemically resistant material, coating of the inner surface of ampoules with special films, replacement of ampoule glass with polymer, compliance with the principle of gas protection.

Chemical methods are based on the addition of stabilizers or antioxidants. Stabilizers can slow down or eliminate unwanted chemical reactions, create a certain pH value of solutions, increase the solubility of medicinal substances or keep them in a suspended state. The choice of stabilizer depends, first of all, on the nature of medicinal substances.

The stability of medicines depends on:

· storage temperature ;

· illumination;

· the composition of the environment;

· cooking method ;

· auxiliary substances;

· the type of dosage form (especially the aggregate state);

· packaging.

Stabilization methods

1. Physical methods of stabilization

Physical processes occurring in medicinal preparations:

· thickening of dispersed phase particles;

· layering;

· change in consistency;

· evaporation;

· sublimation.

2. Chemical methods of stabilization

The chemical stability of solutions depends on:

quality of solvents and medicinal substances;

class and brand of glass bottles ;

· presence of oxygen in water and solutions;

pH of solutions;

temperature and time of sterilization ;

presence of heavy metal ions;

· storage conditions of drugs.

Chemical processes occurring in medicinal preparations:

· hydrolysis;

· saponification;

oxidation-reduction reaction ;

· decarboxylation;

· isomerization;

· racemization;

· polymerization;

· photochemical destruction.

Chemical methods involve increasing the stability of medicinal substances and preparations in general by adding substances - stabilizers.

Stabilizers are substances that increase the chemical stability of medicinal substances in solutions for injections.

Requirements for stabilizers:

· must be safe for the patient both in its pure form and in combination with the components of the medicinal product (pharmacological indifference);

· must be allowed for use in medical practice;

· must be effective in the used concentrations (perform their functional purpose);

· chemical purity;

· availability.

Mechanism of action of stabilizers

· translation of insoluble active substances into soluble salts or complex compounds;

· creation of a certain pH value of the medium;

· selection of appropriate solvent systems;

· prevention of oxidation-reduction processes

3. Stabilizers of solutions of easily oxidizing substances

Oxidation of medicinal substances in the process of preparation of injection solutions occurs in the presence of oxygen contained in water and above the solution. The oxidation process is significantly enhanced under the influence of sensitizing factors:

· light;

heat ;

value of the environment, etc.

Stabilization of solutions of easily oxidizable substances is carried out by:

introduction of antioxidants;

introduction of complexes for binding heavy metal ions;

· creation of optimal pH limits;

· reduction of the oxygen content in the solvent and above the solution (saturation of CO_2, filling in the stream of inert gas);

· use of light-proof containers to reduce exposure to the initiating light.

Characteristics of antioxidants

To stabilize solutions of easily oxidized substances in pharmaceutical practice, auxiliary substances that prevent oxidation are used - antioxidants.

Antioxidant requirements:

harmlessness in the used doses of both the antioxidants themselves and the products of their metabolism (absence of irritating and allergenic effects);

· efficiency at minimum concentrations;

· good solubility in dispersion medium

Classification of antioxidants

Direct antioxidants include strong reductants with a higher oxidation capacity than medicinal substances stabilized by them.

Indirect antioxidants include substances that form complexes with metal cations, enter into solutions of medicinal substances as impurities from medicinal preparations and are catalysts of oxidation processes.

4. Complex methods of stabilization

Stabilization of solutions for injections by complex methods is carried out by introducing several stabilizers of different types:

several direct antioxidants ;

· direct and indirect antioxidant;

· an antioxidant and a substance that ensures the pH of the environment;

· antioxidant and preservative.

Characteristics of preservatives

Microbiological instability - changes in medicinal products of an oxidative, hydrolytic and other nature under the influence of microorganisms and their products of life (toxins or enzymes).

It is possible to prevent microbiological instability of solutions for injections by adding to them various chemical substances of antibacterial action - antimicrobial stabilizers (preservatives).

Preservatives are auxiliary substances used to prevent contamination and reproduction of microorganisms in medicines.

The choice of preservative is determined by:

· the composition of the medicinal product;

pH of the medium;

· regimen of drug use.

Preservative requirements:

· pharmacological indifference in the used concentration (absence of general toxic, allergenic and local irritant effects);

· a wide range of antimicrobial action at low concentrations;

· good solubility in dispersion medium;

· chemical indifference (absence of chemical interaction with medicinal and auxiliary substances, packaging material;

· stability in a wide range of pH and temperature during the shelf life of the medicinal product;

lack of influence on the organoleptic properties of medicinal products;

maintaining the sterility of medicinal forms during the entire period of their use (reliable antimicrobial activity);

· lack of ability to form resistant forms of microorganisms.

Materials on the activation of students of higher education during the lecture: questions, situational tasks, etc.:

Question:

1. Methods of obtaining injection solutions. The equipment used to obtain them in factory conditions.
2. Methods of filling ampoules with injection solutions.
3. Method of sealing ampoules. Determination of the tightness of ampoules.
4. The concept of "grade for injections". Additional cleaning during the production of injection solutions.

General material and bulk-methodological support of the lecture:

- educational premises - the auditorium of the department;
- equipment - computer, tables;
- equipment – multimedia projector;
- illustrative materials - presentation, slides.

Questions for self-control :

1. Special cleaning of injection solutions of magnesium sulfate, calcium chloride, glucose from chemical impurities.
2. Methods of depyrogenization of injection solutions.
3. Sterilization of injection solutions in ampoules, vials.
4. Chemical and physical methods of sterilization.
5. Sterility control. Step-by-step quality control of injection solutions.
6. Concept of stability of medicines. The basic principle of stabilization.
7. Factors affecting the stability of injection solutions.
8. Stabilization of solutions of salts of weak bases and strong acids.
9. Stabilization of solutions of salts of strong bases and weak acids.

10. Stabilization of glucose solutions for injections.

11. Stabilization of solutions of easily oxidized substances.

12. Use of preservatives.

13. Features of the production technology of oil solutions for injections.

References:

1. Study guide for independent work of students of the Faculty of Pharmacy for the licensing exam "Step 2. Pharmacy" / V.Yu. Anisimov, O.I. Belyaeva, H.G. Vidavska, V.O. Helmboldt, A.V. Zamkova, I.V. Lytvynchuk, A.V. Nikitin, B.V. Pristupa, I.B. Petkova, Ya.V. Rozhkovskyi, S.B. Strechen, L.M. Unguryan, N.C. Fizor Odesa: Odesa.nats.med. Univ. 2020. - 240 p.

Mode of access to lecture texts for students of the Faculty of Pharmacy: https://info.odmu.edu.ua/chair/drugs/files/390/ua

Literature used by the lecturer to prepare the lecture.

Main:

1. Industrial technology of medicines: a basic textbook for students. Higher. student pharmacy institutions (pharmacological institutions) / E.V. Gladukh, O.A. Ruban, I.V. Saiko et al. - Kh.: NFaU: Original, 2016. - 632p. : Name - (National textbook series)

2. Workshop on industrial technology of medicinal products specialty "Pharmacy" / Ed. Ruban O.A. - Kh .: NFaU, 2015. - 374 p

3 . INDUSTRIAL technology of medicines : education. manual for students' independent work / O. A. RUBAN , V. D. RYBACHUK , L. M. Khohlova etc. - KH.: NATIONAL UNIVERSITY OF UKRAINE, 2015. - 120 p.

- Excipients in the production of drugs: training. manual for students higher pharmacy education closing / O. A. RUBAN , I. M. Pertsev, S. A. Kutsenko, Yu. S. Maslii; under the editorship I. M. Pertseva. – Kh.: Golden Pages, 2016. – 720 p.
- Technology of drugs for industrial production: tutorial. for university students education closing : in 2 parts / V. I. Chuyeshov, E. V. Gladukh, I. V. Saiko and others. – 2nd ed., revision. and additional - Kh.: National University of Applied Sciences: Original, 2012. - Part 1. - 694 p.

- Technology of drugs for industrial production: tutorial. for university students education closing : in 2 parts / V. I. Chuyeshov, E. V. Gladukh, I. V. Saiko and others. – 2nd ed., revision. and additional - Kh.: National Academy of Sciences: Original, 2013. - Part 2. - 638 p.
- Modern pharmaceutical technologies: education. manual to laboratory classes of full-time, evening and part-time master's students of the specialty 8.110201 "Pharmacy" / under the editorship. O. A. Ruban. - Kh.: Publishing House of the National Academy of Sciences, 2016. - 256 p.
- Encyclopedia of Pharmaceutical Technology: 3-d Ed. / ed. by J. Swarbrick. – New York; London: Informa Healthcare, 2007. – 4128 p.
- European Pharmacopoeia 8.0 [8th edition] / European Directorate for the Quality of Medicines & Healthcare. - Strasbourg, 2013. - 3638 p.
- Handbook of Pharmaceutical Excipients, 6th edition / RC Rowe, PJ Sheskey, ME Quinn. - Pharmaceutical Press and American Pharmacists Association, 2009. - 521 p.
- State Pharmacopoeia of Ukraine / State enterprise " Ukrainian scientific officinal center quality medical means " - 2- e kind . - Kharkiv : State enterprise " Ukrainian scientific officinal center quality medical means ", 2015. - Vol . 1. - 1128 p .
- State Pharmacopoeia of Ukraine / State enterprise " Ukrainian scientific officinal center quality medical means " - 2- e kind . - Kharkiv : State enterprise " Ukrainian scientific officinal center quality medical means ", 2014. - Vol . 2. – 724 s .
- State Pharmacopoeia of Ukraine / State enterprise " Ukrainian scientific officinal center quality medical means " - 2- e kind . - Kharkiv : State enterprise " Ukrainian scientific officinal center quality medical means ", 2015. - Vol . 3. – 732 p .
- About medicinal products: the law of Ukraine dated 04/04/96 No. 123/96 // Bulletin of the Verkhovna Rada of Ukraine. - 1996. - No. 123.
- Zujkina SS The pharmacotechnological studies of the phytospecies composition for the complex therapy of mastopathy / SS Zujkina, LI Vishnevska // Visnyk pharmacy . – 2017. – No. 2 (90). - WITH . 43-47.

- Bogutska , O. _ IS . The main ones directions solution problems pharmaceutical of incompatibilities / O . IS . Bogutska // Contemporary achievement pharmaceutical technologies and biotechnology : collection scientific works _ – issue 2. – Kharkiv . : Type - in NFaU , 2017. - S. 29–31.
- Polovka N . P. _ Rating biopharmaceuticals factors at developers and production new ones medical means / N. _ P. _ Polovko , L. _ And . Vishnevska , O. _ WITH . Shpychak // Modern achievement pharmaceutical technologies and biotechnology : collection scientific works , issue 2. – X .: Ed NFaU , 2017. - S. 155-160.
- Prospects for the creation of new original drugs based on substances of plant origin / O.A. Ruban, S.A. Malinovska, Murad Al-Tawaiti, S.I. Mazurets // Phytotherapy. – 2012. – No. 2. - pp. 63–65.
- The current state of creation, production and quality control of capsules / M.B. Chubka, L.V. Vronska, N.O. Zarivna et al. // Pharmaceutical journal. 2012. No. 2. P. 165168.
- Murachanian, D. Two-Piece Hard Capsules for Pharmaceutical Formulations / D. Murachanian // Journal of GXP Compliance. 2010. Vol. 14. P. 3142.
- Patel H. New pharmaceutical excipients in solid dosage forms – A review / H. Patel, V. Shah, U. Upadhyay // Int. J. of Pharm. & Life Sci. - 2011. - Vol. 2. – P. 1006–1019.
- Recent Trends of Treatment and Medication Peptic Ulcerative Disorder / D. Bhowmik, Chiranjib, KK Tripathi [et al.] // International Journal of PharmTech Research. - 2010. - Vol. 2. – P. 970–980
- The effects of powder compressibility, speed of capsule filling and pre-compression on plug densification / M. Llusa , E. Faulhammer , S. Biserni [et al.] // Int. J. Pharm. – 2014. – Vol. 471. – P. 182–188.

Electronic information resources

- Lecture materials, methodological developments for seminar classes and independent work at the Department of Social Pharmacy: Access mode: http://socpharm.nuph.edu.ua.

- Scientific library of the National Academy of Sciences: Access mode: http://dspace.ukrfa.kharkov.ua; http://lib.nuph.edu.ua
- www.moz.gov.ua is the official website of the Ministry of Health of Ukraine
- nuph.edu.ua is the official website of the National Pharmaceutical University
- library@nuph.edu.ua - website of the library of the National Academy of Sciences of Ukraine
- The website of the Department of Scientific Research of the National Academy of Sciences of the Russian Academy of Sciences. – Access mode: ztl.nuph.edu.ua.
- The website of the Department of Drug Technologies of ONMedU http://info.odmu.edu.ua/chair/drugs/files/195/ua
- The site of distance learning of the National Academy of Sciences: the page of the ZTL department - [Electronic resource]. – Access mode: http://pharmel.kharkiv.edu/moodle/course/index.php?categoryid=154
- fp.com.ua - website of the magazine "Pharmacist Praktik"
- www.provisor.com.ua – the official website of the magazine "Provisor"
- Compendium: drugs. - [Electronic resource]. - Access mode: http://compendium.com.ua/ - as of October 10, 2016.
- State Register of Medicinal Products of Ukraine. - [Electronic resource]. - Access mode: http://www.drlz.com.ua/ - as of January 10, 2017.
- Database "Equalizer" LLC "Business Credit" - [Electronic resource]. - Access mode: http://eq.bck.com.ua/ - as of September 20, 2016.

Lecture No. 2

Topic: " Requirements for sterile products. Determination of the main indicators of the quality of ampoule glass. Industrial production of injection solutions" - 2 hours.

Relevance of the topic: Drug technology (industrial technology of drugs) is one of the fundamental technological sciences. It consists of several key aspects that are important for modern medicine and patients: Effectiveness and safety - Modern technologies make it possible to produce drugs with high efficiency and safety for patients. Exact dosage, quality control and the absence of impurities make medicines more effective and safer. Innovations in medicine: New technologies allow the creation of innovative drugs that can be more targeted and effective drug therapy. For example, drugs designed to precisely affect specific cells or genes provide more effective treatments. Minimization of side effects: Technologies make it possible to develop medicinal formulas that minimize side effects and negative effects on the body. This provides a more comfortable and safe treatment for patients. Fast production and delivery process: The use of modern technologies allows to speed up the production process of medicines, which is especially important in the conditions of a rapidly changing medical environment, such as the spread of diseases or epidemics. Individual approach to treatment: Technologies make it possible to develop medicines that take into account the individual characteristics of the patient, which leads to a personalized approach to treatment and increases its effectiveness. Cost-effectiveness and availability Improved manufacturing technologies can reduce production costs, making drugs more accessible to a wide range of patients, providing cost-effectiveness in healthcare.

Thus , the use of modern technologies for the production of medicines is an important factor for improving the effectiveness of treatment, patient safety and the general state of public health.

Goal: to get acquainted with the main stages of the industrial production of dosage forms and the discipline "Medicine Technology", to characterize eye, ear and nasal dosage forms and to describe the current state of their industrial production.

Basic concepts: ***Ocular dosage forms.***

The main requirements that eye drops must meet:

- *sterility;*
- *absence of mechanical inclusions;*

- *comfort (isotonicity, optimal pH value);*
- *chemical stability;*
- *prolongation of action.*

Eye drops are water or oil solutions, the thinnest suspensions and emulsions for instillation into the conjunctival sac. Solvents are water for injections, sterile fatty oils - peach, almond, and liquid paraffin.

Features of their industrial production include the use, in addition to antioxidants, of gas protection for easily oxidizing substances (morphine hydrochloride, sodium sulfacyl, ascorbic acid), improved packaging (tubes - drops - droppers).

Solutions in dropper tubes are prepared in rooms of the 2nd cleanliness class under aseptic conditions. Dissolution is carried out in reactors with stirrers, the solution is freed from mechanical inclusions, subjected to sterile filtration and collected in a sterilized apparatus for further filling of tubes - droppers.

In parallel with this, housings and caps of tubes - droppers are made. The case with a capacity of 1.5 ml is obtained on a machine in several stages by blowing and stamping from high-pressure polyethylene granules. Caps with a puncture pin are cast under pressure from molten low- pressure PE granules. After manufacturing, they are washed with purified water, dried and subjected to gas sterilization at 40-50ºC with a mixture of ethylene oxide and 10% CO2 for 2 hours. Ethylene oxide is removed from products by keeping them for 12 hours in a sterile room.

Further, in aseptic conditions, in the unit with an excess pressure of sterile air, the caps are screwed onto the body, it is filled with a liquid solution using dosing pumps and sealed by heat welding. *Filled tubes* - droppers are checked visually for the absence of mechanical inclusions on a black and white background illuminated by a 60 W electric lamp.

Eye ointments.

Eye ointments are applied by laying on the eyelid. The composition of ointments is diverse - with a/b, sulfonamides, mercury oxide, etc. The purpose of application can be different (disinfection, pain relief, expansion or narrowing of the pupil, reduction of intraocular pressure).

Eye ointments, in addition to the general requirements (uniformity of distribution of

liquid, indifference and stability of the base), are subject to a number of additional requirements, which is explained by the method of their application:

- the ointment base should not contain any extraneous impurities, should be neutral, sterile, evenly distributed over the mucous membrane of the eye;
- eye ointments must be prepared in compliance with aseptic conditions;
- LV in eye ointments should be in the most dispersed state to avoid damage to the mucous membrane.

Eye films. (LPG) .

They are solid oval-shaped plates with even edges (length 6 - 9 mm, width 3 - 4.5 mm, thickness 0.35 mm, weight 0.015 g).

HLPs have a number of advantages over other ocular LFs: with their help, it is possible to prolong the action and increase the concentration of LF in the tissues of the eye, reduce the number of injections from 5 - 8 to 1 - 2 times a day. GLP are placed in the conjunctival sac, in 10-15 seconds they are moistened with tear fluid and become elastic. After 20-30 minutes, the film turns into a viscous lump of polymer, which after about 90 minutes completely dissolves, creating a thin uniform film.

As a film former - polyacrylamide or its copolymers with acrylic and vinyl monomers, polyvinyl alcohol, NaCMTS. The proposed base for HLP: 60 parts of acrylamide copolymer, 20 parts of vinylpyrrolidone, 20 parts of ethyl acrylate and 50 parts of plasticizer - polyethylene glycol succinate.

Ear medications — liquid, soft or solid LPs intended for instillation, spraying, blowing or application in the auditory opening or for rinsing the ear. In addition to active substances and a solvent, they may contain auxiliary substances designed to regulate tonicity or viscosity, create or stabilize the required pH level, increase the solubility of active substances, ensure stability or provide appropriate antimicrobial properties. Excipients should not adversely affect the effect of the drug and have a toxic or undesirable irritant effect.

Ear drops and aerosols are solutions, emulsions or suspensions that contain one or more active substances in suitable solvents and are intended to be introduced into the auditory opening without exerting dangerous pressure on the eardrum. They can also be introduced into the auditory hole (without creating dangerous pressure) using a

turunda impregnated with LP. Emulsions can separate, but should easily turn into an emulsion when shaken. Suspensions may form a precipitate which, when shaken, quickly resuspends to form a suspension stable enough to provide the required dose upon administration. When preparing drops, water, alcohol, glycerol, oils, and combined solvents are used as solvents.

Aerosols are most often used in otorhinolaryngology for burns of the auricle (externally) and some forms of otitis.

Ear washes — LP in the form of aqueous solutions with a pH level that corresponds to physiological limits, intended for cleaning the external auditory opening.

Nasal medicinal preparations — liquid, soft or solid LPs, intended for introduction into the nasal cavities, of general or local action. They contain one or more active substances, do not have an irritating or other effect on the mucous membrane of the nose and its hairs. Aqueous LPs are usually isotonic.

Plan and organizational structure of the lecture:

No p.p.	**The main stages of the lecture and their content.**	**Goals in levels of abstraction.**	**Type of lecture, lecture equipment.**	**Time allocation.**
1	**2**	**3**	**4**	**5**
I 1. 2. II 3.	***Preparatory stage*** Determination of educational goals. Providing positive motivation. ***The main stage*** Presentation of lecture material. Plan: Classification of eye		The lecture is combined Slides	1% 2% 90%

	dosage forms. Their main characteristics . 2. The principle of sterility . 3. Eye drops of prolonged action .	I II		
III 4. 5. 6.	***The final stage*** Summary of the lecture, general conclusions. Lecturer's answers to possible questions. Tasks for self-training of students.	III	List of references, questions, assignments.	2% 3% 2%

Structural and logical scheme of the content of the lecture

Classification of eye dosage forms. Their main characteristics .

2. The principle of sterility .

3. Eye drops of prolonged action .

Content of lecture material (lecture text)

Classification of eye dosage forms. Their main characteristics

In practice, various dosage forms are currently used in the treatment of eye diseases. From a pharmaceutical point of view, ophthalmic dosage forms are a special kind of medicine, intended for the most delicate, sensitive, biologically and physiologically peculiar organ of sense - the organ of sight.

According to the definition of the Pharmacopoeia of the leading countries of the world, ophthalmic medicinal products are sterile liquid, soft or solid preparations intended for application to the eyeball and/or conjunctiva or introduction into the conjunctival sac.

Ophthalmic drugs are classified as follows:

- Eye lotions
- Eye drops
- Eye Sprays
- See Ophthalmological soft drugs
- Eye Inserts

In addition, they may include:

-ophthalmological injections;

- Subconjunctival injection, injected into the conjunctival sac, in which the medicinal substance diffuses through the sclera into the eye;

- Retrobulbar injections administered behind the eyeball;

- Ointments for the eyelids, which are intended for application to the outer side of the eyelid;

- Fluids for processing contact lenses - sterile, wetting, moisturizing and disinfecting aqueous solutions for storage, cleaning and facilitating the application of contact lenses or contact glasses of ophthalmic devices used for eye research.

Eye solutions Presented by washing solutions, lotions, as well as eye drops and preparations for injections.

Eye drops are a medicinal form in the form of aqueous, oily solutions or the thinnest suspensions of medicinal substances for infusion into the conjunctival sac in a small amount. To prolong the action of these substances, the composition of the solvent includes methylcellulose, sodium salt of carboxymethylcellulose and polyvinyl alcohol.

Eye drops are the simplest form of administration of medicinal substances in the diagnosis, prevention and treatment of eye diseases. Instillations of aqueous solutions of eye drops are simple and are easily performed by the patients themselves.

Eye solutions should be sterile, isotonic, stable during storage, transparent and free of mechanical contamination. In some cases, they provide a prolonged therapeutic effect. Medicinal substances in eye solutions must have an exact concentration, show maximum biological activity and be released in a package that is convenient for use. Should not have a toxic or irritating effect.

The principle of sterility .

Normally, tear fluid contains a special antibiotic substance - lysozyme, which has the ability to lyse microorganisms that enter the conjunctiva.

Gram-positive microorganisms with relatively simple cell walls 15-50 nm thick, the main component of which is a large polymer, are most sensitive to the action of lysozyme. One of them is peptidoglycon (murein) and forms a rigid fibrous structure that gives cells shape and strength, and also allows them to withstand high internal osmotic pressure. Another component of teichoic acid is substituted poly- (B-ribotol-5-phosphate), which ensures strong polarity of the cell surface.

In some cases, partial or complete lysis of gram-negative cultures is observed under the action of lysozyme.

In most eye diseases, the content of lysozyme in the tear fluid decreases, as a result of which the eye is not sufficiently protected against the effects of microorganisms, so the use of non-sterile drugs can have serious consequences, and sometimes lead to loss of vision.

The problems of preventing microbial contamination of medicines for the eyes and solutions for injections are related to the fact that in medicines, which are systems with a volume of liquid phase that is significant compared to the content of active substances, favorable conditions for the reproduction of microorganisms are created. The degree of risk of insemination of drugs depends on many factors, such as the presence of pathogenic microflora, the nature of the decomposition products of the drug as a result of exposure to it, developing microorganisms that initiate a wide variety of reactions (oxidation, reduction, polymerization, etc.). Microbial contamination of pharmaceuticals can occur at all stages of receipt, storage, transportation and use. But this is unacceptable not only from a sanitary and hygienic point of view, but also from the point of view of preserving the chemical stability of drugs, since inoculation with microorganisms accelerates the decomposition of medicinal drugs under the action of bacterial enzymes and renders them unsuitable for use. Therefore, aseptic conditions for the preparation of dosage forms are of great importance. However, such conditions do not yet provide a guarantee of complete prevention of solutions from microbial contamination, and the very term "sterilization", which means "sterilization", is very relative. It means either the destruction of microorganisms in the solution, or the

removal of microorganisms, in particular the waste products of bacteria, from objects of sterilization. In the first case, this is achieved by using methods of thermal, chemical or radiation treatment of objects, in the second - by centrifugation, filtering, flocculation, application of static electricity, etc.

In order to prevent microbial insemination of eye medicines, the industry uses a variety of methods that allow obtaining medicines in strictly aseptic conditions, and in the future, to increase guarantees, sterilize this medicine using technology that ensures the preservation of sterility. Modern production has technological capabilities that completely exclude the contact of the manufactured medicine with sources of potential contamination with microorganisms.

Strict compliance with the rules of asepsis is equally mandatory both for the work of pharmacy institutions and for pharmaceutical enterprises, including those that produce ophthalmic drugs that are subsequently sterilized, since this process does not free the medicine from either dead microorganisms or from those released by them toxins, many of which are stable at high temperatures.

The role of asepsis is especially increasing in the production of ophthalmic drugs that are not subject to heat treatment - powders containing heat-labile medicinal substances, emulsions and suspensions. When heated in them, the processes of recrystallization, flocculation, and coalescence increase dramatically. Adherence to the rules of asepsis is the only way to ensure the proper quality of manufactured drugs.

In practice, this is achieved by the fact that heat-labile substances, weighed in aseptic conditions, are dissolved in a pre-sterilized solvent or in a base for an ointment in a sterile dish, adding preservatives and stabilizers if necessary. These manipulations are carried out in special sterile workshops, blocks, and boxes.

Medicinal substances used in the composition of eye drops are classified according to the degree of resistance to sterilization into groups, the aqueous solutions of which are:

- withstand sterilization at a temperature of 100 °C for 30 minutes without adding stabilizers;

- Do not withstand thermal sterilization (antibiotics, collargol, protargol, silver nitrate, deoxyribonuclease, lidase, trypsin, chymopsin, ethacridine, physostigmine);

- Sterilization is carried out at a temperature of 100 °C for 15-30 minutes with the addition of stabilizers.

The principle of isotonicity . Isotonicity is a necessary condition for the preparation of such dosage forms as eye drops. It is known that both hypertonic and hypotonic solutions are poorly tolerated by patients, because when a solution with a high osmotic pressure (above 7.4 atm) is introduced, as a result of the pressure difference, water is released from the cells in contact with the solution, which leads to their shrinkage. The introduction of a solution with a small osmotic pressure causes the cells to swell, and the cell membrane ruptures. In both cases, these phenomena are accompanied by severe pain. Therefore, an important task is the preparation of drops whose osmotic pressure would correspond to the osmotic pressure of tear fluid.

One of the methods of calculating the isotonic concentration is based on Van't Hoff's law, which can be used to determine the isotonic concentration of a diluted non-electrolyte solution. The relationship between osmotic pressure, concentration and temperature can be expressed by the Clapeyron equation, from which it follows that to prepare an isotonic solution of any non-electrolyte, it is necessary to take 0.29 g/mol of this substance per 1 liter of solution.

When calculating the isotonic concentration of electrolytes, a correction factor called the isotonic coefficient is introduced into the Clapeyron equation. For solutions of completely dissociating electrolytes, it is approximately 0.143, for solutions of weakly dissociating electrolytes - 0.2.

As a more universal and accurate method of calculating isotonic concentrations of solutions, a method based on the use of the so-called isotonic equivalents of medicinal substances based on sodium chloride is used. Isotonic concentrations are also determined by other methods, for example cryoscopic, based on the comparison of depression constants of the freezing temperature of blood plasma and solutions of corresponding medicinal substances.

Currently, methods of preparing eye drops using buffer solvents are increasingly being introduced into pharmaceutical practice. The use of buffer solvents, along with an increase in chemical stability, in some cases helps to increase the therapeutic activity

of medicinal components of eye drops, and also reduces the feeling of discomfort in the eyeball area.

The production of eye drops based on buffer solvents is carried out by choosing such a buffer solution, the composition and pH of which maximally ensure the stability of the medicinal substance in the dosage form. Properly selected solvents allow you to adjust the concentration of hydrogen ions not only for the purpose of stabilizing solutions, but also to create such a pH value at which medicinal substances show the maximum therapeutic effect.

Eye drops of prolonged action

Prolongation of the effect of medicinal substances is important in the therapy of many diseases, as it ensures a constant concentration of active ingredients at a therapeutic level for a long time.

The requirements for long-acting drugs are that the optimal level of the medicinal substance in them should be ensured for a certain time, its concentration should not be subject to significant fluctuations as it is released from the dosage form, and the methods used to obtain the effect of prolongation , should be economical and do not have a negative effect on the body.

Most often, water is used as a solvent for preparing eye drops. However, aqueous solutions have a short-term therapeutic effect.

In order to increase the duration of action of medicinal substances in eye drops, they tried to replace water with various oils: sterile fish oil, refined sunflower oil, but these solvents were not widely used for various reasons.

In recent years, biodegradable polymer materials of synthetic origin have been proposed to replace water, the use of which for the deposition of medicinal substances removes the harmful effects associated with the long-term impact of polymer products on the body. At the same time, the study of biodegradation of polymers in the body and in model environments is a necessary stage on the way to improving old and creating new materials that have the ability to destroy under the influence of environmental factors.

A good solvent for obtaining long-acting eye drops is PEG-400 solution. It contributes to the duration of the period of therapeutic action, increases the

bioavailability of drugs, and also allows you to obtain stable drugs for 18 months. solutions of a number of local anesthetics (dicaine, novocaine, etc.) after sterilization by autoclaving for 8 minutes. It is also possible to use solutions of polyvinyl alcohol, polyacrylamide and methylcellulose derivatives.

Materials on the activation of students of higher education during the lecture: questions, situational tasks, etc.:

Question:

1. Creation of aseptic conditions during the production of ophthalmic dosage forms.
2. Methods of stabilization of low-stable dosage forms.
3. Modern classification of ophthalmic dosage forms.

Task:

1. Draw up a working prescription and prepare 50 ml of the following infusion drugs: sodium chloride solution 0.9% and 10% for injections.
2. Make a working prescription and prepare 2 vials of the following eye drops: 30% sodium sulfacyl solution, 1% pilocarpine hydrochloride solution from methylcellulose.
3. Assess the quality of the finished product according to the relevant NTD.
4. Carry out packaging and labeling of the finished product.

General material and bulk-methodological support of the lecture:

- educational premises - the auditorium of the department;
- equipment - computer, tables;
- equipment – multimedia projector;
- illustrative materials - presentation, slides.

Questions for self-control:

1. Requirements for ophthalmic dosage forms.
2. General technological scheme of production of eye drops.
3. General characteristics of medicated eye films. Excipients used in LPG production.
4. Types of eye drops packaging, their advantages and disadvantages

References:

1. Study guide for independent work of students of the Faculty of Pharmacy for the licensing exam "Step 2. Pharmacy" / V.Yu. Anisimov, O.I. Belyaeva, H.G. Vidavska, V.O. Helmboldt, A.V. Zamkova, I.V. Lytvynchuk, A.V. Nikitin, B.V. Pristupa, I.B. Petkova, Ya.V. Rozhkovskyi, S.B. Strechen, L.M. Unguryan, N.C. Fizor Odesa: Odesa.nats.med. Univ. 2020. - 240 p.

Mode of access to lecture texts for students of the Faculty of Pharmacy: https://info.odmu.edu.ua/chair/drugs/files/390/ua

Literature used by the lecturer to prepare the lecture.

Main:

1. Industrial technology of medicines: a basic textbook for students. Higher. student pharmacy institutions (pharmacological institutions) / E.V. Gladukh, O.A. Ruban, I.V. Saiko et al. - Kh.: NFaU: Original, 2016. - 632p. : Name - (National textbook series)

2. Workshop on industrial technology of medicinal products specialty "Pharmacy" / Ed. Ruban O.A. - Kh .: NFaU, 2015. - 374 p

3 . INDUSTRIAL technology of medicines : education. manual for students' independent work / O. A. RUBAN , V. D. RYBACHUK , L. M. Khohlova etc. - KH.: NATIONAL UNIVERSITY OF UKRAINE, 2015. - 120 p.

- Excipients in the production of drugs: training. manual for students higher pharmacy education closing / O. A. RUBAN , I. M. Pertsev, S. A. Kutsenko, Yu. S. Maslii; under the editorship I. M. Pertseva. – Kh.: Golden Pages, 2016. – 720 p.
- Technology of drugs for industrial production: tutorial. for university students education closing : in 2 parts / V. I. Chuyeshov, E. V. Gladukh, I. V. Saiko and others. – 2nd ed., revision. and additional - Kh.: National University of Applied Sciences: Original, 2012. - Part 1. - 694 p.
- Technology of drugs for industrial production: tutorial. for university students education closing : in 2 parts / V. I. Chuyeshov, E. V. Gladukh, I. V. Saiko

and others. – 2nd ed., revision. and additional - Kh.: National Academy of Sciences: Original, 2013. - Part 2. - 638 p.

- Modern pharmaceutical technologies: education. manual to laboratory classes of full-time, evening and part-time master's students of the specialty 8.110201 "Pharmacy" / under the editorship. O. A. Ruban. - Kh.: Publishing House of the National Academy of Sciences, 2016. - 256 p.
- Encyclopedia of Pharmaceutical Technology: 3-d Ed. / ed. by J. Swarbrick. – New York; London: Informa Healthcare, 2007. – 4128 p.
- European Pharmacopoeia 8.0 [8th edition] / European Directorate for the Quality of Medicines & Healthcare. - Strasbourg, 2013. - 3638 p.
- Handbook of Pharmaceutical Excipients, 6th edition / RC Rowe, PJ Sheskey, ME Quinn. - Pharmaceutical Press and American Pharmacists Association, 2009. - 521 p.
- State Pharmacopoeia of Ukraine / State enterprise " Ukrainian scientific officinal center quality medical means " - 2- e kind . - Kharkiv : State enterprise " Ukrainian scientific officinal center quality medical means ", 2015. - Vol . 1. - 1128 p .
- State Pharmacopoeia of Ukraine / State enterprise " Ukrainian scientific officinal center quality medical means " - 2- e kind . - Kharkiv : State enterprise " Ukrainian scientific officinal center quality medical means ", 2014. - Vol . 2. – 724 s .
- State Pharmacopoeia of Ukraine / State enterprise " Ukrainian scientific officinal center quality medical means " - 2- e kind . - Kharkiv : State enterprise " Ukrainian scientific officinal center quality medical means ", 2015. - Vol . 3. – 732 p .
- About medicinal products: the law of Ukraine dated 04/04/96 No. 123/96 // Bulletin of the Verkhovna Rada of Ukraine. - 1996. - No. 123.
- Zujkina SS The pharmacotechnological studies of the phytospecies composition for the complex therapy of mastopathy / SS Zujkina, LI Vishnevska // Visnyk pharmacy . – 2017. – No. 2 (90). - WITH . 43-47.
- Bogutska , O. _ IS . The main ones directions solution problems pharmaceutical of incompatibilities / O . IS . Bogutska // Contemporary achievement

pharmaceutical technologies and biotechnology : collection scientific works _ – issue 2. – Kharkiv . : Type - in NFaU , 2017. - S. 29–31.

- Polovka N . P. _ Rating biopharmaceuticals factors at developers and production new ones medical means / N. _ P. _ Polovko , L. _ And . Vishnevska , O. _ WITH . Shpychak // Modern achievement pharmaceutical technologies and biotechnology : collection scientific works , issue 2. – X .: Ed NFaU , 2017. - S. 155-160.
- Prospects for the creation of new original drugs based on substances of plant origin / O.A. Ruban, S.A. Malinovska, Murad Al-Tawaiti, S.I. Mazurets // Phytotherapy. – 2012. – No. 2. - pp. 63–65.
- The current state of creation, production and quality control of capsules / M.B. Chubka, L.V. Vronska, N.O. Zarivna et al. // Pharmaceutical journal. 2012. No. 2. P. 165168.
- Murachanian, D. Two-Piece Hard Capsules for Pharmaceutical Formulations / D. Murachanian // Journal of GXP Compliance. 2010. Vol. 14. P. 3142.
- Patel H. New pharmaceutical excipients in solid dosage forms – A review / H. Patel, V. Shah, U. Upadhyay // Int. J. of Pharm. & Life Sci. - 2011. - Vol. 2. – P. 1006–1019.
- Recent Trends of Treatment and Medication Peptic Ulcerative Disorder / D. Bhowmik, Chiranjib, KK Tripathi [et al.] // International Journal of PharmTech Research. - 2010. - Vol. 2. – P. 970–980
- The effects of powder compressibility, speed of capsule filling and pre-compression on plug densification / M. Llusa , E. Faulhammer , S. Biserni [et al.] // Int. J. Pharm. – 2014. – Vol. 471. - P. 182–188.

Electronic information resources

- Lecture materials, methodological developments for seminar classes and independent work at the Department of Social Pharmacy: Access mode: http://socpharm.nuph.edu.ua.
- Scientific library of the National Academy of Sciences: Access mode: http://dspace.ukrfa.kharkov.ua; http://lib.nuph.edu.ua
- www.moz.gov.ua is the official website of the Ministry of Health of Ukraine

- nuph.edu.ua is the official website of the National Pharmaceutical University
- library@nuph.edu.ua - website of the library of the National Academy of Sciences of Ukraine
- The website of the Department of Scientific Research of the National Academy of Sciences of the Russian Academy of Sciences. – Access mode: ztl.nuph.edu.ua.
- The website of the Department of Drug Technologies of ONMedU http://info.odmu.edu.ua/chair/drugs/files/195/ua
- The site of distance learning of the National Academy of Sciences: the page of the ZTL department - [Electronic resource]. – Access mode: http://pharmel.kharkiv.edu/moodle/course/index.php?categoryid=154
- fp.com.ua - website of the magazine "Pharmacist Praktik"
- www.provisor.com.ua – the official website of the magazine "Provisor"
- Compendium: drugs. - [Electronic resource]. - Access mode: http://compendium.com.ua/ - as of October 10, 2016.
- State Register of Medicinal Products of Ukraine. - [Electronic resource]. - Access mode: http://www.drlz.com.ua/ - as of January 10, 2017.
- Database "Equalizer" LLC "Business Credit" - [Electronic resource]. - Access mode: http://eq.bck.com.ua/ - as of September 20, 2016.

Lecture No. 3

Topic: " Theoretical foundations of extracting. Production of tinctures. Spiritometry. Production of liquid extracts » - 2 hours.

Relevance of the topic: Drug technology (industrial technology of drugs) is one of the fundamental technological sciences. It consists of several key aspects that are important for modern medicine and patients: Effectiveness and safety - Modern technologies make it possible to produce drugs with high efficiency and safety for patients. Exact dosage, quality control and the absence of impurities make medicines more effective and safer. Innovations in medicine: New technologies allow the creation

of innovative drugs that can be more targeted and effective drug therapy. For example, drugs designed to precisely affect specific cells or genes provide more effective treatments. Minimization of side effects: Technologies make it possible to develop medicinal formulas that minimize side effects and negative effects on the body. This provides a more comfortable and safe treatment for patients. Fast production and delivery process: The use of modern technologies allows to speed up the production process of medicines, which is especially important in the conditions of a rapidly changing medical environment, such as the spread of diseases or epidemics. Individual approach to treatment: Technologies make it possible to develop medicines that take into account the individual characteristics of the patient, which leads to a personalized approach to treatment and increases its effectiveness. Cost-effectiveness and availability Improved manufacturing technologies can reduce production costs, making drugs more accessible to a wide range of patients, providing cost-effectiveness in healthcare.

Thus, the use of modern technologies for the production of medicines is an important factor for improving the effectiveness of treatment, patient safety and the general state of public health.

Goal: get acquainted with the main stages of the industrial production of dosage forms and the discipline "Drug Technology", describe the pharmaceutical development of the production of tinctures, liquid extracts and describe the current state of the pharmaceutical industry.

Basic concepts: *Tinctures* (*Tincturae*) - are dyed liquids of alcoholic or water-alcohol extraction from medicinal plant raw materials, which are obtained without heating and removing the extractant.

When making tinctures, 5 parts by volume of the finished product are obtained from one weight part of plant raw materials; of potent raw materials - 10 parts. In some cases, tinctures are prepared (1:10) from raw materials that do not contain potent substances (tincture of arnica, calendula, hawthorn) and in other ratios.

Tinctures can be simple, which are obtained from one type of raw material, and complex, which are a mixture of extracts from several plants, sometimes with the

addition of medicinal substances. To obtain tinctures, dried plant material is often used, in some cases - fresh raw materials.

Cooking methods

To prepare tinctures, the following methods are used: - maceration and its varieties;

- percolation;

- dissolution of thick and dry extracts.

maceration

Previously, the method of maceration, or infusion, (from the Latin Maceratio - soaking) was widely used to obtain tinctures. Currently, its use is gradually reduced, because during extraction by this method it is difficult to achieve complete extraction of medicinal substances from plant material.

Maceration is carried out as follows. Crushed raw materials with the proposed amount of extractant are loaded into the maceration tank and infused at a temperature of 15-20 °C, stirring periodically. If the terms are not specifically stipulated, then insistence is carried out within 7 days. After that, the extract is drained, the residue is squeezed, the extracted extract is washed with a small amount of extractant, it is squeezed again, the extracted extract is added to the merged extract, after which the combined extract is brought to the required volume with the extractant.

This method is ineffective - it flows slowly, raw materials are not completely exhausted. From methane intensification of material extraction, the process is carried out using fractional maceration (remaceration), maceration with forced circulation of the extractant, vortex extraction (turboextraction), ultrasound, etc.

Remaceration, or crushed maceration with the separation of the extractant, or raw materials and extractant. The total amount of the extractant is divided into 3-4 parts and the raw materials are successively insisted with the first part of the extractant, then from the second, third and fourth, draining the hood each time. The time of infusion depends on the properties of the plant material. Such an extraction process allows for more complete depletion of raw materials with less time spent, as a high concentration difference in raw materials and extractant is constantly maintained.

Vortex extraction, or turboextraction , is based on a vortex, very intense mixing of raw materials and extractant with simultaneous grinding of raw materials. The turbine mixer rotates at a speed of 8000-13000 rpm. The extraction time is reduced to 10 minutes, the tinctures are standard.

Ultrasonic extraction. Effective use of ultrasonic vibrations to intensify the maceration process. At the same time, the extraction is accelerated and the complete extraction of the active substances is achieved. The source of ultrasound is placed in the treated medium or attached to the body of the maceration tank in a place filled with extractant and raw materials. The greatest effect of the influence of ultrasound is revealed when the cell of the extracted material is well impregnated with ultrasound-conducting extractants. The emerging ultrasonic waves create sign-changing pressure, cavitation and "sonic wind". As a result, the impregnation of the material and the dissolution of the cell contents are accelerated, the speed of the flow around the raw material particles increases, and turbulent and eddy currents appear in the boundary diffusion layer of the extractant. Molecular diffusion inside the cells of the material and in the diffusion layer changes to convective, which leads to the intensification of mass transfer. The occurrence of cavitation causes the destruction of cells. At the same time, extraction is accelerated due to the washing out of extractive substances from destroyed cells and tissue. When voicing, you can get the hood within a few minutes.

Other types of dynamization of maceration include: grinding of raw materials in an extractant environment, for example in a ball mill; remaceration, accompanied by pressing on hydraulic presses or rollers. In the latter case, the process is repeated until equilibrium concentrations are reached. The method allows to reduce losses of active substances and extractant, as a small amount of extract remains in the meal. The finished tincture contains a high amount of extractive substances.

Percolation - filtering the extractant through plant material from methane extraction of substances soluble in the extractant. The process is carried out in containers of various designs, which are called extractor percolators. They can be cylindrical or conical, with or without a steam jacket, tiltable and self-unloading, made of stainless steel, aluminum, tinned copper and other materials. Cylindrical percolators

are convenient in operation when unloading raw materials, conical - provide more uniform extraction.

The resulting withdrawals are cloudy liquids containing a significant amount of suspended particles. **cleaning of extracts** is carried out by settling at a temperature not higher than 10 °C until a clear liquid is obtained. At this temperature, the solubility of the extracted substances decreases and therefore in the future, during the storage of tinctures at a temperature of 15 °C, the probability of the appearance of sediment is small. After settling for at least 2 days, filtration is carried out by decantation (i.e., without disturbing the sediment) and it is filtered from inclusions that accidentally got into it. Filter presses, filter presses, and centrifuges are used for filtration. It is not recommended to use notch filters due to the possible loss of the extractant. The final stage of the process of obtaining drugs from raw materials with a cellular structure is the recovery of the extractant from meal, i.e. spent raw materials.

Standardization

In the vast majority of tinctures, the content of active substances is determined by chemical (tinctures containing alkaloids, tannins, essential oils, organic acids, etc.) or biological (tinctures containing glycosides of the cardiac group and bitter substances) method. If the amount of active substances in the setting is higher than the established limit or greater biological activity, they are diluted with the addition of a pure extractant or a weakly concentrated tincture. If the content of active substances is below the norm, they are strengthened by adding a more concentrated tincture.

General methods of testing tinctures include: checking of organoleptic features, quantitative determination of alcohol, extractive substances, heavy metals, density.

Inspection of organoleptic signs. Tinctures should be transparent and retain the taste and smell of the substances contained in the original medicinal raw materials.

The alcohol content of tinctures is determined by one of the GF XI methods:

a) distillation;

b) by boiling point.

The density of tinctures is determined according to the methods of GF XI, (issue 1, p. 24):

a) using a pycnometer;

b) hydrometer (densimeter).

Dry residue (extractive substances) and heavy metals in tinctures are determined according to GF XI.

Plan and organizational structure of the lecture:

No p.p.	The main stages of the lecture and their content.	Goals in levels of abstraction.	Type of lecture, lecture equipment.	Time allocation.
1	2	3	4	5
I 1.	***Preparatory stage*** Determination of educational goals.		The lecture is combined	1%
2.	Providing positive motivation.			2%
	The main stage Presentation of lecture material.			90%
II 3.	Plan: 1. Concept of Tincture 2. Maceration. 3. Remaceration. 4. Percolation 5. Standardization of extracts. 6. Storage of tinctures	I II	Slides	
III 4.	***The final stage*** Summary of the lecture, general conclusions.	III	List of	

5. 6.	Lecturer's answers to possible questions. Tasks for self-training of students.		references, questions, assignments.	2% 3% 2%

Structural and logical scheme of the content of the lecture

1. Concept of Tincture
2. Maceration.
3. Remaceration.
4. Percolation
5. Standardization of extracts.
6. Storage of tinctures

Content of lecture material (lecture text)

Tinctures (Tincturae) are colored liquid alcohol or water alcohol extracts from medicinal plant raw materials, obtained without heating and removing the extractant.

Tinctures - medicinal form, introduced into medical practice by Paracelsus (1493-1541), has not lost its importance until now. They are Official on DF XI.

When making tinctures, 5 parts by volume of the finished product are obtained from one weight part of plant raw materials; of potent raw materials - 10 parts. In some cases, tinctures are prepared (1:10) from raw materials that do not contain potent substances (tincture of arnica, calendula, hawthorn) and in other ratios.

Tinctures can be simple, obtained from one type of raw material, and complex, representing a mixture of extracts from several plants, sometimes with the addition of medicinal substances. To obtain tinctures, dried plant material is often used, in some cases - fresh raw materials.

Cooking methods

The following methods are used to prepare tinctures:

- Maceration and its varieties;

- Percolation;

- Dissolving thick and dry extracts.

Maceration

Previously, the method of maceration, or infusion, (from the Latin Maceratio - soaking) was widely used for obtaining tinctures. Currently, its use is gradually decreasing, because it is difficult to achieve complete extraction of medicinal substances from plant material during extraction by this method.

Maceration is carried out as follows. Crushed raw materials with the proposed amount of extractant are loaded into the maceration tank and infused at a temperature of 15-20 °C, stirring periodically. If the terms are not specifically stipulated, then insistence is carried out within 7 days. After that, the extract is drained, the residue is squeezed, the extracted extract is washed with a small amount of extractant, it is squeezed again, the extracted extract is added to the merged extract, after which the combined extract is brought to the required volume with the extractant.

This method is ineffective - it flows slowly, raw materials are not completely exhausted. In order to intensify the extraction of the material, the process is carried out using fractional maceration (remaceration), maceration with forced circulation of the extractant, vortex extraction (turboextraction), ultrasound, etc.

Remaceration , or fractional maceration with separation into parts of extractant, or raw materials and extractant. The total amount of the extractant is divided into 3-4 parts and the raw materials are successively pressed with the first part of the extractant, then with the second, third and fourth, draining the hood each time. The time of infusion depends on the properties of the plant material. This extraction process allows for a more complete exhaustion of the raw materials with less time spent, because a high concentration difference in the raw materials and the extractant is constantly maintained.

Maceration with forced circulation of the extractant. It is carried out in a maceration tank with a false (perforated) bottom, on which filter material is placed. The extractant, separated from the raw material by a false bottom, is pumped through the raw material with the help of a pump until the equilibrium concentration is reached. At the same time, the infusion time is reduced several times. Fractional maceration is

also carried out with forced circulation of the extractant. In this case, a more complete depletion of raw materials is achieved with the same amount of extractant.

Vortex extraction, or turboextraction, is based on the vortex, very intensive mixing of raw materials and extractant with simultaneous grinding of raw materials. The turbine mixer rotates at a speed of 8,000-13,000 rpm. The extraction time is reduced to 10 minutes, the tinctures are standard.

Ultrasonic extraction. Effective use of ultrasonic vibrations to intensify the maceration process. At the same time, extraction is accelerated and complete extraction of active substances is achieved. The source of ultrasound is placed in the treated medium or attached to the body of the maceration tank in a place filled with extractant and raw materials. The greatest effect of the influence of ultrasound is revealed when the cell is extracted well impregnated with the ultrasound-conducting extractant. The resulting ultrasonic waves create alternating pressure, cavitation and "sonic wind". As a result, the impregnation of the material and the dissolution of the cell contents are accelerated, the speed of the flow around the raw material particles increases, and turbulent and eddy currents appear in the boundary diffusion layer of the extractant. Molecular diffusion inside the cells of the material and in the diffusion layer changes to convective, which leads to the intensification of mass transfer. The occurrence of cavitation causes the destruction of cells. At the same time, extraction is accelerated due to the washing out of extractive substances from destroyed cells and tissue. When voicing, you can get the hood within a few minutes.

Other types of dynamization of maceration include: grinding of raw materials in an extractant environment, for example in a ball mill; remaceration, accompanied by pressing on hydraulic presses or rollers. In the latter case, the process is repeated until equilibrium concentrations are reached. The method allows to reduce losses of active substances and extractant, since a small amount of extract remains in the meal. The finished tincture contains a high amount of extractive substances.

Percolation

Percolation (from the Latin *Percolation* - percolation through ...), i.e. Percolation of the extractant through plant material with the aim of extracting substances soluble in extractants. The process is carried out in containers of various

designs, called extractor percolators. They can be cylindrical or conical, with or without a steam jacket, tiltable and self-unloading, made of stainless steel, aluminum, tinned copper and other materials. In the lower part of the percolator there is a false bottom (perforated mesh), on which the filter material (burlap, cloth, etc.) is placed, and the raw materials are loaded. Cylindrical percolators are convenient in operation when unloading raw materials, conical ones provide more uniform extraction.

The percolation method includes three consecutive stages: soaking of raw materials (swelling of raw materials), infusion, percolation itself.

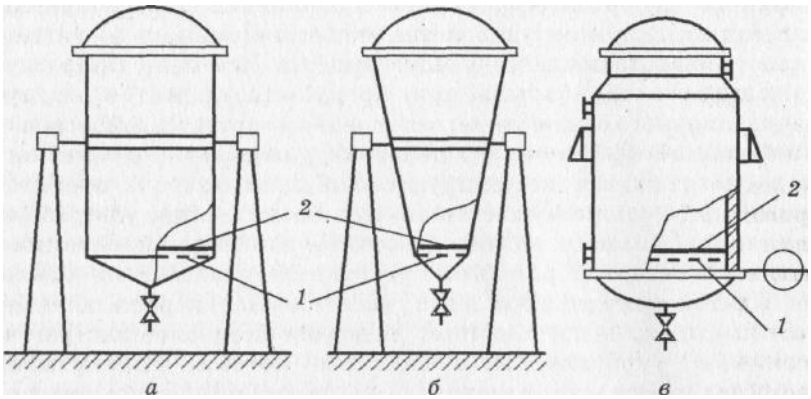


Figure 1. Percolator-extractors

Soaking (swelling) is carried out outside the percolator. Most often, maceration tanks or other containers are used for this, from which it is convenient to unload soaked raw materials. For soaking, 50 to 100% of the extractant is used in relation to the mass of raw materials. After mixing, the raw materials are left for 4-5 hours in a closed container. During this time, the extractant penetrates between the particles of the plant material and inside the cells, the raw material swells, increasing in volume. At the same time, active substances are dissolved inside the cell.

In production conditions, soaking can be combined with infusion, but if the raw material can swell a lot, the soaking stage must be carried out in a separate container, because due to the large increase in the volume of the material in the percolator, it can be strongly compressed and not pass the extractant at all.

Infusion is the second stage of the percolation process. Swollen or dry material is loaded into the percolator on a false bottom with optimal density so that as little air as possible remains in the raw material. The top is covered with filter material, pressed

with a perforated disk and filled with extractant so as to displace the air as much as possible. It is possible to load the material into a bag of filter material that fills the entire volume of the percolator. In the upper part, the bag is tied and the cargo is placed. The raw material is poured with an extractant until a "mirror" is formed, the height of which layer above the raw material should be about 30-40 mm, and insistence is carried out for 24-48 hours, during which the equilibrium concentration will be reached. For many types of raw materials, the infusion time can be shortened.

Percolation itself is the continuous passage of the extractant through a layer of raw materials and the collection of percolate. At the same time, the draining of the percolate and the simultaneous supply of the extractant from above is carried out at a rate not exceeding 1/24 or 1/48 (for large productions) of part of the used volume of the percolator in 1 hour. At the same time, the saturated extract is displaced from the plant material by a stream of fresh extractant and a difference in the concentration of extracted substances in the raw material and the extractant is created. The speed of percolation should be such that the diffusion of the extracted substances into the hood has time to occur. When preparing tinctures, the percolation is finished by obtaining five or ten volumes (depending on the properties of the raw material) of the hood in relation to the weight of the loaded raw material.

When obtaining tinctures in industry, with the aim of maximum intensification of extraction, changes are made in the percolation process. Often, instead of typical percolation, insistence, circulation and their combination are used.

In one of the percolation options, the first, fairly concentrated extract is drained separately, completely draining it from the percolator. Then the percolator is filled with fresh extractant, which after infusing for 3-6 hours is drained completely. The obtained second extract is attached to the first, and another 1-2 similar operations are carried out with the raw material until the required amount of extract is collected.

Otherwise, in the process of infusion, the extractant is circulated in the percolator-extractor with the help of a pump that supplies the extract from the lower part to the upper part. Such circulation of the extractant is carried out until the equilibrium concentration. The infusion time is reduced many times. Next, percolation is carried out by displacement with a pure extractant as described in the stage "proper

percolation".

The obtained extractions are cloudy liquids containing a significant amount of suspended particles. Extracts are purified by settling at a temperature not higher than 10 °C until a clear liquid is obtained. At this temperature, the solubility of the extracted substances decreases and therefore in the future, during the storage of tinctures at a temperature of 15 °C, the probability of the appearance of sediment is small. After settling for at least 2 days, filter by decantation (ie, without wetting the sediment) and filter 6t of accidentally caught inclusions. Filter presses, filter presses, and centrifuges are used for filtration. It is not recommended to use notch filters due to the possible loss of the extractant. The final stage of the process of obtaining drugs from raw materials with a cellular structure is the recovery of the extractant from meal, i.e. spent raw materials. (Recovery methods see "Recovery and rectification of ethanol").

Dissolving thick or dry extracts

A small number of tinctures are prepared by dissolving dry or thick extracts in alcohol of the required concentration. This method produces a tincture of chilibukha, which has poisonous seeds that are difficult to pulverize due to their high hardness. At the same time, dry extract is used. *A breast elixir is prepared by dissolving a thick or dry licorice extract.*

The technology of obtaining tinctures by this method is reduced to simple dissolution in a reactor with a stirrer of the calculated amount of dry or thick extract in alcohol of the required concentration. The resulting solutions are filtered. This method is characterized by a significant reduction in the time of obtaining the tincture.

Standardization

In the vast majority of tinctures, the content of active substances is determined by chemical (tinctures containing alkaloids, tannins, essential oils, organic acids, etc.) or biological (tinctures containing glycosides of the cardiac group and bitter substances) method. If the amount of active substances in the tinctures is above the established limit or greater biological activity, they are diluted by adding a pure extractant or a weakly concentrated tincture. If the content of active substances is below the norm, they are strengthened by adding a more concentrated tincture.

General methods of testing tinctures include: checking of organoleptic features,

quantitative determination of alcohol, extractive substances, heavy metals, density.

Inspection of organoleptic signs. Tinctures should be transparent and retain the taste and texture of the substances contained in the original medicinal raw materials.

The alcohol content in tinctures is determined by one of the DF XI methods:

a) Distillation;

b) by boiling point.

The density of tinctures is determined according to the methods of GF XI, (issue 1, p. 24):

a) using a pycnometer;

b) hydrometer (densimeter).

Dry residue (extractive substances) and heavy metals in tinctures are determined according to GF XI.

Storage of tinctures

Tinctures should be stored in well-stoppered glasses in a place protected from direct sunlight at a temperature of 15 °C. With the passage of time, precipitation may appear, and if the storage rules are followed, the tinctures "get old". This is due to a change in the solubility of biologically active substances and the formation of insoluble compounds as a result of the interaction of the substances present in the tinctures. The sediment may contain sugars, tannins, organic acids, pigments, traces of alkaloids, glycosides, and others, the tinctures with the sediment are filtered and re-standardized. If the numerical indicators meet the requirements of the GF, they are allowed to be used.

Tinctures are also used for external use.

Classification and nomenclature of tinctures

All tinctures can be divided into two groups: simple and complex.

Tinctures are simple. All simple tinctures are more often obtained by the percolation method. When obtaining tinctures in a ratio of 1: 5 in order to achieve complete exhaustion of raw materials, extraction is carried out using circulation mixing with the help of centrifugal pumps.

Nomenclature (from the register of medicines) and the main ones

indicators (by HF and VFS) of simple tinctures

Name	**Raw materials, alcohol, correlation, method of receipt**	**Basic information about preparation**
Aralia tincture (*Tinctura Araliae*)	Roots, 70%, 1:5, percolation	Triterpene saponins. Tonic means
Arnica tincture (*Tinctura Arnicae*)	Flowers, 70%, 1:5, percolation	Essential oil. Carotenoids. Externally with blows and small ones injuries also in obstetricians and gynecologists
Tincture of ginseng (*Tinctura Ginseng*)	Roots, 70%, 1:10, maceration	Tetracyclic saponins. Central nervous system
Tincture of ginseng (*Tinctura Echinopanacis*)	Rhizomes and roots, 70%, 1:5, percolation	Steroidal saponins. Tonic
Tincture of St. John's wort (*Tinctura Hyperici*)	Grass, 40%, 1:5, percolation	Anthracene derivatives. In the treatment of gingivitis and stomatitis
Tincture of common barberry leaves (*Tinctu foliorum Berberidis vulgaris*)	Leaves, 70%, 1:10, percolation	Alkaloids, berberine, oxyacanthine, berbamine, yatroricin. With anatomical bleeding in the postpartum period, subinvolution of the
Tincture of hawthorn (*Tincture Crataegi*)	Fruits, 70%, 1:10, percolation	Flavonoids. With functional disorders of cardiac activity

Calendula infusion (*Tinctura Calendulae*)	Nail flowers, 70%, 1:10, percolation	Vitamins. In case of cuts, purulent wounds and ulcers. choleretic
Tincture of beauty (*Tincture*	Leaves, 40%, 1:10, percolation	Alkaloids 0.027-0.033%. Antispasmodic agent. List B
Tincture of lily of the valley (*Tinctura*	Grass, 70%, 1:10, percolation	Cardenolides, 10-13 LED. Cardiotonic agent
Tincture of lemongrass (Tinctura Schizandrae)	Seeds, 95%, 1:5, maceration	Lignans, essential oil. Central nervous system stimulant
Mint tincture pepper (*Tinctura Menth piperitae*)	Leaves and essential butter, 90%, 1:20 4 5% oils, percolation and repercolation	Essential oil (menthol). For nausea and for improvement digestion. Included in the composition mixture as a corrector
Pepper tincture (*Tinctur capsicum*)	Fruits, 90%, 1:10, percolation	Alkaloids. External annoying and distracting
Tincture of peony (*Tinc Paeoniae*)	Roots, rhizomes and dodging peony grass 40%, 1:10, percolation	Sedative. With neurasthenia, insomnia, vegetative-vascular disorders
Tincture of wormwood (*Tinctura Absinthii*)	Grass, 70%, 1:5, percolation	Essential oil, bitter glycosides. Aromatic bitterness
Motherwort tincture (*Tinctura Leonuri*)	Grass, 70%, 1:5, percolation	Flavonoids. Sedative means
Tincture of Japanese sophora (*Tinctura Sophorae japonica*)	Fruits, 48%, 1:2, percolation	Flavonoids. For the treatment of ulcers and burns

Tincture of stelnik field *Tincture Ononidis*)	Roots, 20%, 1:15, percolation	Triterpene saponins and flavonoids. With hemorrhoids
Tincture of sterculiae (*Tinctura Sterculiae*)	Leaves, 70%, 1:5, percolation	Alkaloids. Tonic
Eucalyptus tincture (*Tinctura Eucalypti*)	Leaves, 70%, 1:5, percolation	Essential oil (cyanol). Disinfectant (Lotions, rinses), antimalarial

Tinctures are complex. A representative of this previously large group of tinctures is bitter tincture (*Tinctura amara*), which includes: goldenseal grass - 6 g; trefoil leaves - 6 g; plantain rhizomes - 3 g; wormwood herb - 3 g; tangerine peel - 1.5 g. The tincture is prepared on 40% alcohol by the percolation method, which is activated by circulation. It is used as an aromatic bitter to stimulate appetite and improve digestion.

Recovery of extractants from spent raw materials

2 to 3 volumes of the extractant in relation to the mass of the raw material remain in the spent medicinal plant raw material (LRS) - meal. This extractant must be recovered, that is, extracted by various methods and returned to production.

If there is no water vapor as a heat carrier at a pharmaceutical enterprise (which often happens in pharmaceutical factories), ethanol recovery from meal is carried out by the method of washing with water. In order to reduce losses of extractive substances and extractant from meal, the extractant is pre-squeezed on a press and the obtained extract is used in the corresponding production process. After the press, the meal is poured with water and infused for 1.5 hours. At the same time, ethanol diffuses from the raw material into the water. After that, washing water is obtained at the rate of percolation. Their number depends on the concentration of the extractant.

Thus, for the recovery of 70% ethanol, about 5 volumes of washing water are obtained in relation to the raw material, for 40% ethanol, about 3 volumes are obtained. Wash waters containing 5-30% ethanol can be used to dilute strong ethanol in the preparation of the extractant. More often, the washing water is subjected to simple distillation in order to strengthen the ethanol. The washing water in the container is heated to boiling with an electric heater, gas or any other available coolant. The formed vapors of

alcohol and water enter the condenser, from which the condensate is collected in the distillation collector. At the same time, a distillate containing up to 88% alcohol is obtained.

The obtained decoction is used as an extractant, if its concentration corresponds to the required one. At other concentrations, the distillate is used to prepare an extractant for the raw material of the same name, since the aromatic compounds of the raw material are distilled together with ethanol. Recuperates and distillates with 30-40% ethanol and above can be strengthened and purified by rectification.

Extracts

Extracts (from the Latin *extractum* - extract, extract) are concentrated extracts from medicinal plant raw materials (LPR).

They can be classified depending on the consistency into liquid extracts (*Extracta fluida*), thick extracts (*Extracta spissa*) and dry extracts (*Extracta sicca*); or from the used extractant: aqueous (*Extracta aquosa*), alcoholic (*Extracta spirituosa*), ethereal (*Extracta aetherea*), oily (*Extracta oleosa*) and obtained with the help of liquefied gases. In addition, standardized extracts (*Extracta standartisata*) or extracts-concentrates.

Liquid extracts are only alcoholic; others can be alcohol, water, ether, etc.

Liquid extracts

Liquid extracts are liquid concentrated water-alcohol extracts from LRS, obtained in a ratio of 1: 1. At pharmaceutical enterprises, liquid extracts are prepared by weight (from 1 kg of raw materials, 1 kg of liquid extract is obtained).

Liquid extracts are widely used in the pharmaceutical industry, as they have the following advantages:

1) the same ratio between the active substances contained in medicinal raw materials and in the finished drug;

2) convenience in measuring in pharmacies with burettes and pipettes;

3) the possibility of obtaining without the use of evaporation allows obtaining liquid extracts containing volatile substances (essential oils).

Disadvantages of liquid extracts include: 1

) their saturation with accompanying substances extracted from plant raw materials;

2) the appearance of precipitation with slight decreases in temperature or partial evaporation of alcohol;

3) the need for airtight sealing and storage at a temperature of 15-20 °C;

4) liquid extracts contain large amounts of extractant, which is why they are poorly transportable drugs.

Methods of obtaining

Liquid extracts are obtained by the methods of percolation, repercolation (in various versions), fractional maceration in various modifications, dissolution of thick and dry extracts. The best quality liquid extracts are obtained using methods of preparation that exclude evaporation.

Percolation in the production of liquid extracts at the stages of swelling and infusion is no different from percolation in the production of tinctures. At the actual percolation stage, the process is carried out similarly and at the same speed as for tinctures. The difference lies in the collection of ready extracts. For liquid extracts, extraction is divided into two portions. The first portion in the amount of 85% in relation to the mass of raw materials is collected in a separate container. Then percolation is carried out in another container until the raw materials are completely exhausted. At the same time, they receive 5-8 times (in relation to the mass of raw materials loaded into the percolator) more weak extracts, which are called "release". This "vacation" is evaporated under vacuum at a temperature of 50-60 °C to 15% in relation to the mass of raw materials loaded into the percolator. After cooling, this thickened residue is dissolved in the first extraction portion. Extracts are obtained in a ratio of 1: 1 in relation to raw materials.

Repercolation , i.e., repeated (repeated) percolation, which allows you to make maximum use of the dissolving ability of the extractant, to obtain concentrated extractions when the raw materials are completely exhausted. In all cases, the process is carried out in several percolators (from 3 to 10), which work in connection, in the so-called battery of percolators. In this battery, the finished product is drained from the last percolator, in which the raw materials are always fresh, and the fresh extractant is fed to the first percolator, in which the raw materials are exhausted. Extracts from the first percolator process raw materials in the previous percolator, and so in the entire battery - raw materials in further percolators are extracted with extracts obtained from previous percolators. Thus, from the 1st to the last percolator in the battery, the raw material and the extractant are counter-flowed.

There are various options for repercolation with the distribution of raw materials into equal and unequal parts, with a completed and unfinished cycle. Some of them allow you to get concentrated extracts without further evaporation.

Solution . Liquid extracts can be obtained by dissolving dry or thick extracts. The method is used relatively rarely, although it deserves greater implementation in practice due to the reduction of the time of the technological process. The preparation technology boils down to dissolving a thick or dry extractant in a suitable extractant followed by purification and standardization.

Cleaning

Obtained by any of the methods described above, extracts in the production of liquid extracts stand for at least 2 days at a temperature not higher than 10 °C until a clear liquid is obtained. The settling is sometimes allowed to be carried out in the presence of adsorbents, which contributes to better cleaning and greater stability during storage and transportation. The settled, transparent part of the extraction is filtered from accidentally introduced impurities through printing filters, filter presses or centrifuged. Finally, the remaining extracts with sediment are filtered. Filtered hoods are thoroughly mixed and standardized.

Standardization

In liquid extracts, the content of active substances is determined by chemical methods (with the exception of liquid extract of hawthorn, the quality of which is controlled biologically). The quality of some liquid extracts is determined by the sum of extractive substances (for the method of determining the dry residue, see the topic "Tinctures"), according to the methods specified in separate articles, the alcohol content is determined (GF XI, issue 2, p. 26), or density (GF XI, issue 1, p. 24), heavy metals (GF XI, issue 1, p. 161).

Nomenclature of liquid extracts

Liquid extracts (nomenclature according to the State Register) and main indicators (according to GF and VFS).

Name	**Raw materials and alcohol**	**Basic information about preparation**
Hawthorn extract liquid (*Extractum Crataegi fluid* m)	Fruits, 70%	Flavonoids. For stimulation and regulation of the cardiovascular system
Valerian extract liquid (*Extractum Valerianae fluidum*)	Roots and rhizomes , 70%	Essential oil 0.5 - 2%; free isovaleric acid, tannins, alkaloids. Sedative, antispasmodic agent
Water pepper extract liquid (*Extractum Pophygoni hydropiperis fluidum*)	Grass, 70%	Flavonoids, vitamin K. Anticoagulant
Liquid shingles extract (*Exstractum Frangulae fluidum*)	Bark, 70%	Anthracene derivatives. Laxative
Liquid extract of corn stigmas (*Exstractum stigmatum Maydis fluidum*)	Ritsia corn , 70%	Flavonoids, vitamins K, etc. Bile diuretic (cholecystitis, cholangitis, hepatitis with delayed biliary secretion)
Levzea extract, or maralego root, liquid (*Exstract* um *Leuzeae fluidum*)	Rhizomes and roots, 70%	Lingnans Stimulant for patients with functional diseases of the nervous system and for overtiredness

Passiflora liquid extract (*Exstractum Passiflorae fluidum*)	Grass, 70%	Alkaloids. Sedative agent for neurasthenia, insomnia
Shepherd's purse liquid extract (*Exstractum Bursae pastoris fluidum*)	Grass, 70%	Vitamins K, etc. Hemorrhagic with uterine, renal and pulmonary bleeding
Liquid dog nettle extract (*Exstractum Leonuri fluidum*)	Grass, 70%	Essential oil, saponins, tannins, alkaloids. Sedative agent for increased nervous excitability, cardiovascular neuroses, early stages of hypertension
Rhodiola liquid extract (*Exstractum Rhodiolae fluidum*)	Roots, 40%	Glycosides of phenolic alcohols. Tonic
Thyme extract liquid (*Extractum Thymi serpylli fluidum*)	Rhizomes, 30%	Essential oil containing thymol and carvacrol. It is part of the expectorant drug - pertussis
Eleutherococcus extract. liquid (*Extractum Eleutherococci fluidum*)	rhizomes, 40%	Triterpene saponins. Means that stimulates the central nervous system

Cleansing extract of Buvytsetsvetny liquid (*Exstractum Stachydis betonicaeflorae fluidum*)	Above ground parts, 40%	Strengthens the contraction of the uterus. It is used for subinvolution of the uterus after childbirth and abortions, for functional uterine bleeding (of an inflammatory nature), bleeding due to fibroids.

Storage

Liquid extracts are stored in tightly closed vials at a temperature of 12-15 °C and, if necessary, in a place protected from light. In the process of storage, precipitation may occur. If the extracts after filtering the sediment and checking the quality meet the established requirements, they are considered suitable for use.

Thick and dry extracts

Thick extracts are concentrated extracts from medicinal plant raw materials, which are viscous masses with a moisture content of no more than 25%. They usually do not pour out of the vessel, but are stretched into threads, which then merge into a solid mass.

Due to their high viscosity, thick extracts are used as binders and form-forming substances in the production of pills in a pharmacy. In addition, they can be included as corrigents in the composition of syrups, mixtures or elixirs. Thick extracts are used as intermediate products for a number of dosage forms (tinctures, tablets).

Disadvantages of thick extracts include the inconvenience of their use, which requires certain techniques in Weighing. In addition, in dry air they dry up and become hard; in humid air - they become damp and moldy. Therefore, they require airtight packaging.

Dry extracts are concentrated extracts from medicinal plant raw materials, which are loose masses with a moisture content of no more than 5%. They should be considered the most rational type of extracts. They are convenient to use, have the

minimum possible weight. The disadvantages of dry extracts include their high hygroscopicity, as a result of which they turn into globular masses, losing their fluidity.

Dry extracts are divided into extracts with a limited upper limit of active substances and extracts with an unlimited upper limit of active substances.

Extracts with a limited upper limit of active substances are obtained from raw materials containing highly biologically active compounds. Such extracts must contain active substances in a strictly defined amount. This is achieved by adding fillers or mixing extracts containing more and less active substances in certain ratios. Milk sugar, glucose, potato dextrin, etc. are used as fillers. Fillers are often added to the dried product at the grinding stage.

Extracts with an unlimited upper limit of active substances are obtained without adding fillers to them. Such extracts are obtained from medicinal raw materials containing inactive substances.

Methods of obtaining

The production process of thick extracts includes three main stages:

1) obtaining a hood;

2) its cleaning and

3) thickening. The production of dry extracts can be carried out according to two schemes. In the first case, the process consists of four stages:

1) obtaining a hood;

2) cleaning the hood;

3) thickening of the hood;

4) drying of the thickened hood. In the second case, the production process of dry extracts is carried out bypassing the thickening stage, and then it includes three stages:

1) obtaining a hood;

2) cleaning the hood;

3) drying of liquid or slightly thickened extract. Drying of liquid extract can be carried out in spray or sublimation (lyophilic, molecular) dryers. The slightly thickened extract is dried in vacuum roller dryers.

In the production of thick and dry extracts, water (in some cases hot), aqueous solutions of ammonia, chloroform water, ethanol of various concentrations, organic solvents, liquefied gases, vegetable and mineral oils are used as extractants.

Obtaining hoods

In the production of thick and dry extracts, various methods are used to obtain extracts from raw materials: 1) remaceration and its variants; 2) percolation; 3) Repercolation; 4) circulation extraction; 5) countercurrent extraction in batteries of percolators with circulation mixing; 6) continuous countercurrent extraction with movement of raw materials and extractant; as well as other methods that include grinding raw materials in an extractant environment; vortex extraction; extraction using electromagnetic vibrations, ultrasound, electric discharges, electroplasmolysis, electrodialysis, etc.

Percolation. The process of percolation at the stages of soaking and infusion is carried out in the same way as when obtaining tinctures and liquid extracts. In fact, percolations lead at the same speed to the complete exhaustion of raw materials without dividing them into primary and secondary extracts, since then all obtained extracts are thickened or dried.

Cleaning the hood

Water and water-alcohol extracts with a small amount of ethanol (20-40%) contain many high-molecular compounds (water-soluble proteins, sugars, enzymes, pectins, mucus, starch), which must be removed before evaporation. Depending on the amount and properties of ballast substances, different cleaning methods are used. In some cases, cleaning is carried out by boiling - if there is no BAR inactivation. Proteins coagulated at the same time peel off quickly. Sometimes adsorbents are used (kaolin, bentonite, talc, etc.) or a combination of adsorbents with boiling. The method of removing ballast substances by precipitating them with alcohol is often used. Alcohol cleaning is carried out with preliminary evaporation of hoods to half the volume relative to the mass of the raw material. After cooling, a double volume of strong (95-96%) ethanol is added to it. Everything is thoroughly mixed and left for 5-6 days at a temperature not higher than 10 °C. The settled layer is drained from the sediment and filtered. The cleaned extract, if necessary, is subjected to further thickening.

For chloroform (carbon tetrachloride) extractions, the extractant replacement method is used. At the same time, water in the amount equal to the mass of raw materials is added to the extractor to evaporate to half the volume relative to the mass of the raw material. Soluble in chloroform (carbon tetrachloride) chlorophyll, resinous substances precipitate, as they do not dissolve in water. The extract is settled, filtered and subjected to further processing.

Thickening of the hood

Cleaned hoods are evaporated under vacuum at a temperature of 50-60 °C and a dilution of 600-650 mm Hg. Art. to the required consistency. When thickening alcohol hoods or hoods after alcohol purification, alcohol is first driven off, without including a vacuum.

The equipment used for evaporating hoods in pharmaceutical production has its own characteristics. This is explained by the fact that the hood contains biologically active substances that, when vaporized, can settle on the walls of vaporizers heated by steam and lose their activity due to the high temperature of the walls. Therefore, devices in which there is no circulation of evaporating hoods or there is a weak circulation (as in an evaporating cube) are used extremely rarely in pharmaceutical production.

Not all designs with intensive circulation proposed in recent years are widely used in factory production. Thus, the highly efficient Centriterm centrifugal rotary-film device, having high productivity in industry, did not find application due to the vibrations and large noise effect that arise during operation. The greatest application at this stage, as reliable in operation, highly efficient, easy to maintain and low-energy found such designs as direct-flow rotary, circulating vacuum-evaporator and foam evaporator.

Drying hood

Drying of cleaned hoods can be carried out according to two schemes:

1) without thickening of the liquid extract and

2) through the thickening stage followed by drying.

In the first case, the drying of hoods is carried out in spray dryers, where the liquid hood is sprayed into very small drops in a large chamber. From below, toward

the settling drops, heated air (its temperature is about 150-200 °C) is supplied with the help of a fan, while overheating of the material does not occur, since all the heat of the air goes to change the aggregate state of moisture from the hood droplets. The temperature of the material to be dried does not exceed 50-60 °C. According to the first scheme, drying is carried out in drum (roll) vacuum dryers. The hood is slightly evaporated (so that a sufficient layer of dry extract is formed on the rotating rollers after drying) and fed between the rotating rollers towards each other, heated from the inside by streets. The crust of dry extractant removed from the rollers is then ground in a ball mill.

From the liquid state, drying can also be carried out in sublimation (lyophilic, molecular) dryers. At the same time, the solution (extract) is frozen, placed in a sublimation chamber, where a deep vacuum is created (residual pressure of several micrometers). Under such conditions, moisture from the frozen material sublimates, that is, evaporates, bypassing the liquid phase. The drying temperature in this case is 20-30 °C. The resulting powder dissolves very easily, contains all biologically active substances in an unchanged form.

In the second case, drying is carried out in vacuum drying cabinets. The thickened extract is applied in the form of a thin layer on the sheets and dried at a residual pressure of 110-160 mm Hg. Art. (vacuum 600-650 mm Hg). During the drying process, the volume of the extract increases several dozen times. As a result, a very loose, light mass is obtained in the form of cakes, which are colored on a ball mill.

Standardization

Standardization of thick and dry extracts is carried out according to the content of active substances or biological activity. The moisture content is also determined by the GF XI method. In thick extracts, the moisture content is no more than 25%, in dry - no more than 5%.

Storage

Thick extracts are stored in a hermetically sealed container that does not allow drying out. Dry extracts, characterized by high hygroscopicity, must be stored in small-capacity, wide-mouthed jars, hermetically sealed, with a capacity of no more than 100

m

If necessary, the extracts are stored in a cool place protected from light.

ESSENTIAL OILS

Even in the ancient world, fragrant plants attracted attention as a source of fragrances. Until the beginning of the 16th century. such fragrant plants as rosemary, lavender, sage, watercress, cashews, etc. were known. And in the Middle Ages, the technique of producing aromatic substances developed intensively.

Essential oils are used in the pharmaceutical, food and especially widely in the perfumery industry. Despite the development of the production of synthetic substances, the best perfume compositions are still made with the use of natural essential oils that transmit the scents of rose, lily of the valley, violet, clove, lemon, etc.

Currently, several thousand essential oils are known.

Essential oils (Olea aetherea) are mixtures of aromatic substances belonging to various classes of organic compounds, mainly terpenoids, less often aromatic or aliphatic compounds. They include both fragrant and non-scented substances produced by essential oil plants and possessing a characteristic smell characteristic of the fragrant part of this plant. The role of essential oils in plant metabolism is still unclear. A number of authors suggest that essential oils are necessary to protect plants from pests and animals; for closing wounds in wood, bark and preventing them from ingress of moisture, infection with fungal diseases, as well as for attracting pollinating insects, etc.

Because of their volatility and ability to evaporate with water vapor, essential oils are called essential oils, and because of their external similarity to fatty oils, they are called oils.

Essential oils are obtained from vegetable raw materials, from various essential plants: flowers (flower petals and flower heads), leaves (mint, eucalyptus), needles and paws (waste from wood harvesting from fir, pine), peels of fruits (citrus), roots (valerian) or rhizomes (iris), fruits (almond), bark (cinnamon, camphor tree), wood (cedar) - both in a free state and in the form of glycosides, for example in almond fruits.

The content of essential oils varies widely: violet flowers contain about 0.004; rose flowers - 0.07-0.1; cumin seeds - 3-7; and in the kidneys of cloves it reaches 20-22%.

The composition of the essential oil of each name at the time of production is more or less constant and depends on the composition of the soil, insolation, humidity, climatic conditions, solar radiation, the area of growth, the season and even the time of day (for roses , the maximum accumulation is early morning (4-6 hours), and in lavender flowers it accumulates the most in the afternoon), the age of the plant. The ratio of constituent parts of essential oil may change slightly while the nature of the smell remains relatively unchanged.

The composition of essential oils changes during the development of plants and often fluctuates in their individual parts. Moreover, as a result of significant variations in the ratios of essential oil components, its aromatic bouquet changes significantly. Thus, during the ripening process of coriander seeds, its essential oil has floral tones with a predominance of aromas of violets and lilies of the valley. The composition of the essential oil of certain types of plants varies significantly depending on the conditions of cultivation or the place of growth. For example, lavender oil from the mountainous regions of France has a fruity-sweet aroma, and English lavender has a camphor shade. More valuable - lemon and orange oils - are produced in Sicily.

During the period of flowering and ripening of seeds, plants contain the largest amount of essential oil, which accumulates in special formations - places that are located in various plant organs and are divided into two groups depending on the location:

- Exogenous;
- Endogenous.

Exogenous receptacles include: iron spots formed on the petals of flowers (rose), iron hairs on the epidermis of leaves and flowers (geranium), glands of various types (lipflowers).

Endogenous receptacles include: rounded receptacles found in the parenchyma of roots and rhizomes, the skin of fruits, in a leaf (the root of a delusion, a leaf of a eucalyptus, a lemon fruit), individual cells (the rhizome of a plantain), groups of cells

or areas of tissue (the hypodermis in the root of valerian) , an elongated container in the form of "tubules" and passages (umbrella fruits and coniferous wood).

Features of the localization of essential oils must be taken into account when obtaining them. With exogenous localization, the oils are released more easily and the raw materials do not require careful grinding, while with endogenous localization, the raw materials are carefully crushed.

The name of the essential oil comes most often from the name of the plant, the only exception being citrus. Essential oil obtained from citrus leaves is called petitgrain, from flowers - neroli, from fruits - by the name of the plant.

Most essential oils are obtained in countries with a tropical or subtropical climate (patchouli, bergamot). A smaller part of essential oil plants (coriander, anise) is grown in the middle lane. There are 77 families (about 1050) of plants containing essential oils in the CIS. Currently, essential oil raw materials are grown in specialized farms - factories in the North Caucasus (coriander, lavender, mint, rose, anise, basil, sage), Ukraine (coriander, lavender, mint, rose, cumin, fennel, sage), Moldova (lavender, mint, rose, sage), Georgia (basil, geranium, jasmine, rose, eucalyptus), Armenia and Tajikistan (geranium), Kyrgyzstan (mint, sage), Belarus and Lithuania (mint), Azerbaijan (rose). In the production of some of them, the CIS countries take a leading place in the world: more than 90% of the world's production of coriander oil, 75-80% of clary sage oil, and 60% of rose oil are concentrated here.

Basically, essential oils have a burning taste, are poorly soluble in water (this property is used for their isolation by distillation with steam), but are well soluble in organic media (ether, alcohol, resins) and fats of plant and animal origin (honey, milk, mink fat). These are clear, colorless or colored to dark brown liquids. When essential oils are cooled, part of them hardens into a crystalline digestive su - stearoptene, and the remaining liquid part is called eleopten. Boiling point - 160-240 °C. Essential oils, as a rule, are lighter than water and form a thin oily film when dissolved. However, there are oils heavier than water (eugenolic basil oil, vetiver oil, clove oil, etc.). Essential oils of different types are mixed in all ratios.

Ways (methods) of obtaining essential oils:

1. Mechanical methods - squeezing essential oils - pressing method.

2. Distillation of essential oils with steam - hydrodistillation method.

3. Extraction of essential oils with volatile solvents - extraction method.

4. Absorptions are released from fresh flowers of vapors of essential oils by fats - method of enfleurage and dynamic adsorption.

The final products produced by the first two methods are called essential oils, the third - extraction essential oils, and the fourth - floral lipsticks.

Mechanical methods. In this way, only essential oils of citrus fruits (lemon, orange, tangerine, bergamot) are obtained, where the oils are concentrated only in their peels in fairly large areas. Until 1930, essential oils were obtained by pressing the peel into a sponge. Currently, using a mechanical method, the skin is usually removed, passed through toothed rollers, mixed with a small amount of water, and then subjected to pressing in hydraulic presses. The remaining (about 30%) essential oil in the peel is further extracted by steam distillation. Do not allow the product to be heated, as this will destroy important volatile compounds. Yield of essential oils by the mechanical method (from 1000 fruits, g):

lemon 360-600;

tangerine 4100;

orange 700-800.

Steam distillation is the most common method of obtaining essential oil. It is used in cases where the raw material contains a relatively large amount of essential oil and the distillation temperature (about 100 °C) does not affect the quality of the finished product.

The boiling point of individual components of essential oils ranges from 150 to 350 °C. So, for example, pinene boils at 160 °C; limonene - at 177 °C, geraniol - at 229 °C, thymol - at 233 °C. However, all these substances are distilled in the presence of water vapor at a temperature below 100 °C.

The theoretical basis of the steam distillation process obeys Dalton's law of partial pressures, according to which a mixture of liquids (mutually insoluble and chemically not acting on each other) boils when the sum of the elasticities of their vapors reaches atmospheric pressure.

According to Dalton's law, the total pressure of the mixture is equal to the sum of the partial pressures of the components. As a result, the vapor pressure of the mixture reaches atmospheric pressure even before water boils. So, for example, a mixture of fir oil and water at atmospheric pressure will be distilled at a temperature of 95.5 °C (instead of 160 °C for pinene - the main component of fir oil).

Steam distillation is carried out in continuous or batch stills, container-type stills, etc.

Often, in order to avoid draining of the raw materials and destruction of the constituent parts of the oil (saponification of complex esters, etc.), the raw materials are placed on perforated grids, the bottom of which is above the condensate level, and driven off with the help of hot steam. The distillate (a mixture of water and essential oil) is cooled in a refrigerator and the so-called decanted oil is separated, and the distilled water is re-distilled by heating with dull steam or subjecting it to additional treatment with activated carbon and volatile solvents. With this method, fragrant water is obtained at the same time. flows out through the drain pipe, which is strengthened in the tube at the bottom of the glass (Fig. 1) through the tube fixed in the upper part of the glass.

In those cases when the distillation (runoff) waters obtained after separating the essential oil contain a lot of valuable essential oil in a dissolved or emulsified state (for example, when obtaining rose oil), the latter is separated from it with the help of cohobation. The process of cohobation consists in the fact that the distilled water is distilled a second time, while with the first portions most of the retained oil is distilled off.

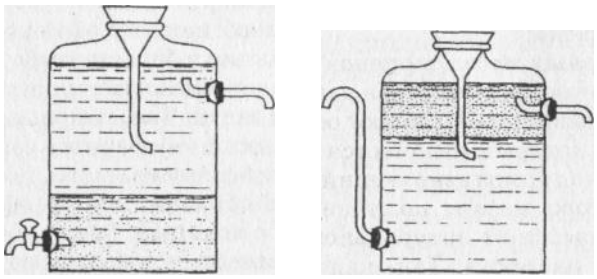


Figure 1. Florentine glasses: / - for essential oils, it is lighter than water; 2 - essential oils are heavier than water.

For the processing of large quantities of raw materials, continuously operating stills are used. Steam distillation can be carried out not only at atmospheric pressure, but also under superheated steam pressure. In this case, the ratio of water and essential oil changes favorably in favor of increasing the distillation of the oil. This is explained by the fact that the decrease in the elasticity of water vapor is stronger, almost out of proportion to the change in the elasticity of essential oil vapors.

When obtaining essential oil by steam distillation, you can use individual parts of plants (flowers, leaves, seeds, stems, roots) both raw and dried. It is better to use dried leaves, so they are easier to grind, ensuring a more complete extraction. Distillation should not be done too quickly, about 2 hours, as part of the steam is used involuntarily, and the oil is emulsified at the same time.

The yield of essential oils, %, during distillation with steam varies greatly depending on their content in the fragrant parts of plants, for example: fun from flowers 0.2-0.3; argon from fruits - up to 9.

Most essential oils are obtained in this way, taking into account the cheapness and simplicity of the equipment, but it is necessary to note significant disadvantages:

- Relatively high distillation temperature for some aromatic substances included in this essential oil, which sometimes causes their decomposition;

- The solubility of some aromatic substances in water during its condensation from water vapor, due to which aromatic substances are absent in the composition of the essential oil after its settling;

- The distillation temperature is not high enough for some non-volatile aromatic substances that are extracted from plant raw materials and, therefore, are absent in the distilled essential oil;

- The presence of terpenes and sesqui-terpenes in most essential oils, which reduce their solubility in alcohol, and in some cases their smell. So, for example, sesquiterpenes have a special, specific camphor smell, which differs from the main smell of the essential oil, but often harmonizes with it.

Thus , the smell of the essential oil obtained during distillation with steam differs from the natural smell of the essential oil directly in the plant. So, for example, until now it has not been possible to obtain essential oils from flowers such as lily of the

valley, jasmine, lilac, etc. using this method. It is possible to achieve the maximum approximation of the smell of the essential oil to the natural one by the so-called obesterpenivation method (distillation in a vacuum or hydrovacuum, hydrodistillation, treatment with alcohol of reduced strength).

During the distillation of essential oils, terpenes are the first to be distilled off and therefore can be easily separated from the component parts that determine the peculiarity of the smell and distilled at a higher temperature. Sesquiterpenes are often the last to be driven off. During distillation, a certain amount of the main odor carrier is captured along with the terpenes, depending on the distillation method and fraction. Non-terpene oils are characterized by:

1) greater solubility in water and alcohol;

2) greater strength, that is, the concentration of the main smell;

3) the property of quickly forming and maintaining the transparency of alcohol solutions.

These properties of non-terpene oils are used in perfumery. Yes, only non-sterpene citrus oils can be completely dissolved in alcohol. When marking such oils, the prefix D (for perfumes) is used. However, very often in terpene-free oil there is some change in the smell, which does not correspond to the freshness and integrity of natural oil containing terpenes. Non-terpene oils should not be used in medicine, since the given therapeutic effect is observed only when using essential oils with the most complete composition, i.e. containing as many active components as possible.

The extraction method was used from the second half of the 19th century. Unlike the previous ones, this method requires more complex equipment. A well-purified solvent is also required.

Essential oils dissolve in many organic solvents. This property is used in those cases when the components of the essential oil are thermolabile and are subject to destruction during distillation with steam.

The following solvents are used: ethyl alcohol, benzene, chloroform, methyl alcohol, acetone, liquid or gaseous butane, carbon dioxide. But petroleum ether (a liquid petroleum product, a mixture of light hydrocarbons) is most often used.

The equipment used is quite diverse. Basically, it consists of an extractor, a distillation cube with a refrigerator, into which a solvent with oil enters from the extractor.

During extraction, the raw material is poured one or more times with a solvent, which, after saturation with aromatic substances, is drained from the raw material. From the fused hood, called MICELLES, the solvent is removed under pressure, then under vacuum. The resulting essential oils are called extractable or "fragrant waxes" (*Essences concretes*). In smell, they are closer to essential oils found in plants than oils obtained by the method of steam distillation. This especially applies to raw materials with a pleasant smell, which when distilled with steam gives too little oil (rose, narcissus, violet, carnation).

The solvent extracts from plants not only essential oils, but also wax, paraffins, gums and fats, so the primary extraction products have a solid consistency and do not completely dissolve in alcohol. Such oils are called concrete.

To get rid of ballast substances, specific oils are extracted once again with ethyl alcohol, and after its distillation and filtration with cooling, the secondary products of extraction are obtained - absolute oils. Absolute oils are completely soluble in alcohol, they are also devoid of terpenes and sesquiter-penovs. When used as an ethyl alcohol extractant, this form of extraction is called risinoid and is used in the production of essential oil from various plants:

yield of specific oils - from 0.08 (tuberose)

up to 0.98% (ylang-ylang);

yield of absolute oils - from 0.18 (tuberose)

up to 80% (ylang-ylang).

It must be remembered that essential oils extracted with organic solvents cannot be taken inside to avoid the manifestation of an allergic reaction and the weakening of the immune system, since the solvents are highly toxic, and their separation from the essential oil is incomplete.

Maceration of flower raw materials with fats is also an extraction method for obtaining essential oils. Raw materials in fabric bags are immersed in a container with a fat body for 24-48 hours at a temperature of 50-70 °C. This operation is repeated 10-

15 times until the smell of a certain strength is obtained. Animal fats are usually used - beef or pork, and vegetable fats - olive oil. Sometimes paraffin with a melting point of 60 °C is used. Fats and oils must be clean, odorless and prepared according to a special recipe. Next, the essential oil is extracted with alcohol (see Enflerage).

Recently, the extraction of essential oils began to be carried out with liquefied gases (carbon dioxide, freons, butane, etc.).

The enfleurage method is the most ancient of the above, it is usually used in the processing of jasmine, lily of the valley, and tuberose (that is, raw materials with a low content of essential oils).

The method is based on the ability of essential oils released by plants (mainly from flowers) to pass into the gas phase and then be absorbed by fats and sorbents. This process is carried out in special chassis frames (size 5x50x50), hermetically assembled in 30-40 pieces. (one to the other) in the battery. In the middle of such a frame there is a glass plate, on which an adsorbent is applied on both sides. Flowers (without cups) up to 3 mm thick are laid out on an adsorbent (activated carbon or a mixture of pork and beef fat, etc.) with a thickness of approximately 3-5 mm, and the edges of the plate by 4 cm remain uncovered. Grooves are made with a spatula to increase the fat absorption surface. Within 1-3 days, the evaporated essential oils are absorbed by the adsorbent. Then the raw materials are removed and fresh raw materials are placed on the frames. This operation is carried out repeatedly (up to 30 times) until the adsorbent is completely saturated with essential oil. Since the used raw material still contains a certain amount of essential oil (heavy fractions), it is additionally processed by extraction. And the fat, saturated with essential oil, is then scraped off the glass.

This product with a rather high quality of smell enters the market under the name of flower lipstick. The essential oil is extracted from the flower lipstick with alcohol. The alcohol extract is frozen, and impurities that have precipitated are removed from it by filtration. Then the alcohol is distilled off in a vacuum and pure essential oil is obtained.

Currently, the enfleurage method is rarely used. This is primarily due to the high price of the final product.

The dynamic sorption method is essentially an improved enfleurage method. The raw materials (flowers collected early in the morning) are placed in a chamber on grids. Then the chamber is hermetically closed and heated air is blown through it, which, capturing vapors of essential oils, passes through activated carbon or silica gel, where absorption (sorption) of vapors of essential oil of loaded colors occurs. Extraction of the sorbent (silicone or activated carbon) releases the essential oil, after which the ether is distilled from the solution and a pure essential oil close to absolute is obtained. This method is promising and becoming more and more widespread.

Determination of the quality of essential oils

The effect of an essential oil primarily depends on its quality. Among the many factors affecting the quality of essential oil, one of the most important is the method of production.

In the CIS, when preparing regulatory and technical documents and technical level maps, the quality of products is compared with the best foreign samples, the requirements of national standards of importers of essential oils, national pharmacopoeias and international standards, which are prepared and agreed by the Technical Committee (TK-54) of the International Organization for Standardization (ISO).

The following standards are also internationally recognized and guarantee high quality:

- Standards of EOA - American Essential Oil Association;
- Norms of the Pharmacopoeia of Great Britain (UK), etc.

The absence of an IFRA ban (International

Fragranse Association) and the implementation of the recommendations of this organization regarding the restriction of the use of some essential oils.

Due to the fact that the climatic conditions of our country do not allow growing many essential oil plants, such oils as ylang ylang, patchouli, sandalwood, jasmine and others are imported. To choose an imported essential oil that meets the requirements for it in our country, its properties and national standards are given.

The authenticity of essential oils is determined by their physical and chemical properties. They mainly determine the indicators for absolute oils. Individual indicators

are put forward for each essential oil. However, for almost all essential oils, the following quality indicators are determined: acid value is the number of milligrams of potassium hydroxide used to neutralize free acids contained in 1 g of essential oil. This important indicator is, as a rule, 0.5-5. When storing oil, the acid value increases due to the decomposition (saponification) of the ethers contained in it.

The essential number means the number of milligrams of caustic potassium needed to neutralize free acids and saponify complex fats contained in 1 g of essential oil; and also establish the content of volatile substances and ethyl alcohol and the solubility of one volume of oil in 96% ethyl alcohol. The solubility of an essential oil in alcohol of 96% or 70% gives an idea of its authenticity and quality. Most hydrocarbons are poorly soluble in alcohol, especially diluted alcohol. It should be noted that the physical and chemical properties of the same oil differ depending on the country of manufacture.

According to the draft ISO standard TK-54, No. 1082-73 F, quality indicators should correspond to the following data:

- Acid number, mg KOH 5-10;
- Ether number, mg KOH 46-78;
- Ether number, mg KOH after acetylation 220-235;
- Solubility of 1 volume of oil in 70% ethyl alcohol at 20 °C in three volumes.

In order to distinguish the essential oil bought in a store or pharmacy from a fake, the consumer can conduct an independent mini-test: put 1 drop on filter paper. Real oil evaporates quickly at room temperature without leaving a trace. If an oily stain remains, it is a fake. Cheap oils should be avoided, as they are poorly or not at all purified and contain impurities that can cause a strong allergic reaction.

Storage of essential oils

Essential oils are stored in containers made of dark glass or white tin, and for short-term storage - in containers made of galvanized or black iron with a double (polyethylene or vinyl) stopper. For better insulation from the air, it is recommended to use tightly packed corks, they protect well from evaporation and exposure to air.

Containers with essential oils are stored in a vertical position in a dark, cool place (not higher than 15 °C), inaccessible to children.

Due to easy oxidization, containers should be filled to the maximum. Do not store essential oil in plastic containers. Essential oils, first of all, must be stored from oxidation, polymerization, resin formation. Essential oils undergo oxidation due to the terpenes and sesquiterpenes contained in them. The product of oxidation is resin: colorless oils turn yellow or brown; dyed ones lose or change their color.

Under normal conditions, essential oils in their pure form are stored for at least a year, except for citrus oils, which have a short shelf life

PRODUCTION OF EXTRACTION PREPARATIONS.

Currently, extraction preparations from medicinal plant raw materials can be divided into 3 groups according to the production technology:

1) total (galenic) preparations;

2) new galenic (maximum purified) preparations;

3) preparations of individual substances.

Galenic drugs should be considered as a specific group of drugs, which, along with chemical-pharmaceutical and other drugs, are included in the composition of drugs. They are called Galenovs after the famous Roman doctor and pharmacist Claudius Galen, who lived in 131-201 BC. e. The term "Galenic drugs" appeared in pharmacy 13 centuries after the death of Galen.

Extracts from raw materials in the production of galena preparations are pre-cleaned by settling and filtering. Therefore, such preparations (tinctures, extracts, etc.) are not chemically individual substances, but represent a complex of substances of more or less complex composition. Extracts containing a complex of substances often act somewhat differently than a single chemically pure substance isolated from it. Therefore, the therapeutic effect of galenic drugs is due to the whole complex of biologically active substances contained in them, strengthening, weakening or changing the action of the main substances.

Extraction processes form the basis of the production of extractive preparations. In pharmacy, they are widely used in the preparation of preparations from medicinal

plant raw materials (tinctures, liquid, thick and dry extracts, concentrated extracts, maximally purified (new galenic) preparations, extraction from fresh plants, etc.) and from raw materials of animal origin (hormone preparations, enzymes and drugs of non-specific action - pantocrin, vitohepat, etc.).

A distinction is made between extraction in a solid-liquid system and liquid-liquid extraction, or liquid extraction. Extraction in the solid-liquid system is most widely used in pharmaceutical production, where the solid is medicinal plant raw materials or raw materials of animal origin, and the liquid is the extractant. Liquid extraction is used in the purification of hoods in the production of maximally purified preparations and preparations of individual substances from medicinal plant raw materials.

Theoretical foundations of extraction.

The extraction process refers to mass exchange processes and occurs due to diffusion from a zone with a high concentration. These are, as a rule, cells of animal or plant material containing biologically active substances. Extraction is based on the diffusion of biologically active substances from the internal structures of material particles into the extractant and ends when equilibrium concentrations are reached. In the equilibrium state, the same number of molecules passes from the material to the extractant as from the extractant to the material. The concentration remains constant. At the same time, the concentration of the material is usually higher than that of the extractants.

Diffusion is *molecular* and *convective* .

Molecular diffusion is the process of transferring a distributed substance (biologically active substance - BAR) due to the chaotic movement of the molecules themselves in a stationary medium. It is characterized by the molecular diffusion coefficient. The molecular diffusion coefficient characterizes the ability of a given substance to penetrate a stationary medium due to diffusion and increases with increasing temperature and decreases with increasing viscosity of the medium and the size of the diffusing particles of the substance.

Therefore, the smaller the radius of the diffusing particles, the faster the

diffusion. Thus, solutions of proteins, mucus, pectins, etc., which have large molecules, are characterized by very low diffusion coefficients. Substances with small molecular sizes (which are more often BARs) diffuse much faster.

Peculiarities of extraction from plant raw materials with a cellular structure.

During extraction from medicinal plant raw materials, BAR diffuses from the internal structures of the material particles. In this process, the extract has its own characteristics. First of all, the presence of a porous partition, intercellular space and cell passages reduces the rate of diffusion. Further, only those substances whose particles do not exceed the size of the pores can pass through the pores of the partition. Finally, there is another significant feature - the desorption phenomenon observed in the cell after the extractant penetrates it. Since the substances inside the cell are bound by the forces of gravity, it is necessary first of all to overcome these adsorption forces. The entire complex of diffusion phenomena occurring inside pieces of plant material is called internal diffusion.

The peculiarities of extracting biologically active substances from materials with a cellular structure are connected with the fact that on the way to the substances contained in the cell, there is a cell wall, the physiological state of which can be different. Thus, a living plant cell has wall layers of protoplasm of a certain thickness. It imposes a special imprint on the properties of the cell wall, as a partition that separates the solution inside the cell (cell juice) from the fluid outside the cell.

As long as the protoplasm is alive, the cell wall is a semi-permeable partition that does not let substances dissolved in the cell juice out. In this case, only the penetration of the extractant into the cell (osmosis) is possible.

A dead cell behaves in a completely different way. As a result of the death of protoplasm (plasmolysis), the cell wall loses the character of a semipermeable partition and begins to pass substances in both directions (dialysis). That is, the cell wall acquires the properties of a porous partition, through which biologically active substances can diffuse, the molecules of which do not exceed the size of the pores.

The vast majority of extraction preparations are obtained from dried plant material. Dehydrated by thermal drying. In the case of obtaining preparations from

fresh plants, the cells are killed with ethyl alcohol. It is very hygroscopic and upon contact with a plant cell dehydrates it, causing the strongest plasmolysis. Cell death of animal raw materials is achieved by the same methods: drying or dehydration with alcohol and acetone.

When obtaining preparations from fresh raw materials, the cells of which are not dehydrated, the washing out of cell juice from destroyed cells and open pores takes place faster than the extraction process.

Stages of the extraction process and their quantitative characteristics

In the process of extraction, mass transfer occurs, characterized by the transition of one or more substances from one phase (raw material) to another (extractant). Mass transfer from raw materials with a cellular structure is a complex process in which three stages can be distinguished: 1) "internal diffusion", which includes all phenomena of substance transfer inside the raw material particles; 2) substance transfer within the limits of the directly diffusive boundary layer; 3) transfer of matter by a moving extractant (convective diffusion).

At the first stage, extraction from dehydrated raw materials with a cellular structure begins with the penetration of the extractant into the material, wetting of the substances inside the cell, their dissolution and desorption. This is followed by the molecular transfer of dissolved substances, first to the extractant located in the intercellular space, then to the extractant that fills the micro- and macrocracks, and finally, to the surface of the pieces of material.

In the second stage, substances diffuse from the surface of the particle to the outer surface of the diffusion boundary layer. Currently, the existence of a wall layer, an extractant called a diffusion boundary layer, on the surface of pieces of raw material is generally recognized. The boundary diffusion layer strongly resists further transfer of extracted substances into the extractant. The thickness of this layer depends on the hydrodynamics of the process and, mainly, on the speed of mixing the extractant. The greater the mixing speed, the smaller the thickness of the boundary layer. Within the diffusion boundary layer, the transfer of substances is carried out according to the law of free diffusion. The extraction process depends on many factors, the main of which are: hydrodynamic conditions, phase interface, concentration difference, duration of

the process, viscosity of the extractant, temperature.

In addition, the completeness and speed of extraction are influenced by: the addition of surface-active substances, the nature of loading of raw materials, the choice of extractant, the porosity and porosity of raw materials, the leaching coefficient, the influence of vibrations, pulsations, electric pulse discharge in a liquid medium, crushing and deformation of raw materials in extractants. Let's consider the influence of each of these factors.

The main factors affecting the completeness and speed of extraction

Hydrodynamic conditions. The mass transfer coefficient K includes coefficients of all types of diffusion and can vary depending on the hydrodynamic conditions of the process. Thus, in the absence of convection, that is, without mixing, the coefficient of convective diffusion is zero, and the thickness of the diffusion layer becomes equal to the thickness of the entire extractant layer. Therefore, the third stage of extraction is omitted, and the mass transfer coefficient is determined only by internal diffusion in the raw material and free molecular diffusion in the stationary liquid.

This phenomenon is observed during maceration (infusion) without stirring. This method of extraction is the longest.

In the case when the extractant moves at least at a slight speed, the mass transfer coefficient is determined by the quantitative characteristics of all three stages of the process. The speed of this method of extraction is higher, because the layer of stationary liquid decreases, convection currents appear, which contribute to the transfer of substances. This mode of extraction is typical for maceration with stirring, percolation, rapid repercolation, continuous countercurrent extraction, etc.

And finally, with very intense mixing, the second and third stages of the diffusion path may be missing. In this case, the convective diffusion coefficient increases to infinity, i.e., convective mass transfer is instantaneous. At the same time, the thickness of the boundary diffusion layer also becomes zero. The mass transfer coefficient in such cases is determined only by the diffusion coefficient in the pores of the plant material.

Recently, extraction with the use of ultrasound, with the help of electric

charges with the use of electroplasmolysis and electrodialysis has been proposed.

The phase interface (F), "solid medicinal raw material - liquid" depends on the degree of grinding of the raw material and will be larger, the smaller its particles. However, in practice, it is known that with excessively fine grinding, the raw materials can become agglomerated, and with the content of mucous substances - slimy, as a result of which the extractant will pass through such masses very poorly. If the grinding is too fine, the number of broken cells increases dramatically, which leads to the washing out of accompanying substances contaminating the extract (proteins, mucus, pectins and other high molecular weight compounds). In addition, a large amount of suspended particles passes into the extractant. As a result, the hoods are cloudy, poorly lit and poorly filtered. It follows from this that coarse raw materials should be chopped to optimal sizes: leaves, flowers, herbs up to 3-5 mm; stems, roots, bark up to 1-3 mm, fruits and seeds up to 0.3-0.5 mm. At the same time, the cell structure will be preserved in the source material and diffusion processes will prevail, extraction will slow down, but the resulting extract will contain fewer mechanical impurities and be easier to clean.

The difference in concentrations in the raw material Cg and extractant C4 is the driving force of the extraction process. During the extraction, it is necessary to strive for the maximum concentration difference, which is achieved by changing the extractant more often (remaceration instead of maceration), conducting a countercurrent process, etc.

Time (duration) of extraction. It follows from the basic mass transfer equation that the amount of substance diffusing through a certain layer is directly proportional to the extraction time. However, it is necessary to strive for the maximum completeness of the extraction in the shortest possible time, making the most of all other factors that lead to the intensification of the process.

Excessive duration of extraction leads to contamination of extracts with associated high molecular weight compounds, the rate of diffusion of which is significantly lower than that of biologically active substances. During long-term extraction, undesirable processes may occur under the influence of enzymes. The

total duration of extraction is most often determined by economic considerations. At the same time, it is advisable to stop the process at some point, taking into account that the additionally extracted amounts of substances will not pay off the excess costs and the losses of valuable extractants (alcohol, ether) will increase.

Viscosity of the extractant. According to Fick's law, the amount of soluble substance diffusing through a certain layer of extractant is inversely proportional to the viscosity of this extractant at a given temperature. Therefore, less viscous solutions have a greater diffusion capacity. Heating is used to reduce viscosity during extraction with vegetable oils.

Temperature. An increase in temperature accelerates the extraction process, but in the conditions of phytochemical production, heating is used only for aqueous extracts. Alcoholic and even more so ether extraction is carried out at room (or lower) temperature, since with its increase the loss of extractants increases, and therefore, the harmfulness and danger of working with them.

As mentioned above, heating is used during extraction with vegetable oils. But for heat-labile substances, the use of a hot extractant is permissible only for short periods of time. An increase in the temperature of the extractant is undesirable for essential oil raw materials, since essential oils are largely lost when heated. It is necessary to take into account that when using hot water, pasteurization of starch, peptization of substances occurs; hoods in this case become mucous and further work with them becomes much more difficult. An increase in temperature is advisable when extracting from roots, rhizomes, bark and leathery leaves. In this case, hot water contributes to a better separation of tissues and rupture of cell walls, thus accelerating the course of the diffusion process.

The addition of surfactants (surfactants). It has been experimentally established that the addition of small amounts of surfactant (0.01-0.1%) improves the extraction process. At the same time, the number of extracted substances - alkaloids, glycosides, essential oils, and others - increases, and in some cases complete extraction is achieved with a smaller amount of extractant.

Surfactant additives reduce the surface tension at the phase interface, improving the wettability of the cell contents and facilitating the penetration of the extractant. In addition, a significant role is played by the solubilizing ability of surfactants.

Choice of extractant. To ensure complete extraction of active substances and maximum speed of extraction, the following requirements are put forward to the extractant: selectivity (selective solubility); chemical and pharmaceutical indifference; low toxicity; accessibility.

The choice of the extractant is determined by the degree of hydrophilicity of the extracted substances. To extract polar substances with a high dielectric constant, polar solvents are used: water, methanol, glycerin; for non-polar - acetic acid, chloroform, ethyl ether and other organic solvents. Most often, ethanol is used as an extractant - a low-polarity solvent, which, when mixed with water, gives solutions of varying degrees of polarity, which allows it to be used for the selective extraction of various biologically active substances. In addition to ethanol, acetone, propanol, butanol are used as less polar solvents.

Porosity and porosity of raw materials. The porosity of the raw material is the amount of voids inside the plant tissue. The higher it is, the more internal juice is produced during swelling. Porosity is the size of voids between pieces of crushed material. The rate of wetting and swelling of the material depends on the amount of porosity and porosity. The rate of swelling increases with preliminary vacuuming of raw materials, as well as with increasing pressure and temperature.

The absorption capacity of the raw material is directly dependent on the degree of its grinding.

Elution coefficient. It characterizes the degree of destroyed cells in the crushed raw material. If it is low, it means that there are few destroyed cells in the raw material, the extraction is slow and is determined mainly by the rate of molecular diffusion. The amount of substances in the hood, obtained from a certain amount of raw material, at a certain ratio (raw material-extractant) when extracting the raw material for one hour

at the appropriate mixing speed, is taken as the value of the leaching coefficient.

The influence of vibrations, pulsations, crushing and deformation of raw materials in the medium of the extractant. The use of extraction methods, in which vibrations, pulsations, grinding and deformation in the medium of the extractant take place, allows to significantly increase the speed and completeness of extraction from raw materials. This is explained by the fact that:

1) With intense impact on solid particles, strong turbulent currents, hydrodynamic microflows appear, contributing to mass transfer and dissolution of substances. This phenomenon is observed both outside solid particles and inside them. As a result, intense mixing is achieved even within individual cells.

2) With intensive oscillation of raw material particles in places of friction, there is a local increase in temperature, a decrease in the viscosity of the extractant, and therefore, an increase in the internal diffusion coefficient.

3) As a result of increased turbulence, disruption of the structure of adjacent layers, the boundary diffusion layer is depleted or will have an extremely small thickness.

4) The result of intense fluctuations is the alternation of compression and stretching zones. At the same time, at the time of stretching, fluid rupture cavities are formed in the extractants, which close with a force of several hundred atmospheres. The positive quality of this process is the dispersion of particles, which leads to an increase in the interfacial surface.

As a result of the appearance of turbulent mixing both inside and outside the cells, the molecular-kinetic movement is replaced by convective, which allows maintaining the concentration difference in the phase collision zone at a high level.

The effect of electric impulse discharges. When extracting with the help of electric discharges, the process of extracting BAV is accelerated because a micro-explosion occurs in the raw material due to a spark discharge, which breaks the cellular structures of the material. The extraction process proceeds faster due to the leaching of extractive substances and pulsation, which increase the speed of the extractant. Oscillations occurring in the liquid shorten the extraction time and increase the yield of biologically active substances.

Requirements for extractants

Extractants are subject to certain requirements arising from the specific features of pharmaceutical production. The extraction agent must possess:

- Selectivity, i.e. dissolve substances as much as possible, and ballast substances as little as possible;

- High wetting ability, which ensures good penetration of it through the pores of the material and cell walls;

- The ability to prevent the development of microflora in the extract;

- Volatility, possible low boiling point, easy regeneration;

- Minimal toxicity and flammability;

- Availability at cost.

From two equivalent extractants, choose a less flammable, affordable, pharmacologically less harmful, etc. If the extractant does not meet the specified needs, then mixtures are used, for example, acidified water, alcohol with water, ether with alcohol, etc. p.

One of the most frequently used extractants is water, which has the following advantages:

- Penetrates well through cell membranes that are not impregnated with hydrophobic substances;

- Dissolves and extracts many substances better than other liquids;

- Pharmacologically indifferent;

- Widespread;

- Non-flammable and non-explosive;

- Affordable.

However, as an extractant, it has a number of negative sides, for example:

- Dissolves and does not extract hydrophobic substances;

- Does not have antiseptic properties, as a result of which microorganisms may develop in aqueous extracts, which may cause spoilage of the extracted extract;

- Due to water, hydrolytic splitting of many substances occurs, especially at high temperature;

- In an aqueous environment, enzymes can break down medicinal substances,

etc.

Ethyl alcohol is the most commonly used extractant after water.

The quality of rectified alcohol is regulated by GF X and GOST 5962-51.

Alcohol as an extractant:

- It is a good solvent for many compounds that cannot be extracted with water, such as fats, alkaloids, chlorophyll, glycosides, essential oils, resins, etc.;

- It has antiseptic properties (microorganisms and molds do not develop in water-alcohol solutions of more than 20%);

- The stronger the alcohol, the less possible hydrolytic processes in its environment.

- Alcohol inactivates enzymes; is quite volatile, so alcohol extracts are easily thickened and dried to powdery substances. To preserve thermolabile substances, evaporation and drying are carried out under vacuum;

- It is a limited product, released by the pharmaceutical industry in accordance with the established procedure;

- Much harder than water, it penetrates through cell walls, depriving water from proteins and mucous substances, turning them into precipitates, clogging cell pores and thus impairing diffusion. The lower the concentration of alcohol, the lighter it is

penetrates inside the cells;

- Pharmacologically indifferent; it provides both a local and a general effect, which must be taken into account when producing extracts;

- Flammable and combustible.

Therefore, alcohol-extractant has a wider range of BAR extraction than water, and its extractability depends on the concentration. When extracted with ethanol in a concentration of at least 70%, extracts free from biopolymers (proteins, mucus, pectins) are obtained.

Acetone (CHgCOCHg). Colorless liquid with a characteristic smell. The relative density is 0.798. It boils at 56.2 °C. It is miscible in all respects with water and organic solvents. It is used as an extractant for alkaloids, resins, oils, etc.

Ethyl ether ($CH_2H_5OS_2H_5$). Colorless liquid with extreme volatility, boiling point - from 34 to 36 °C. Soluble in 12 parts of water, miscible in all ratios with acetone,

alcohol, petroleum ether, fatty and essential oils. Specific gravity 0.714 (at 20 °C). Ether vapors have a high specific gravity (2.56 in relation to air), they creep on the floor, are poisonous, can move and accumulate far from the source of ether evaporation. In contact with fire or hot objects, they can cause an explosion of great force (the flash point of ether is 40 °C). Therefore, when working with ether, it is necessary to observe special safety measures, which limits its use as an extractant. Ethyl acetate mixed with ethanol in a ratio of 9:1 is used in the liquid extraction of flavonoids in the production of flavin.

Chloroform (SNS1 $_3$). Colorless, transparent, volatile liquid, miscible in all ratios with alcohol, ether, gasoline, with many fatty and essential oils, soluble in water (1: 200) and immiscible with glycerin. The specific gravity is 1.52, it boils at 59.5-62 °C. Chloroform vapors are poisonous, but not flammable or explosive.

It is a good solvent for many medicinal substances: alkaloids, glycosides, oils, etc.

Dichloroethane ($_{C1CH2CH2C1}$) . _ Colorless, transparent liquid that does not mix with water. It has an odor reminiscent of chloroform. Density 1.252-1.235. The boiling point is 83.0-84.0 °C. Mixes with alcohol and ether, fats, mineral oils, resins. Dichloroethane is low-flammability (ignition temperature 21.1 °C). Inhalation of vapors causes poisoning. Dichloroethane mixed with chloroform (at a density of 1.315) is used to extract glycosides.

Methylene chloride (CH $_2$ C1 $_2$). An extractant with a high relative density - 3.33 and a boiling point of 41 °C. It is used to extract hydrophobic substances (glycosides, alkaloids, etc.).

Methanol , methyl, or wood alcohol (CH $_3$ OH). Currently, it is produced synthetically. Transparent, colorless liquid with a weak odor, reminiscent of ethyl alcohol. Mixes with water in all respects, forming transparent solutions without traces of turbidity and opalescence. The density is not more than 0.793. The boiling point is 64-67 °C. Strong poison. Ingestion of 10 ml causes atrophy of the optic nerve, doses of 15-20 ml are fatal. They are allowed to work with methyl alcohol only after special instruction. Store in a closed container. It is used in the extraction of coumarins. To separate the mixture of glycosides , a mixture of methanol and water (density 0.9464)

is used.

Vegetable oils . They use vegetable oils of cold pressing, which have stood up well; yellow color Peach, almond and sunflower oils are most often used. Fatty oils are mixed with ether, chloroform, gasoline, essential oils and mineral oils. All oils, except castor oil, do not mix with alcohol and water. It turns bitter, which entails an increase in the acid number. Fatty oils have selective ability as extractants.

Liquefied gases. Recently proposed liquefied gases are promising for extraction: carbon dioxide, propane, butane, liquid ammonia, refrigerants (chlorofluorocarbons), etc. Liquefied carbon dioxide is good at extracting essential, fatty oils and other hydrophobic substances. Hydrophilic substances are well extracted with liquefied gases with high dielectric constant (ammonia, methyl chloride, methylene oxide, etc.)

Extraction with liquefied gases is carried out under pressure, when it is removed, the extractant evaporates, and the extractive substances remain in their pure form.

Tinctures

Tinctures (Tincturae) are colored liquid alcohol or water alcohol extracts from medicinal plant raw materials, obtained without heating and removing the extractant.

Tinctures - medicinal form, introduced into medical practice by Paracelsus (1493-1541), has not lost its importance until now. They are Official under GF XI.

When making tinctures, 5 parts by volume of the finished product are obtained from one weight part of plant raw materials; of potent raw materials - 10 parts. In some cases, tinctures are prepared (1:10) from raw materials that do not contain potent substances (tincture of arnica, calendula, hawthorn) and in other ratios.

Tinctures can be simple, obtained from one type of raw material, and complex, representing a mixture of extracts from several plants, sometimes with the addition of medicinal substances. To obtain tinctures, dried plant material is often used, in some cases - fresh raw materials.

cooking methods

The following methods are used to prepare tinctures:

—- Maceration and its varieties;

—- Percolation;

—- Dissolving thick and dry extracts.

Maceration

Previously, the method of maceration, or infusion, (from the Latin Maceratio - soaking) was widely used for obtaining tinctures. Currently, its use is gradually decreasing, because it is difficult to achieve complete extraction of medicinal substances from plant material during extraction by this method.

Maceration is carried out as follows. Crushed raw materials with the proposed amount of extractant are loaded into the maceration tank and infused at a temperature of 15-20 °C, stirring periodically. If the terms are not specifically stipulated, then insistence is carried out within 7 days. After that, the extract is drained, the residue is squeezed, the extracted extract is washed with a small amount of extractant, it is squeezed again, the extracted extract is added to the merged extract, after which the combined extract is brought to the required volume with the extractant.

This method is ineffective - it flows slowly, raw materials are not completely exhausted. In order to intensify the extraction of the material, the process is carried out using fractional maceration (remaceration), maceration with forced circulation of the extractant, vortex extraction (turboextraction), ultrasound, etc.

Remaceration, or fractional maceration with separation into parts of the extractant, or raw materials and extractant . The total amount of the extractant is divided into 3-4 parts and the raw materials are successively pressed with the first part of the extractant, then with the second, third and fourth, draining the hood each time. The time of infusion depends on the properties of the plant material. This extraction process allows for a more complete exhaustion of the raw materials with less time spent, because a high concentration difference in the raw materials and the extractant is constantly maintained.

Maceration with forced circulation of the extractant. It is carried out in a maceration tank with a false (perforated) bottom, on which filter material is placed. The extractant, separated from the raw material by a false bottom, is pumped through the raw material with the help of a pump until the equilibrium concentration is reached. At the same time, the infusion time is reduced several times. Fractional maceration is also carried out with forced circulation of the extractant. In this case, a more complete

depletion of raw materials is achieved with the same amount of extractant.

Vortex extraction, or turboextraction, is based on the vortex, very intensive mixing of raw materials and extractant with simultaneous grinding of raw materials. The turbine mixer rotates at a speed of 8,000-13,000 rpm. The extraction time is reduced to 10 minutes, the tinctures are standard.

Ultrasonic extraction . Effective use of ultrasonic vibrations to intensify the maceration process. At the same time, extraction is accelerated and complete extraction of active substances is achieved. The source of ultrasound is placed in the treated environment or attached to the body of the maceration tank in a place filled with extractant and raw materials. The greatest effect of the influence of ultrasound is revealed when the cell is extracted well impregnated with the ultrasound-conducting extractant. The resulting ultrasonic waves create alternating pressure, cavitation and "sonic wind". As a result, the impregnation of the material and the dissolution of the cell contents are accelerated, the speed of the flow around the raw material particles increases, and turbulent and eddy currents appear in the boundary diffusion layer of the extractant. Molecular diffusion inside the cells of the material and in the diffusion layer changes to convective, which leads to the intensification of mass transfer. The occurrence of cavitation causes the destruction of cells. At the same time, extraction is accelerated due to the washing out of extractive substances from destroyed cells and tissue. When voicing, you can get the hood within a few minutes.

Other types of dynamization of maceration include: grinding of raw materials in an extractant environment, for example in a ball mill; remaceration, accompanied by pressing on hydraulic presses or rollers. In the latter case, the process is repeated until equilibrium concentrations are reached. The method allows to reduce losses of active substances and extractant, since a small amount of extract remains in the meal. The finished tincture contains a high amount of extractive substances.

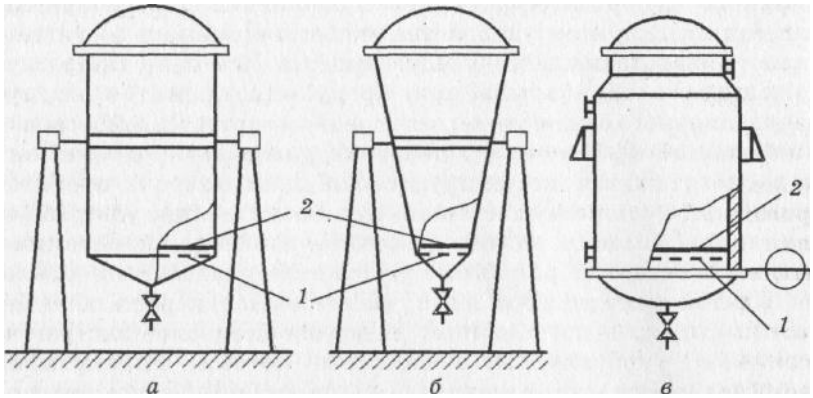
Percolation

Percolation (from the Latin Percolation - percolation through ...), i.e. Percolation of the extractant through plant material with the aim of extracting substances soluble in extractants. The process is carried out in containers of various designs, called extractor percolators. They can be cylindrical or conical, with or without a steam jacket, tiltable and

self-unloading, made of stainless steel, aluminum, tinned copper and other materials. In the lower part of the percolator there is a false bottom (perforated mesh), on which the filter material (burlap, cloth, etc.) is placed, and the raw materials are loaded. Cylindrical percolators are convenient in operation when unloading raw materials, conical ones provide more uniform extraction.

Figure 1. Percolator-extractors

The percolation method includes three consecutive stages: soaking of raw materials



(swelling of raw materials), infusion, percolation itself.

Soaking (swelling) is carried out outside the percolator. Most often, maceration tanks or other containers are used for this purpose, from which it is convenient to unload soaked raw materials. For soaking, 50 to 100% of the extractant is used in relation to the mass of raw materials. After mixing, the raw materials are left for 4-5 hours in a closed container. During this time, the extractant penetrates between the particles of the plant material and inside the cells, the raw material swells, increasing in volume. At the same time, active substances are dissolved inside the cell.

In production conditions, soaking can be combined with infusion, but if the raw material can swell a lot, the soaking stage must be carried out in a separate container, because due to the large increase in the volume of the material in the percolator, it can be strongly compressed and not pass the extractant at all.

Insistence is the second stage of the percolation process. Swollen or dry material is loaded into the percolator on a false bottom with optimal density so that as little air as possible remains in the raw material. The top is covered with filter material, pressed with a perforated disk and filled with extractant so as to displace the air as much as possible. It is possible to load the material into a bag of filter material

that fills the entire volume of the percolator. In the upper part, the bag is tied and the cargo is placed. The raw material is poured with an extractant until a "mirror" is formed, the height of which layer above the raw material should be about 30-40 mm, and insistence is carried out for 24-48 hours, during which the equilibrium concentration will be reached. For many types of raw materials, the infusion time can be shortened.

Percolation itself is the continuous passage of the extractant through a layer of raw materials and the collection of percolate. At the same time, draining of the percolate and simultaneous feeding of the extractant from above is carried out at a rate not exceeding 1/24 or 1/48 (for large productions) of the used volume of the percolator in 1 hour. At the same time, the saturated extract is displaced from the plant material by a stream of fresh extractant and a concentration difference of the extracted substances in the raw material and the extractant is created. The speed of percolation should be such that the diffusion of the extracted substances into the hood has time to occur. When preparing tinctures, the percolation is finished by obtaining five or ten volumes (depending on the properties of the raw material) of the hood in relation to the weight of the loaded raw material.

When obtaining tinctures in industry, with the aim of maximum intensification of extraction, changes are made in the percolation process. Often, instead of typical percolation, insistence, circulation and their combination are used.

In one of the percolation options, the first, fairly concentrated extract is drained separately, completely draining it from the percolator. Then the percolator is filled with fresh extractant, which after infusing for 3-6 hours is drained completely. The obtained second extract is attached to the first, and another 1-2 similar operations are carried out with the raw material until the required amount of extract is collected.

Otherwise, in the process of infusion, the extractant is circulated in the percolator-extractor with the help of a pump that supplies the extract from the lower part to the upper part. Such circulation of the extractant is carried out until the equilibrium concentration. The infusion time is reduced many times. Next, percolation is carried out by displacement with a pure extractant as described in the stage "proper percolation".

The obtained extractions are cloudy liquids containing a significant amount of suspended particles. Extracts are purified by settling at a temperature not higher than 10 °C until a clear liquid is obtained. At this temperature, the solubility of the extracted substances decreases and therefore in the future, during the storage of tinctures at a temperature of 15 °C, the probability of the appearance of sediment is small. After settling for at least 2 days, filter by decantation (i.e., without disturbing the sediment) and filter 6t of accidentally caught inclusions. Filter presses, filter presses, and centrifuges are used for filtration. It is not recommended to use notch filters due to the possible loss of the extractant. The final stage of the process of obtaining drugs from raw materials with a cellular structure is the recovery of the extractant from meal, i.e. spent raw materials. (Recovery methods see "Recovery and rectification of ethanol").

Dissolving thick and dry extracts

A small number of tinctures are prepared by dissolving dry and thick extracts in alcohol of the required concentration. This method produces a tincture of chilibukha, which has poisonous seeds that are difficult to powder due to their high hardness. At the same time, dry extract is used.

A breast elixir is prepared by dissolving a thick or dry licorice extract.

The technology of obtaining tinctures by this method is reduced to a simple dissolution in a reactor with a stirrer of the calculated amount of dry or thick extract in alcohol of the required concentration. The resulting solutions are filtered. This method is characterized by a significant reduction in the time of obtaining the tincture.

Standardization

In the vast majority of tinctures, the content of active substances is determined by chemical (tinctures containing alkaloids, tannins, essential oils, organic acids, etc.) or biological (tinctures containing glycosides of the cardiac group and bitter substances) method. If the amount of active substances in the tinctures is higher than the established limit or greater biological activity, they are diluted by adding a pure extractant or a weakly concentrated tincture. If the content of active substances is below the norm, they are strengthened by adding a more concentrated tincture.

General methods of testing tinctures include: checking of organoleptic features, quantitative determination of alcohol, extractive substances, heavy metals, density.

Inspection of organoleptic signs. Tinctures should be transparent and retain the taste and texture of the substances contained in the original medicinal raw materials.

The alcohol content in tinctures is determined by one of the GF XI methods:

a) Distillation;

b) by boiling point.

The density of tinctures is determined according to the methods of GF XI, (issue 1, p. 24):

a) using a pycnometer;

b) hydrometer (densimeter).

Dry residue (extractive substances) and heavy metals in tinctures are determined according to GF XI.

Storage of tinctures

Tinctures should be stored in well-stoppered glasses in a place protected from direct sunlight at a temperature of 15 °C. With the passage of time, precipitation may appear, and if the storage rules are followed, the tinctures "get old". This is due to a change in the solubility of biologically active substances and the formation of insoluble compounds as a result of the interaction of the substances present in the tinctures. The sediment may contain sugars, tannins, organic acids, pigments, traces of alkaloids, glycosides, and others, the tinctures with the sediment are filtered and re-standardized. If the numerical indicators meet the requirements of the GF, they are allowed to be used.

Tinctures are also used for external use.

Classification and nomenclature of tinctures

All tinctures can be divided into two groups: simple and complex.

Tinctures are simple. All simple tinctures are more often obtained by the percolation method. When obtaining tinctures in a ratio of 1: 5 in order to achieve

complete exhaustion of raw materials, extraction is carried out using circulation mixing with the help of centrifugal pumps.

Tinctures are complex . A representative of this previously large group of tinctures is bitter tincture (*Tinctura amara*), which includes: goldenseal grass - 6 g; trefoil leaves - 6 g; plantain rhizomes - 3 g; wormwood herb - 3 g; tangerine peel - 1.5 g. The tincture is prepared on 40% alcohol by the percolation method, which is activated by circulation. It is used as an aromatic bitter to stimulate appetite and improve digestion.

Extracts

Extracts (from Latin Extractum - - extract, extraction) are concentrated extracts from *medicinal* plant raw materials (LPS).

They can be classified depending on the consistency into liquid extracts (*Extracta fluida*), thick extracts (*Extracta spissa*) and dry extracts (*Extracta sica*); or from the used extractant: aqueous (*Extracta aquosa*), alcoholic (*Extracta spirituosa*), ethereal (*Extracta aetherea*), oily (*Extracta oleosa*) and obtained with the help of liquefied gases. In addition, standardized extracts (*Extracta standartisata*) or extract concentrates are allocated.

Liquid extracts are only alcoholic; others can be alcohol, water, ether, etc.

Liquid extracts

Liquid extracts are liquid concentrated water-alcohol extracts from LRS, obtained in a ratio of 1: 1. At pharmaceutical enterprises, liquid extracts are prepared by weight (from 1 kg of raw materials, 1 kg of liquid extract is obtained).

Liquid extracts are widely used in the pharmaceutical industry, as they have the following advantages: 1) the same ratio between the active substances contained in medicinal raw materials and in the finished drug; 2) convenience in measuring in pharmacies with burettes and pipettes; 3) the possibility of obtaining without the use of evaporation allows obtaining liquid extracts containing volatile substances (essential oils).

Disadvantages of liquid extracts include: 1) their saturation with accompanying substances extracted from plant raw materials; 2) the appearance of precipitation with

slight decreases in temperature or partial evaporation of alcohol; 3) the need for airtight sealing and storage at a temperature of 15-20 °C; 4) liquid extracts contain large amounts of extractant, which is why they are poorly transportable drugs.

methods of obtaining

Liquid extracts are obtained by the methods of percolation, repercolation (in various versions), fractional maceration in various modifications, dissolution of thick and dry extracts. The best quality liquid extracts are obtained using methods of preparation that exclude evaporation.

Percolation in the production of liquid extracts at the stages of swelling and infusion is no different from percolation in the production of tinctures. At the actual percolation stage, the process is carried out similarly and at the same speed as for tinctures. The difference lies in the collection of ready extracts. For liquid extracts, extraction is divided into two portions. The first portion in the amount of 85% in relation to the mass of raw materials is collected in a separate container. Then percolation is carried out in another container until the raw materials are completely exhausted. At the same time, they receive 5-8 times (in relation to the mass of raw materials loaded into the percolator) more weak extracts, which are called "release". This "vacation" is evaporated under vacuum at a temperature of 50-60 °C to 15% in relation to the mass of raw materials loaded into the percolator. After cooling, this thickened residue is dissolved in the first extraction portion. Extracts are obtained in a ratio of 1: 1 in relation to raw materials.

Repercolation, i.e. Repeated (repeated) percolation, which allows you to make maximum use of the dissolving ability of the extractant, to obtain concentrated extractions when the raw materials are completely exhausted. In all cases, the process is carried out in several percolators (from 3 to 10), which work in connection, in the so-called battery of percolators. In this battery, the finished product is drained from the last percolator, in which the raw materials are always fresh, and the fresh extractant is fed to the first percolator, in which the raw materials are exhausted. Extracts from the first percolator process raw materials in the previous percolator, and so in the entire battery - raw materials in further percolators are extracted with extracts obtained from previous percolators. Thus, from the 1st to the last percolator in the battery, the raw

material and the extractant are counter-flowed.

There are various options for repercolation with the distribution of raw materials into equal and unequal parts, with a completed and unfinished cycle. Some of them allow you to obtain the concentration of the hood without further evaporation.

Solution . Liquid extracts can be obtained by dissolving dry or thick extracts. The method is used relatively rarely, although it deserves greater implementation in practice due to the reduction of the time of the technological process. The preparation technology boils down to dissolving a thick or dry extractant in a suitable extractant followed by purification and standardization.

Cleaning

Obtained by any of the methods described above, extracts in the production of liquid extracts stand for at least 2 days at a temperature not higher than 10 °C until a clear liquid is obtained. The settling is sometimes allowed to be carried out in the presence of adsorbents, which contributes to better cleaning and greater stability during storage and transportation. The settled, transparent part of the extraction is filtered from accidentally introduced impurities through printing filters, filter presses or centrifuged. Finally, the remaining extracts with sediment are filtered. Filtered hoods are thoroughly mixed and standardized.

standardization

In liquid extracts, the content of active substances is determined by chemical methods (with the exception of liquid extract of hawthorn, the quality of which is controlled biologically). The quality of some liquid extracts is determined by the sum of extractive substances (for the method of determining the dry residue, see the topic "Tinctures"), according to the methods specified in the early articles, the alcohol content is determined (GF XI, issue 2, p. 26), or the density (GF XI, issue 1, p. 24), heavy metals (GF XI, issue 1, p. 161).

storage

Liquid extracts are stored in tightly closed vials at a temperature of 12-15 °C and, if necessary, in a place protected from light. In the process of storage, precipitation may occur. If the extracts after filtering the sediment and checking the quality meet the established requirements, they are considered suitable for use.

Thick and dry extracts

Thick extracts are concentrated extracts from medicinal plant raw materials, which are viscous masses with a moisture content of no more than 25%. They usually do not pour out of the vessel, but are stretched into threads, which then merge into a solid mass.

Due to their high viscosity, thick extracts are used as binders and form-forming substances in the production of pills in a pharmacy. In addition, they can be included as a corrigent in the composition of syrups, mixtures or elixirs. Thick extracts are used as intermediate products for a number of dosage forms (tinctures, tablets).

Disadvantages of thick extracts include the inconvenience of their use, which requires certain techniques in Weighing. In addition, in dry air they dry up and become hard; in humid air - they become damp and moldy. Therefore, they require airtight packaging.

Dry extracts are concentrated extracts from medicinal plant raw materials, which are loose masses with a moisture content of no more than 5%. They should be considered the most rational type of extracts. They are convenient to use, have the minimum possible weight. The disadvantages of dry extracts include their high hygroscopicity, as a result of which they turn into globular masses that lose their fluidity.

Dry extracts are divided into extracts with a limited upper limit of active substances and extracts with an unlimited upper limit of active substances.

Extracts with a limited upper limit of active substances are obtained from raw materials containing highly biologically active compounds. Such extracts must contain active substances in a strictly defined amount. This is achieved by adding fillers or mixing extracts containing more and less active substances in certain ratios. Milk sugar, glucose, potato dextrin, etc. are used as fillers. Fillers are often added to the dried product at the grinding stage.

Extracts with an unlimited upper limit of active substances are obtained without adding fillers to them. Such extracts are obtained from medicinal raw materials containing inactive substances.

Methods of obtaining

The production process of thick extracts includes three main stages: 1) extraction; 2) its purification and 3) thickening. The production of dry extracts can be carried out according to two schemes. In the first case, the process consists of four stages: 1) obtaining a hood; 2) cleaning the hood; 3) thickening of the hood; 4) drying of the thickened hood. In the second case, the process of production of dry extracts is carried out bypassing the thickening stage, and then it includes three stages: 1) extraction; 2) cleaning the hood; 3) drying of liquid or slightly thickened extract. Drying of liquid extract can be carried out in spray or sublimation (lyophilic, molecular) dryers. The slightly thickened extract is dried in vacuum roller dryers.

In the production of thick and dry extracts, water (in some cases hot), aqueous solutions of ammonia, chloroform water, ethanol of various concentrations, organic solvents, liquefied gases, vegetable and mineral oils are used as extractants.

Obtaining hoods

In the production of thick and dry extracts, various methods are used to obtain extracts from raw materials: 1) remaceration and its variants; 2) percolation; 3) Repercolation; 4) circulation extraction; 5) countercurrent extraction in batteries of percolators with circulation mixing; 6) continuous countercurrent extraction with movement of raw materials and extractant; as well as other methods that include grinding raw materials in an extractant environment; vortex extraction; extraction using electromagnetic vibrations, ultrasound, electric discharges, electroplasmolysis, electrodialysis, etc.

Percolation. The process of percolation at the stages of soaking and infusion is carried out in the same way as in the preparation of tinctures and liquid extracts. In fact, percolations lead at the same speed to the complete exhaustion of raw materials without dividing them into primary and secondary extracts, since then all obtained extracts are thickened or dried.

Cleaning the hood

Water and water-alcohol extracts with a small amount of ethanol (20-40%) contain many high-molecular compounds (water-soluble proteins, sugars, enzymes, pectins, mucus, starch), which must be removed before evaporation. Depending on the amount and properties of ballast substances, different cleaning methods are used . In

some cases, cleaning is carried out by boiling - if there is no BAR inactivation. Proteins coagulated at the same time peel off quickly. Sometimes adsorbents are used (kaolin, bentonite, talc, etc.) or a combination of adsorbents with boiling. The method of removing ballast substances by precipitating them with alcohol is often used. Alcohol cleaning is carried out with preliminary evaporation of hoods to half the volume relative to the mass of the raw material. After cooling, a double volume of strong (95-96%) ethanol is added to it. Everything is thoroughly mixed and left for 5-6 days at a temperature not higher than 10 °C. The settled layer is drained from the sediment and filtered. The cleaned extract, if necessary, is subjected to further thickening.

For chloroform (carbon tetrachloride) extractions, the extractant replacement method is used. At the same time, water is added in an amount equal to the mass of the raw material to the vaporized volume relative to the mass of the raw material. Soluble in chloroform (carbon tetrachloride) chlorophyll, resinous substances precipitate, as they do not dissolve in water. The extract is settled, filtered and subjected to further processing.

Thickening of the hood

Cleaned hoods are evaporated under vacuum at a temperature of 50-60 °C and a dilution of 600-650 mm Hg. Art. to the required consistency. When thickening alcohol hoods or hoods after alcohol purification, alcohol is first driven off, without including a vacuum.

The equipment used for evaporating hoods in pharmaceutical production has its own characteristics. This is explained by the fact that the hood contains biologically active substances that, when vaporized, can settle on the walls of vaporizers heated by steam and lose their activity due to the high temperature of the walls. Therefore, devices in which there is no circulation of evaporating hoods or there is a weak circulation (as in an evaporating cube) are used extremely rarely in pharmaceutical production.

Not all designs with intensive circulation proposed in recent years are widely used in factory production. Thus, the highly efficient Centriterm centrifugal rotary-film device, having high productivity in industry, did not find application due to the vibrations and large noise effect that arise during operation. At this stage, such designs

as a direct-flow rotary, circulating vacuum-evaporator and a foam evaporator have found the greatest use at this stage, as they are reliable in operation, highly efficient, and easy to maintain.

Drying hood

Drying of cleaned extracts can be carried out according to two schemes: 1) without thickening of the liquid extract and 2) through the stage of thickening with subsequent drying.

In the first case, the drying of hoods is carried out in spray dryers, where the liquid hood is sprayed into very small drops in a large chamber. From below, toward the settling drops, heated air (its temperature is about 150-200 °C) is supplied with the help of a fan, while overheating of the material does not occur, since all the heat of the air goes to change the aggregate state of moisture from the hood droplets. The temperature of the dried material does not exceed 50-60°C. According to the first scheme, drying is carried out in drum (roll) vacuum dryers. The hood is slightly evaporated (so that a sufficient layer of dry extract is formed on the rotating rollers after drying) and fed between the rotating ones towards each other, heated from the inside by the streets. The crust of dry extractant removed from the rollers is then ground in a ball mill.

From the liquid state, drying can also be carried out in sublimation (lyophilic, molecular) dryers. At the same time, the solution (extract) is frozen, placed in a sublimation chamber, where a deep vacuum is created (residual pressure of several micrometers). Under such conditions, moisture from the frozen material sublimates, i.e. evaporates, bypassing the liquid phase. The drying temperature in this case is 20-30 °C. The resulting powder dissolves very easily, contains all biologically active substances in an unchanged form.

In the second case, drying is carried out in vacuum drying cabinets. The thickened extract is applied in the form of a thin layer on the sheets and dried at a residual pressure of 110-160 mm Hg. Art. (vacuum 600-650 mm Hg). During the drying process , the volume of the extract increases several dozen times. As a result, a very loose, light mass is obtained in the form of cakes, which are colored on a ball mill.

standardization

Standardization of thick and dry extracts is carried out according to the content of active substances or biological activity. The moisture content is also determined by the GF XI method. In thick extracts, the moisture content is no more than 25%, in dry - no more than 5%.

storage

Thick extracts are stored in a hermetically sealed container that does not allow drying out. Dry extracts, characterized by high hygroscopicity, must be stored in small-capacity, wide-mouthed jars, hermetically sealed, with a capacity of no more than 100 m

If necessary, the extracts are stored in a cool place protected from light.

Materials on the activation of students of higher education during the lecture: questions, situational tasks, etc.:

Question:

1. Characteristics and classification of tinctures.
2. Preparation of raw materials and extractant for extraction.
3. Obtaining tinctures by extraction. The essence of the extraction process.
4. Device of maceration tanks and percolators.

Task:

1. Make a working prescription and prepare 30 ml of one of the listed tinctures: calendula, motherwort, lily of the valley, wormwood.
2. Make a material balance of absolute alcohol or active substances.
3. Draw up a technological scheme for the production of the obtained tincture.

General material and bulk-methodological support of the lecture:

- educational premises - the auditorium of the department;
- equipment - computer, tables;
- equipment – multimedia projector;
- illustrative materials - presentation, slides.

Questions for self-control:

1. Methods of intensifying the production of tinctures.
2. Determination of alcohol content in tinctures.
3. Calculation of the amount of raw materials and extractant for obtaining tinctures.
4. Factors affecting the completeness and speed of extraction of active substances.
5. Stages of the method of maceration and remaceration (bismaceration).
6. Sequence of stages during percolation. The equipment used.
7. Methods of purification of tinctures.
8. Standardization. Quality control of tinctures.
9. Storage. Packaging, packaging and labeling of tinctures.

References:

1. Study guide for independent work of students of the Faculty of Pharmacy for the licensing exam "Step 2. Pharmacy" / V.Yu. Anisimov, O.I. Belyaeva, H.G. Vidavska, V.O. Helmboldt, A.V. Zamkova, I.V. Lytvynchuk, A.V. Nikitin, B.V. Pristupa, I.B. Petkova, Ya.V. Rozhkovskyi, S.B. Strechen, L.M. Unguryan, N.C. Fizor Odesa: Odesa.nats.med. Univ. 2020. - 240 p.

Mode of access to lecture texts for students of the Faculty of Pharmacy: https://info.odmu.edu.ua/chair/drugs/files/390/ua

Literature used by the lecturer to prepare the lecture.

Main:

1. Industrial technology of medicines: a basic textbook for students. Higher. student pharmacy institutions (pharmacological institutions) / E.V. Gladukh, O.A. Ruban, I.V. Saiko et al. - Kh.: NFaU: Original, 2016. - 632p. : Name - (National textbook series)

2. Workshop on industrial technology of medicinal products specialty "Pharmacy" / Ed. Ruban O.A. - Kh .: NFaU, 2015. - 374 p

3 . INDUSTRIAL technology of medicines : education. manual for students' independent work / O. A. RUBAN , V. D. RYBACHUK , L. M. Khohlova etc. - KH.: NATIONAL UNIVERSITY OF UKRAINE, 2015. - 120 p.

- Excipients in the production of drugs: training. manual for students higher pharmacy education closing / O. A. RUBAN , I. M. Pertsev, S. A. Kutsenko, Yu. S. Maslii; under the editorship I. M. Pertseva. – Kh.: Golden Pages, 2016. – 720 p.
- Technology of drugs for industrial production: tutorial. for university students education closing : in 2 parts / V. I. Chuyeshov, E. V. Gladukh, I. V. Saiko and others. – 2nd ed., revision. and additional - Kh.: National University of Applied Sciences: Original, 2012. - Part 1. - 694 p.
- Technology of drugs for industrial production: tutorial. for university students education closing : in 2 parts / V. I. Chuyeshov, E. V. Gladukh, I. V. Saiko and others. – 2nd ed., revision. and additional - Kh.: National Academy of Sciences: Original, 2013. - Part 2. - 638 p.
- Modern pharmaceutical technologies: education. manual to laboratory classes of full-time, evening and part-time master's students of the specialty 8.110201 "Pharmacy" / under the editorship. O. A. Ruban. - Kh.: Publishing House of the National Academy of Sciences, 2016. - 256 p.
- Encyclopedia of Pharmaceutical Technology: 3-d Ed. / ed. by J. Swarbrick. – New York; London: Informa Healthcare, 2007. – 4128 p.
- European Pharmacopoeia 8.0 [8th edition] / European Directorate for the Quality of Medicines & Healthcare. - Strasbourg, 2013. - 3638 p.
- Handbook of Pharmaceutical Excipients, 6th edition / RC Rowe, PJ Sheskey, ME Quinn. - Pharmaceutical Press and American Pharmacists Association, 2009. - 521 p.
- State Pharmacopoeia of Ukraine / State enterprise " Ukrainian scientific officinal center quality medical means " - 2- e kind . - Kharkiv : State enterprise " Ukrainian scientific officinal center quality medical means ", 2015. - Vol . 1. - 1128 p .
- State Pharmacopoeia of Ukraine / State enterprise " Ukrainian scientific officinal center quality medical means " - 2- e kind . - Kharkiv : State enterprise " Ukrainian scientific officinal center quality medical means ", 2014. - Vol . 2. – 724 s .

- State Pharmacopoeia of Ukraine / State enterprise " Ukrainian scientific officinal center quality medical means " - 2- e kind . - Kharkiv : State enterprise " Ukrainian scientific officinal center quality medical means ", 2015. - Vol . 3. – 732 p .
- About medicinal products: the law of Ukraine dated 04/04/96 No. 123/96 // Bulletin of the Verkhovna Rada of Ukraine. - 1996. - No. 123.
- Zujkina SS The pharmacotechnological studies of the phytospecies composition for the complex therapy of mastopathy / SS Zujkina, LI Vishnevska // Visnyk pharmacy . – 2017. – No. 2 (90). - WITH . 43-47.
- Bogutska , O. _ IS . The main ones directions solution problems pharmaceutical of incompatibilities / O . IS . Bogutska // Contemporary achievement pharmaceutical technologies and biotechnology : collection scientific works _ – issue 2. – Kharkiv . : Type - in NFaU , 2017. - S. 29–31.
- Polovka N . P. _ Rating biopharmaceuticals factors at developers and production new ones medical means / N. _ P. _ Polovko , L. _ And . Vishnevska , O. _ WITH . Shpychak // Modern achievement pharmaceutical technologies and biotechnology : collection scientific works , issue 2. – X .: Ed NFaU , 2017. - S. 155-160.
- Prospects for the creation of new original drugs based on substances of plant origin / O.A. Ruban, S.A. Malinovska, Murad Al-Tawaiti, S.I. Mazurets // Phytotherapy. – 2012. – No. 2. - pp. 63–65.
- The current state of creation, production and quality control of capsules / M.B. Chubka, L.V. Vronska, N.O. Zarivna et al. // Pharmaceutical journal. 2012. No. 2. P. 165168.
- Murachanian, D. Two-Piece Hard Capsules for Pharmaceutical Formulations / D. Murachanian // Journal of GXP Compliance. 2010. Vol. 14. P. 3142.
- Patel H. New pharmaceutical excipients in solid dosage forms – A review / H. Patel, V. Shah, U. Upadhyay // Int. J. of Pharm. & Life Sci. - 2011. - Vol. 2. – P. 1006–1019.
- Recent Trends of Treatment and Medication Peptic Ulcerative Disorder / D. Bhowmik, Chiranjib, KK Tripathi [et al.] // International Journal of PharmTech Research. - 2010. - Vol. 2. – P. 970–980

- The effects of powder compressibility, speed of capsule filling and pre-compression on plug densification / M. Llusa , E. Faulhammer , S. Biserni [et al.] // Int. J. Pharm. – 2014. – Vol. 471. – P. 182–188.

Electronic information resources

- Lecture materials, methodological developments for seminar classes and independent work at the Department of Social Pharmacy: Access mode: http://socpharm.nuph.edu.ua.
- Scientific library of the National Academy of Sciences: Access mode: http://dspace.ukrfa.kharkov.ua; http://lib.nuph.edu.ua
- www.moz.gov.ua is the official website of the Ministry of Health of Ukraine
- nuph.edu.ua is the official website of the National Pharmaceutical University
- library@nuph.edu.ua - website of the library of the National Academy of Sciences of Ukraine
- The website of the Department of Scientific Research of the National Academy of Sciences of the Russian Academy of Sciences. – Access mode: ztl.nuph.edu.ua.
- The website of the Department of Drug Technologies of ONMedU http://info.odmu.edu.ua/chair/drugs/files/195/ua
- The site of distance learning of the National Academy of Sciences: the page of the ZTL department - [Electronic resource]. – Access mode: http://pharmel.kharkiv.edu/moodle/course/index.php?categoryid=154
- fp.com.ua - website of the magazine "Pharmacist Praktik"
- www.provisor.com.ua – the official website of the magazine "Provisor"
- Compendium: drugs. - [Electronic resource]. - Access mode: http://compendium.com.ua/ - as of October 10, 2016.
- State Register of Medicinal Products of Ukraine. - [Electronic resource]. - Access mode: http://www.drlz.com.ua/ - as of January 10, 2017.

Database "Equalizer" LLC "Business Credit" - [Electronic resource]. - Access mode: http://eq.bck.com.ua/ - as of September 20, 2016.

Lecture No. 4

Topic: " Production of drugs under pressure" - 2 hours.

Relevance of the topic: Drug technology (industrial technology of drugs) is one of the fundamental technological sciences. It consists of several key aspects that are important for modern medicine and patients: Effectiveness and safety - Modern technologies make it possible to produce drugs with high efficiency and safety for patients. Exact dosage, quality control and the absence of impurities make medicines more effective and safer. Innovations in medicine: New technologies allow the creation of innovative drugs that can be more targeted and effective drug therapy. For example, drugs designed to precisely affect specific cells or genes provide more effective treatments. Minimization of side effects: Technologies make it possible to develop medicinal formulas that minimize side effects and negative effects on the body. This provides a more comfortable and safe treatment for patients. Fast production and delivery process: The use of modern technologies allows to speed up the production process of medicines, which is especially important in the conditions of a rapidly changing medical environment, such as the spread of diseases or epidemics. Individual approach to treatment: Technologies make it possible to develop medicines that take into account the individual characteristics of the patient, which leads to a personalized approach to treatment and increases its effectiveness. Cost-effectiveness and availability Improved manufacturing technologies can reduce production costs, making drugs more accessible to a wide range of patients, providing cost-effectiveness in healthcare.

Thus, the use of modern technologies for the production of medicines is an important factor for improving the effectiveness of treatment, patient safety and the general state of public health.

Goal: Purpose: to get acquainted with the main stages of the industrial production of dosage forms and the discipline "Medicine Technology", to describe the production of pressure-sensitive preparations and describe the current state of the pressurized pharmaceutical industry.

Basic concepts:

Aerosols are the smallest liquid droplets or solid particles suspended in a gaseous medium.

Active substances are the main part of the medicinal product, which are under pressure, and all other components are auxiliary and are used for the purpose of issuing active ingredients in the required form.

Solvents are used to dissolve active substances and ensure the distribution of a small amount of LR solution in a large volume of air with the help of a propellant.

Plan and organizational structure of the lecture:

No p.p.	**The main stages of the lecture and their content.**	**Goals in levels of abstraction.**	**Type of lecture, lecture equipment.**	**Time allocation.**
1	**2**	**3**	**4**	**5**
I 1.	***Preparatory stage*** Determination of educational goals.		The lecture is combined	1%
2.	Providing positive motivation.			2%
	The main stage Presentation of lecture material.			90%
II 3.	Plan: 1. The current state of development of the pharmaceutical industry of drugs under pressure. 2. Creation of aerosols. 3. Standardization of	I II	Slides	

	drugs under pressure. ***The final stage***			
III 4.	Summary of the lecture, general conclusions.	III		2%
5.	Lecturer's answers to possible questions.		List of references,	3%
6.	Tasks for self-training of students.		questions, assignments.	2%

Structural and logical scheme of the content of the lecture

1. The current state of development of the pharmaceutical industry of drugs under pressure.

2. Creation of aerosols.

3. Standardization of drugs under pressure.

Content of lecture material (lecture text)

1. The current state of development of the pharmaceutical industry of drugs under pressure.

Pharmaceutical preparations, which are under under pressure, - preparations in which the active and auxiliary substances are under the pressure of a displacer gas (propellant) in an aerosol can, hermetically sealed with a valve. Preparations from aerosol packaging are obtained in the form of liquid and solid particles, particles and films dispersed in a gaseous medium. Vouchers are assigned for inhalation, application to the skin, introduction into the body cavity, etc.

There are several *classifications* of drugs under pressure:

1) Depending on the physical and chemical properties of the composition, they are classified into two- and three-phase systems. In two-phase systems, the liquid phase is usually a solution of active substances in a propellant or a mixture of propellant with a solvent, that is, this system has two phases: gaseous and liquid. In three-phase there are three separate phases: gaseous, solid and liquid

2) Depending on the size of the particles of the dispersed phase, they are divided into spraying (particle diameter up to 50 μm, propellant concentration - up to 80%), shower (particle diameter up to 200 μm, propellant concentration - 30-70%) and foam (particle diameter over 200 μm, propellant concentration - up to 30%).
3) Depending on the application, aerosols are medical and pharmaceutical.

Production of medicinal products under pressure in the form of solutions consists of several stages: preparation of a solution of the active component (concentrate), freeing it from insoluble impurities, packing into containers, sealing, filling with propellant, testing for strength and tightness, standardization, packaging design for further transportation.

An aerosol is a medicine that is under gas pressure in special containers and contains one or more active substances. Propellants provide the pressure necessary for the release of the drug from the container. Medicinal products under pressure are a solution, emulsion or suspension; they are intended for local application to the skin, mucous membranes or for inhalation. In addition to medicinal substances, their composition may also include auxiliaries - emulsifiers, solvents, as well as sliding substances that protect the valve from clogging. Medicinal aerosols are divided into pharmaceutical and medical.

A pharmaceutical aerosol is a ready-made medicinal form consisting of a cylinder, a valve-spraying system and contents of various consistencies that can be expelled from the cylinder with the help of a propellant. The composition of the aerosol includes medicinal, auxiliary substances and necessarily one or more propellants.

A medical aerosol is an aerosol of one or more medicinal preparations in the form of liquid or solid particles obtained with the help of special stationary devices intended for inhalation administration in the conditions of a medical institution.

According to their purpose, pharmaceutical aerosols are classified into the following groups: inhalation, otolaryngological, dermatological, dental. proctological, gynecological, ophthalmological, special purpose (diagnostic, dressing, hemostatic,

etc.). The great popularity of medical aerosols is explained by a number of advantages that favorably distinguish them from other medicinal forms:

- high efficiency of action with relatively small consumption of medicinal substances. Their activity is enhanced by spraying the drug, which increases its free surface many times over;

- during spraying, particles of approximately the same size are formed, which makes it possible to adjust their size; it is especially important for the treatment of bronchial asthma and respiratory diseases;

- special valves can be used to dose different medicinal substances;

- the cylinder is completely sealed, which protects substances from fluctuations in atmospheric conditions, drying, pollution, etc.,

- when the drug is packaged in sterile conditions, sterility is preserved for the entire shelf life;

- medicinal substances from aerosols are quickly absorbed and can be used to provide first aid;

- the economic advantage is the high efficiency of the action in combination with the reduction of the consumption of active substances;

- the possibility of applying medicinal substances directly to the affected areas;

- obtaining products in the form of small splashes, foams, powders, etc. opens wide opportunities for the use of aerosols in various fields of medicine;

- the aerosol method of application is simple, does not cause painful sensations.

2. Creation of aerosols.

A large number of various chemicals are used to create aerosols. All of them can be divided into five main groups: active agents, solvents, aromas, auxiliary substances and propellants.

Active ingredients are the main part of any aerosol formulation. The rest of all the ingredients are auxiliary and serve to issue them in the required form.

For the preparation of various aerosol preparations, organic solvents and water are widely used, which serve to obtain a solution of the active substance and ensure, with the help of a propellant, the distribution of a small amount of it in a large volume of air. To provide a pleasant and mask an unpleasant smell, the composition of the

aerosol may include odorous substances. The type of fragrance (flavoring agent) should correspond to the nature of the product for which it is intended. Benzaldehyde, various essences, essential oils, etc. can be used as aromas.

The group of auxiliary substances includes surface-active substances (emulsifiers, solubilizers), preservatives, consistency substances and others. They are designed to ensure the proper quality of the aerosol, create the necessary form of packaging discharge and more effective use of the drug. Dispersing or scavenging gases, which create pressure inside the cylinder, are important for the release of an aerosol product. These gases are called propellants.

Propellants are classified by their saturated vapor pressure, state of aggregation under normal conditions, and chemical nature.

Depending on the pressure of saturated steam, they can be divided into main and auxiliary. Individual substances, which at 20 °C can produce an internal excessive pressure in the package of at least 2 atm, are called basic propellants. These include freon-12, -22, -142, as well as propane, isobutane, etc. To reduce the pressure, the main propellants are combined with auxiliary propellants, which have a saturated vapor pressure of about 1 atm. and individually cannot serve as pushing agents. These include freon-11, -114, -21, butane, etc.

According to the aggregate state, all substances used as propellants are divided into three main groups.

1. Liquefied gases:

a) organofluorine compounds (fluorine and chlorofluorocarbons, or otherwise - freons);

b) hydrocarbons of the paraffin series (propane, butane, isobutane);

c) chlorinated hydrocarbons (vinyl chloride, methyl chloride, etc.).

2. Compressed (difficult to liquefy) gases. This includes nitrogen, nitrous oxide, carbon dioxide, etc.

3. Volatile organic solvents (methylene chloride, ethylene chloride, etc.).

Freons are most widely used as propellants in pharmaceutical aerosol preparations.

Aerosol packaging consists of a cylinder, valve and contents. The cylinder containing the solution, suspension or emulsion of the drug and the propellant is hermetically sealed with a valve with a spray head.

A siphon tube is immersed in the contents of the cylinder, designed to supply the drug to the hole in the valve stem. The valve allows you to adjust the dose of the drug. Above the contents of the cylinder is a layer of compressed gaseous propellant, which puts pressure on the contents and the walls of the cylinder and promotes the release of the medicinal product.

With a slight vertical pressure on the valve head or with a slight tilt to the side (depending on the design of the valve), a conical jet or ribbon-like mass is emitted from the hole in the head. Depending on the contents of the cylinder, the jet may resemble fog (solutions of medicinal substances), smoke or dust (suspensions). The ribbon-like mass can represent abundant foam or a "worm" squeezed out of the pipe (emulsions, ointments, creams).

The valve of the aerosol package must ensure its tightness at a pressure in the cylinder of up to 20 kgf/cm2. It can be spring or springless.

According to the principle of releasing the contents of the cylinder, the valves are divided into dosing valves and multiple continuous valves. According to the purpose - for liquid and viscous systems, for suspensions, foams, etc.

Depending on the material from which the cylinders are made, they are divided into several groups: metal, glass, plastic and combined.

The capacity of packages can be different: from 3 ml to 3 l, except for glass, the capacity of which is limited to 300 ml.

Metal cylinders are most often made of aluminum, their inner surface is covered with protective varnishes. Various polymer materials, anti-corrosion varnishes or copolymers are used for these purposes.

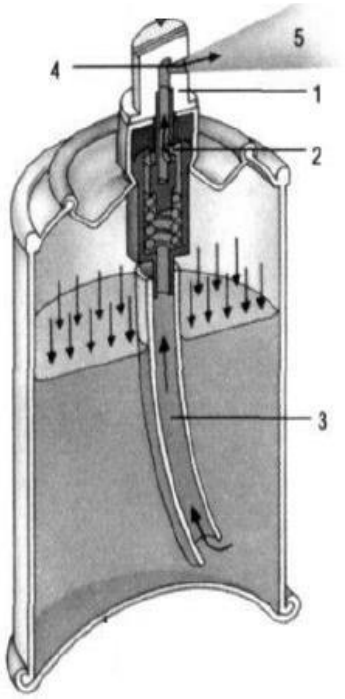


Fig. 8. Device of an aerosol can in:
1 - valve head; 2 - valve; 3 - siphon tube; 4 - nozzle; 5 - atomized substance.

A wide range of plastic cylinders made of polypropylene, nylon, polyethylene, polyformaldehyde, delrin, celcon, etc. are used abroad .

Depending on the degree of displaceability of the components of the main formulation with the propellant, aerosols are divided into solution aerosols, emulsion aerosols, suspension aerosols, and combined systems.

The production of aerosols includes the manufacture of cylinders, valve-spraying systems, preparation of repellents or their mixtures, concentrates, filling of aerosol cylinders and their quality control.

The production of aluminum monobloc cylinders is carried out by forming them from flat blanks on impact presses, and the cylinder neck is formed on special multi-spindle cone-forming machines. At the same time, 12-14 or more operations are performed depending on the diameter of the balloon.

Glass cylinders are made from neutral borosilicate glass HC-1 or HC-2 on automatic high-performance glass forming machines. The process of their production is associated with double annealing in horizontal furnaces with a temperature maximum of 640-650°C, to eliminate or weaken the residual internal stress of the glass.

After forming, the glass cylinders are covered with a polyethylene or polyvinyl chloride protective coating.

Plastic aerosol cans are made by the method of vacuum forming (monoblock) or injection molding on molding or casting machines.

Valve-spraying systems are manufactured at plastic processing plants.

A standard valve-spray system has the following elements:

- *The atomizer (nozzle)* is used to activate the valve and to spray medicine. It can be of different design and configuration, depending on the aggregate state of the medicine and the route of its administration.
- *The stem* serves to open and close the valve. The stem cavity is part of the expansion chamber.
- *The cuff* seals the joint of the stem with the hole in the cup (capsule) of the valve and is sometimes a nipple that closes or opens the hole in the stem.
- *The case* is the place where all the parts are assembled, and its cavity is part of the expansion chamber.
- *The siphon tube* serves to supply the contents from the lower part of the cylinder to the valve.
- *The gasket* seals the attachment points of the valve on the cylinder.
- *The cup (or capsule)* is intended for assembling all the parts of the valve and attaching it to the cylinder.

According to the method of evacuating the drug, valves are divided into valves of continuous and dosing action, which in turn are classified into:

- *standard valves* - used for evacuating products of the perfumery and cosmetic, chemical, pharmaceutical, food industry, leather goods, etc.;
- *universal valves* - spray the contents at any angle and are used to evacuate products of the chemical and perfumery and cosmetic industries;
- *Reversible valves* - spray the contents only in an inverted position and are used mainly for evacuating products of the pharmaceutical industry.

The principle of operation of a standard aerosol valve is as follows: the valve is actuated by pressing the spray head vertically downwards. Together with the head, the rod moves down, compressing the spring. The hole in the stem enters, from under the rubber gasket, into the cavity of the pocket filled with the product. The product goes

into this hole and enters the head for spraying through the cavity of the rod. When the head is released, the spring raises the rod up and the valve action stops.

To date, 4 alternative directions for the creation of harmless extruding agents (propellants) have been identified, new spraying methods have been developed, and existing designs of aerosol packages are being improved:

- packaging from raw materials that do not CONTAIN phenol: saturated paraffin hydrocarbons of the methane series (propane, butane, isobutane) and compressed gases (nitrogen, nitrous oxide, carbon dioxide, etc.);
- cylinders in which the propellant is separated from the product and is not released into the environment (Fig. 2);
- packaging with a pump-type mechanical sprayer;
- compressed polymer and other cylinders.

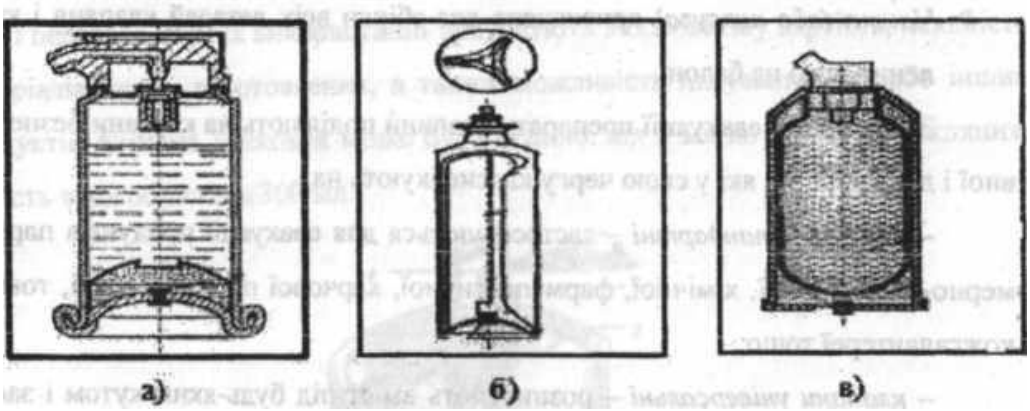


Fig . 2. Two-chamber aerosol packages:

a - aerosol packaging with a piston;

b - aerosol packaging with an insert;

c - aerosol packaging with an inner bag.

Aerosol preparation technology consists of the following stages (see the technological block diagram of aerosol production):

1. production preparation;
2. preparation of raw materials and solvent;
3. preparation of cylinders for filling;
4. preparation and cleaning of aerosol concentrate;
5. packing concentrate into cylinders;

6. clogging of aerosol cans;
7. filling aerosol cans with propellant;
8. checking cylinders for strength and tightness;
9. quality control of drugs under pressure;
10. packaging, labeling is ready: products.

3. Standardization of drugs under pressure.

Standardization:

- organoleptic control (appearance, control for the presence mechanical inclusions);
- physical and chemical control (internal pressure of the cylinder, tightness, determination of the percentage yield of the contents of the container, determination of the average weight of the drug in one dose (for dosing valves), determination of the dispersion of aerosol particles, standards for filling the cylinder);
- chemical control (qualitative and quantitative analysis of active substances);
- biological control

Preparation and transportation of propellant mixtures.

The most complex and specific operations for enterprises producing aerosol packaging are the preparation of mixtures of liquefied propellants and their supply to the filling line. In Russia, enterprises of the chemical industry have organized the production of only one mixture, chladons 11 and 12 in a 50:50 ratio. If the recipe requires a different ratio of chladons or other mixtures, they are prepared in different ways at special stations.

Two methods are used to transport (supply) propellants to the filling line:

1) pressurization of the propellant from the capacity in which it is stored with the help of excess pressure created in the capacity either by nitrogen or by heated vapors of the refrigerants themselves;

2) pumping by pumps.

Concentrates-solutions are prepared, like ordinary solutions of medicinal substances, in reactors with a heat exchanger and a stirrer. Solutions are freed from impurities by settling, filtration or centrifugation.

If concentrates-solutions are obtained with the help of viscous solvents (fatty oils), the dissolution is carried out by heating, and the cleaning is carried out under pressure. In the case of using volatile solvents (ethyl alcohol), dissolution of substances is carried out in closed reactors, and filtration - under pressure. Systems may include stabilizers and preservatives. Standardization of concentrate solutions is carried out taking into account the percentage content of active substances or the density of the solution.

A decisive factor in the technology of medicinal products under pressure in the form of solutions is the pressure inside the container, the control of which can serve as a quantitative characteristic of some physicochemical properties: the completeness of dispensing the contents, dispersibility, as well as the solubility of the propellant in the concentrate. The greater the ability of the concentrate to dissolve the propellant, the lower the pressure in the container.

Testing of medicinal products under pressure is carried out at factories by the quality department in accordance with the NTD for this drug. It should be noted that the quality of this group of drugs depends on many factors and requires a special form of control, because it is impossible to make changes to the composition of the drug after the container is closed.

Standardization of medicinal products under pressure includes several types of control: organoleptic, physicochemical, chemical, microbiological and biological control (for the presence of cardiac glycosides, etc.).

The internal pressure in the container must meet the requirements of a separate article. It is determined by a manometer, the accuracy class of which should be 2.5. Filled packages are checked for strength and tightness.

Qualitative and quantitative indicators are controlled by methods of analysis of individual ingredients of the medicinal product.

Containers during their transportation have their own specific features compared to the current rules adopted for other medicinal forms. The storage conditions specified on the packaging and in the technical documentation should be observed (avoid impacts, exposure to direct sunlight and high temperatures).

Medicinal products under pressure are packed in strong wooden boxes, if the drug is flammable, cardboard transport containers are allowed for less dangerous drugs.

Materials on the activation of students of higher education during the lecture: questions, situational tasks, etc.:

Question:

1. Aerosols, characteristics, classification.
2. What is the composition and principle of operation of an aerosol can?

General material and bulk-methodological support of the lecture:

- educational premises - the auditorium of the department;
- equipment - computer, tables;
- equipment – multimedia projector;
- illustrative materials - presentation, slides.

Questions for self-control:

1. Types of aerosol systems?
2. What auxiliary substances are used to produce an aerosol?

References:

1. Study guide for independent work of students of the Faculty of Pharmacy for the licensing exam "Step 2. Pharmacy" / V.Yu. Anisimov, O.I. Belyaeva, H.G. Vidavska, V.O. Helmboldt, A.V. Zamkova, I.V. Lytvynchuk, A.V. Nikitin, B.V. Pristupa, I.B. Petkova, Ya.V. Rozhkovskyi, S.B. Strechen, L.M. Unguryan, N.C. Fizor Odesa: Odesa.nats.med. Univ. 2020. - 240 p.

Mode of access to lecture texts for students of the Faculty of Pharmacy: https://info.odmu.edu.ua/chair/drugs/files/390/ua

Literature used by the lecturer to prepare the lecture.

Main:

1. Industrial technology of medicines: a basic textbook for students. Higher. student pharmacy institutions (pharmacological institutions) / E.V. Gladukh, O.A. Ruban, I.V. Saiko et al. - Kh.: NFaU: Original, 2016. - 632p. : Name - (National textbook series)

2. Workshop on industrial technology of medicinal products specialty "Pharmacy" / Ed. Ruban O.A. - Kh .: NFaU, 2015. - 374 p

3 . INDUSTRIAL technology of medicines : education. manual for students' independent work / O. A. RUBAN , V. D. RYBACHUK , L. M. Khohlova etc. - KH.: NATIONAL UNIVERSITY OF UKRAINE, 2015. - 120 p.

- Excipients in the production of drugs: training. manual for students higher pharmacy education closing / O. A. RUBAN , I. M. Pertsev, S. A. Kutsenko, Yu. S. Maslii; under the editorship I. M. Pertseva. – Kh.: Golden Pages, 2016. – 720 p.
- Technology of drugs for industrial production: tutorial. for university students education closing : in 2 parts / V. I. Chuyeshov, E. V. Gladukh, I. V. Saiko and others. – 2nd ed., revision. and additional - Kh.: National University of Applied Sciences: Original, 2012. - Part 1. - 694 p.
- Technology of drugs for industrial production: tutorial. for university students education closing : in 2 parts / V. I. Chuyeshov, E. V. Gladukh, I. V. Saiko and others. – 2nd ed., revision. and additional - Kh.: National Academy of Sciences: Original, 2013. - Part 2. - 638 p.
- Modern pharmaceutical technologies: education. manual to laboratory classes of full-time, evening and part-time master's students of the specialty 8.110201 "Pharmacy" / under the editorship. O. A. Ruban. - Kh.: Publishing House of the National Academy of Sciences, 2016. - 256 p.
- Encyclopedia of Pharmaceutical Technology: 3-d Ed. / ed. by J. Swarbrick. – New York; London: Informa Healthcare, 2007. – 4128 p.
- European Pharmacopoeia 8.0 [8th edition] / European Directorate for the Quality of Medicines & Healthcare. - Strasbourg, 2013. - 3638 p.
- Handbook of Pharmaceutical Excipients, 6th edition / RC Rowe, PJ Sheskey, ME Quinn. - Pharmaceutical Press and American Pharmacists Association, 2009. - 521 p.
- State Pharmacopoeia of Ukraine / State enterprise " Ukrainian scientific officinal center quality medical means " - 2- e kind . - Kharkiv : State enterprise " Ukrainian scientific officinal center quality medical means ", 2015. - Vol . 1. - 1128 p .

- State Pharmacopoeia of Ukraine / State enterprise " Ukrainian scientific officinal center quality medical means " - 2- e kind . - Kharkiv : State enterprise " Ukrainian scientific officinal center quality medical means ", 2014. - Vol . 2. – 724 s .
- State Pharmacopoeia of Ukraine / State enterprise " Ukrainian scientific officinal center quality medical means " - 2- e kind . - Kharkiv : State enterprise " Ukrainian scientific officinal center quality medical means ", 2015. - Vol . 3. – 732 p .
- About medicinal products: the law of Ukraine dated 04/04/96 No. 123/96 // Bulletin of the Verkhovna Rada of Ukraine. - 1996. - No. 123.
- Zujkina SS The pharmacotechnological studies of the phytospecies composition for the complex therapy of mastopathy / SS Zujkina, LI Vishnevska // Visnyk pharmacy . – 2017. – No. 2 (90). - WITH . 43-47.
- Bogutska , O. _ IS . The main ones directions solution problems pharmaceutical of incompatibilities / O . IS . Bogutska // Contemporary achievement pharmaceutical technologies and biotechnology : collection scientific works _ – issue 2. – Kharkiv . : Type - in NFaU , 2017. - S. 29–31.
- Polovka N . P. _ Rating biopharmaceuticals factors at developers and production new ones medical means / N. _ P. _ Polovko , L. _ And . Vishnevska , O. _ WITH . Shpychak // Modern achievement pharmaceutical technologies and biotechnology : collection scientific works , issue 2. – X .: Ed NFaU , 2017. - S. 155-160.
- Prospects for the creation of new original drugs based on substances of plant origin / O.A. Ruban, S.A. Malinovska, Murad Al-Tawaiti, S.I. Mazurets // Phytotherapy. – 2012. – No. 2. - pp. 63–65.
- The current state of creation, production and quality control of capsules / M.B. Chubka, L.V. Vronska, N.O. Zarivna et al. // Pharmaceutical journal. 2012. No. 2. P. 165168.
- Murachanian, D. Two-Piece Hard Capsules for Pharmaceutical Formulations / D. Murachanian // Journal of GXP Compliance. 2010. Vol. 14. P. 3142.
- Patel H. New pharmaceutical excipients in solid dosage forms – A review / H. Patel, V. Shah, U. Upadhyay // Int. J. of Pharm. & Life Sci. - 2011. - Vol. 2. – P. 1006–1019.

- Recent Trends of Treatment and Medication Peptic Ulcerative Disorder / D. Bhowmik, Chiranjib, KK Tripathi [et al.] // International Journal of PharmTech Research. - 2010. - Vol. 2. – P. 970–980
- The effects of powder compressibility, speed of capsule filling and pre-compression on plug densification / M. Llusa , E. Faulhammer , S. Biserni [et al.] // Int. J. Pharm. – 2014. – Vol. 471. – P. 182–188.

Electronic information resources

- Lecture materials, methodological developments for seminar classes and independent work at the Department of Social Pharmacy: Access mode: http://socpharm.nuph.edu.ua.
- Scientific library of the National Academy of Sciences: Access mode: http://dspace.ukrfa.kharkov.ua; http://lib.nuph.edu.ua
- www.moz.gov.ua is the official website of the Ministry of Health of Ukraine
- nuph.edu.ua is the official website of the National Pharmaceutical University
- library@nuph.edu.ua - website of the library of the National Academy of Sciences of Ukraine
- The website of the Department of Scientific Research of the National Academy of Sciences of the Russian Academy of Sciences. – Access mode: ztl.nuph.edu.ua.
- The website of the Department of Drug Technologies of ONMedU http://info.odmu.edu.ua/chair/drugs/files/195/ua
- The site of distance learning of the National Academy of Sciences: the page of the ZTL department - [Electronic resource]. – Access mode: http://pharmel.kharkiv.edu/moodle/course/index.php?categoryid=154
- fp.com.ua - website of the magazine "Pharmacist Praktik"
- www.provisor.com.ua – the official website of the magazine "Provisor"
- Compendium: drugs. - [Electronic resource]. - Access mode: http://compendium.com.ua/ - as of October 10, 2016.
- State Register of Medicinal Products of Ukraine. - [Electronic resource]. - Access mode: http://www.drlz.com.ua/ - as of January 10, 2017.

Database "Equalizer" LLC "Business Credit" - [Electronic resource]. - Access mode: http://eq.bck.com.ua/ - as of September 20, 2016.

Lecture No. 5

Topic: " Physico-chemical and technological properties of powders and granules " - 2 hours.

Relevance of the topic: Drug technology (industrial technology of drugs) is one of the fundamental technological sciences. It consists of several key aspects that are important for modern medicine and patients: Effectiveness and safety - Modern technologies make it possible to produce drugs with high efficiency and safety for patients. Exact dosage, quality control and the absence of impurities make medicines more effective and safer. Innovations in medicine: New technologies allow the creation of innovative drugs that can be more targeted and effective drug therapy. For example, drugs designed to precisely affect specific cells or genes provide more effective treatments. Minimization of side effects: Technologies make it possible to develop medicinal formulas that minimize side effects and negative effects on the body. This provides a more comfortable and safe treatment for patients. Fast production and delivery process: The use of modern technologies allows to speed up the production process of medicines, which is especially important in the conditions of a rapidly changing medical environment, such as the spread of diseases or epidemics. Individual approach to treatment: Technologies make it possible to develop medicines that take into account the individual characteristics of the patient, which leads to a personalized approach to treatment and increases its effectiveness. Cost-effectiveness and availability Improved manufacturing technologies can reduce production costs, making drugs more accessible to a wide range of patients, providing cost-effectiveness in healthcare.

Thus, the use of modern technologies for the production of medicines is an important factor for improving the effectiveness of treatment, patient safety and the general state of public health.

Goal: the discipline provides, on the basis of general knowledge and principles, regularities of factory production technology, to form students' knowledge of: theoretical foundations, acquisition of professional skills and skills in the preparation of medicinal forms, step-by-step control, standardization, improvement of dosage. forms and technologies. storage conditions and type of packaging for the stability of dosage forms, study of equipment, including new ones, devices and automatic lines, modern requirements for the production of dosage forms, purity of raw materials, production premises and personnel.

Basic concepts:

The specific surface is the total surface occupied by the powdery substance, and the contact surface is the surface created by the collision of powder particles

The fractional composition of the powder mass for the same drug is unstable and varies within the limits of one chemical-pharmaceutical production.

Bulk (bulk) density is the mass of a unit volume of free powder and depends on the density of the substance, the shape and size of the particles, and their conclusion.

Relative density is the ratio of bulk density to true density.

Porosity - the amount of free space (pores, voids) between powder particles

Basic concepts:

Plan and organizational structure of the lecture:

No p.p.	**The main stages of the lecture and their content.**	**Goals in levels of abstraction.**	**Type of lecture, lecture equipment.**	**allocation .**
1	**2**	**3**	**4**	**5**
I 1. 2.	***Preparatory stage*** Determination of educational goals. Providing positive motivation.		 The lecture is combined	 1% 2%

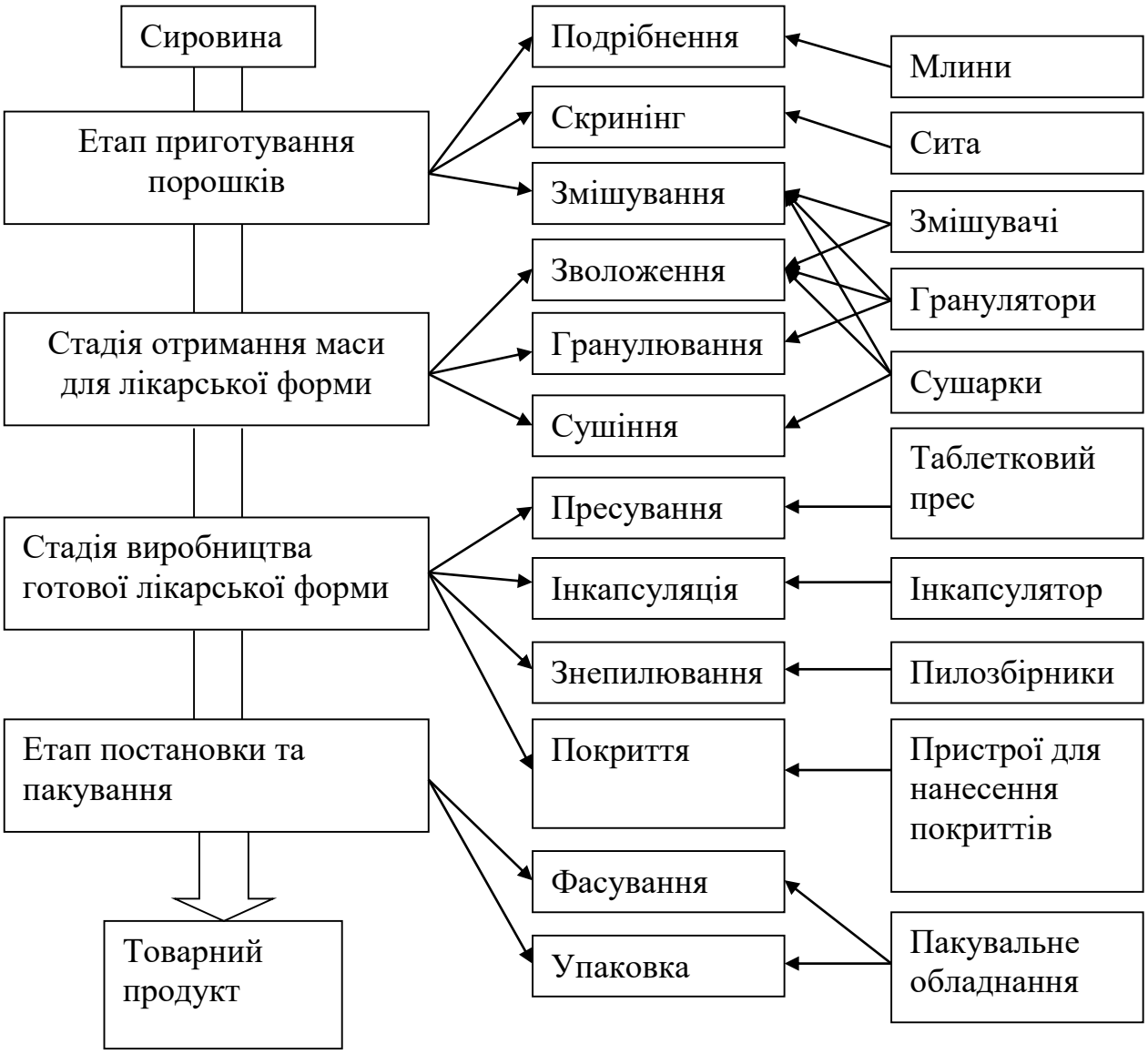
	The main stage Presentation of lecture material.			90%
II 3.	Plan: 1. Physico-chemical properties of powdery substances .	I	Slides	
	2. Shape of powder particles.			
	3. Specific surface .	II		
	5. Granulometric, fractional composition .			
	6. Bulk (bulk) density .			
	7. Porosity .	III		
	8. Flowability.		List of references,	
III 4.	***The final stage*** Summary of the lecture, general conclusions.		questions, assignments.	2%
5.	Lecturer's answers to possible questions.			3%
6.	Tasks for self-training of students.			2%

Structural and logical scheme of the content of the lecture

1. Physico-chemical properties of powdery substances .
2. Shape of powder particles.
3. Specific surface .
5. Granulometric, fractional composition .
6. Bulk (bulk) density .
7. Porosity .

8. Flowability.

Content of lecture material (lecture text)



1. **Physicochemical properties of powdery substances** consist of polydisperse systems that have different shapes and sizes of crystalline particles (an amorphous structure is less common in the manufacture of tablets). The shape and size of powder particles depend: in crystalline substances (chemical-pharmaceutical preparations) - on the structure of the crystal lattice and the conditions of growth of particles during crystallization, in crushed plant raw materials - on the anatomical and morphological features of crushed plant organs and species. disk drive. According to the structure and shape, crystals are of the following types:

- Elongated - formed when the growth of crystals in the process of crystallization

goes in one direction. Here the ratio of length to width and thickness is more than 3: 1 (sticks, needles, etc.);

- Lamellar - obtained by growth of crystals in two directions. The length exceeds the thickness and width by no more than 3 times (plates, scales, leaves, plates, etc.);

- Equiaxial - crystal growth proceeds in all directions (spherical, polyhedral shape).

Elongated and plate-shaped particles belong to anisodiametric (asymmetric, multiaxial) and equiaxial - to isodiametric (symmetric) forms of powder particles.

It is known that directly, that is, by direct pressing, without granulation and auxiliary substances (sodium chloride, potassium bromide), only substances belonging to the cubic system are pressed into tablets.

Usually powders in the form of rods in the form of particles are characterized by fine dispersion, good density and sufficient porosity (analgin, norsulfasol, acridine, etc.).

The physical properties of powders are determined by the specific and contact surface.

The specific surface is the total surface occupied by the powdery substance, and the contact surface is the surface created by the collision of powder particles. The specific surface is determined by the method of air permeability on a device called a surface meter. The specific surface directly depends on the degree of dispersion of the powders and can vary widely. The specific surface area helps in the granulation process to determine the estimated amount of wetting agent - binder solution.

Chemical properties such as the presence of water of crystallization, solubility, wettability and hygroscopicity are also important for tableting. If the elasticity of vapors in the air is greater than their elasticity on the surface of solid particles, then the powdered mass prepared for tableting begins to absorb water vapor from the air and spread in the absorbing water (hygroscopicity). The conditions of storage and preparation for tableting of such drugs are based on this. Crystallization water molecules determine the mechanical (strength, plasticity) and thermal (relative to air temperature) properties of the crystal and significantly influence the behavior of the crystal under pressure. The phenomenon of "cementation" is also closely related to the

presence of water of crystallization in tableted preparations.

The technological characteristics of tableted masses are closely related to the physical and chemical properties of powdered preparations.

The powder is heterogeneous in particle size. Powder particles of the same size make up the fraction. The mass ratio of fractions in percent is called fractional or in the case of granules - Granulometric composition. Fractional composition sometimes affects such technological properties; flowability, pressing, as well as the strength and average weight of the tablets, and therefore, the rhythmicity of the tablets, the stability of the weight of the tablets, the accuracy of the dosage of the drug, as well as the quality characteristics of the tablets (appearance, disintegration, strength, etc.).

The fractional composition of the powder mass for the same drug is unstable and varies within the limits of one chemical-pharmaceutical production. In this regard, it is necessary to check each batch of the drug.

Granular powders are characterized by a polyfractional composition and a complex shape. The granulometric composition obeys the law of normal distribution: the number of large and smallest particles is small, and the main mass has approximately the same size.

Most pharmaceutical preparations for tableting contain a fine fraction (less than 0.2 mm) in the vast majority and therefore have poor flowability. They are poorly dosed by the volume of tablets, the tablets are heterogeneous in weight and strength.

It is very important to determine such volumetric indicators of powders as: bulk and relative density and porosity.

Bulk (bulk) density is the mass of a unit volume of free powder and depends on the density of the substance, the shape and size of the particles, and their conclusion. Dosing of tablet masses (powders or granules) in tablet machines is carried out by volume, it is very important to know the bulk density, which depends on the choice of press tool, i.e. the diameter of the matrix and punches.

Relative density is the ratio of bulk density to true density.

Porosity - the amount of free space (pores, voids) between powder particles. In the loose mass of powdered drugs, the particles come into contact only with certain areas of its surface. Voids (pores) in the powder can occupy 50-80% of the volume.

The porosity of the powder mass depends on the size and shape of the particles. The lower the stacking density, the greater the porosity of the mass and the larger its volume, which requires a large volume of the matrix.

The ability of the powder to compress under pressure depends on all these volume characteristics. The lower the density and the greater the porosity, the greater the degree of compression of the powder.

When tableting, the defining technological properties will be flowability, compressibility and sliding, which allow you to easily push the tablet out of the matrix.

Flowability characterizes the ability of the material to fall out of the container (funnel) under the influence of its own weight. The flowability of powders is a complex characteristic that is determined by the dispersion and shape of the particles, the moisture content of the masses, the granulometric composition, the coefficient of external friction, and the bulk density. This technological characteristic can be used when choosing tableting technology. Powder mixtures containing 80-100% fine fraction (particle size less than 0.2 mm) are poorly dosed, so it is necessary to carry out a targeted increase in the particles of such masses, i.e. granulation. If the fine fraction contains up to 15%, it is possible to use the direct pressing method.

An indirect characteristic of flowability is the angle of natural slope. When the powdered material is poured from the funnel onto a horizontal plane, it crumbles, taking the shape of a cone-shaped mountain. The angle between the foundation and the base of this hill is called the angle of natural slope. The value of the angle of the natural slope, expressed in degrees, can be determined using a protractor, calculated from the height of the hill and the radius of its base, or measured in another way.

The angle of the natural slope varies widely from 25-35° for well-flowing materials and up to 60-70° for less-flowing materials. Therefore, the smaller the angle of inclination, the higher the fluidity.

Pressing powder - the ability of its particles under pressing pressure to take and keep a certain shape and size. In other words, it shows the ability of the particles of a substance under pressure under the influence of various forces to mutual attraction and adhesion with the formation of a strong structure.

Knowing this value allows you to predict the size of the tablets (choose the

appropriate press tool), correctly choose the amount of pressing pressure to obtain tablets, and choose the optimal composition of tablets (excipients) and their manufacturing technology.

There are no direct methods for determining clicks. Indirect breakdown into compressed consists in determining the strength of the tablet model. The higher the strength of the tablet, the better it is pressed and the tablet is formed.

The force of ejection is determined in order to ensure the force of ejection of tablets from the matrices. The emergence of resistance during ejection is due to friction and adhesion (adhesion) between the side surface of the tablet and the wall of the matrix.

Materials on the activation of students of higher education during the lecture: questions, situational tasks, etc.:

Question:

1. What is the physical significance of the grinding process?
2. What features of powders are taken into account during tableting?

Familiarize yourself with the main normative documents regulating the production of medicinal products:

- Law of Ukraine "On Medicinal Products";
- orders of the Ministry of Health of Ukraine;
- State pharmacopoeia.8.

Literature used by the teacher to prepare the lecture.

General material and bulk-methodological support of the lecture:

- educational premises - the auditorium of the department;
- equipment - computer, tables;
- equipment – multimedia projector;
- illustrative materials - presentation, slides.

Questions for self-control:

1. What factors affect flowability?
2. What is called porosity?
3. How are powders and granules classified?

References:

1. Study guide for independent work of students of the Faculty of Pharmacy for the licensing exam "Step 2. Pharmacy" / V.Yu. Anisimov, O.I. Belyaeva, H.G. Vidavska, V.O. Helmboldt, A.V. Zamkova, I.V. Lytvynchuk, A.V. Nikitin, B.V. Pristupa, I.B. Petkova, Ya.V. Rozhkovskyi, S.B. Strechen, L.M. Unguryan, N.C. Fizor Odesa: Odesa.nats.med. Univ. 2020. - 240 p.

Mode of access to lecture texts for students of the Faculty of Pharmacy: https://info.odmu.edu.ua/chair/drugs/files/390/ua

Literature used by the lecturer to prepare the lecture.

Main:

1. Industrial technology of medicines: a basic textbook for students. Higher. student pharmacy institutions (pharmacological institutions) / E.V. Gladukh, O.A. Ruban, I.V. Saiko et al. - Kh.: NFaU: Original, 2016. - 632p. : Name - (National textbook series)

2. Workshop on industrial technology of medicinal products specialty "Pharmacy" / Ed. Ruban O.A. - Kh .: NFaU, 2015. - 374 p

3 . INDUSTRIAL technology of medicines : education. manual for students' independent work / O. A. RUBAN , V. D. RYBACHUK , L. M. Khohlova etc. - KH.: NATIONAL UNIVERSITY OF UKRAINE, 2015. - 120 p.

- Excipients in the production of drugs: training. manual for students higher pharmacy education closing / O. A. RUBAN , I. M. Pertsev, S. A. Kutsenko, Yu. S. Maslii; under the editorship I. M. Pertseva. – Kh.: Golden Pages, 2016. – 720 p.
- Technology of drugs for industrial production: tutorial. for university students education closing : in 2 parts / V. I. Chuyeshov, E. V. Gladukh, I. V. Saiko and others. – 2nd ed., revision. and additional - Kh.: National University of Applied Sciences: Original, 2012. - Part 1. - 694 p.
- Technology of drugs for industrial production: tutorial. for university students education closing : in 2 parts / V. I. Chuyeshov, E. V. Gladukh, I. V. Saiko and others. – 2nd ed., revision. and additional - Kh.: National Academy of Sciences: Original, 2013. - Part 2. - 638 p.

- Modern pharmaceutical technologies: education. manual to laboratory classes of full-time, evening and part-time master's students of the specialty 8.110201 "Pharmacy" / under the editorship. O. A. Ruban. - Kh.: Publishing House of the National Academy of Sciences, 2016. - 256 p.
- Encyclopedia of Pharmaceutical Technology: 3-d Ed. / ed. by J. Swarbrick. – New York; London: Informa Healthcare, 2007. – 4128 p.
- European Pharmacopoeia 8.0 [8th edition] / European Directorate for the Quality of Medicines & Healthcare. - Strasbourg, 2013. - 3638 p.
- Handbook of Pharmaceutical Excipients, 6th edition / RC Rowe, PJ Sheskey, ME Quinn. - Pharmaceutical Press and American Pharmacists Association, 2009. - 521 p.
- State Pharmacopoeia of Ukraine / State enterprise " Ukrainian scientific officinal center quality medical means " - 2- e kind . - Kharkiv : State enterprise " Ukrainian scientific officinal center quality medical means ", 2015. - Vol . 1. - 1128 p .
- State Pharmacopoeia of Ukraine / State enterprise " Ukrainian scientific officinal center quality medical means " - 2- e kind . - Kharkiv : State enterprise " Ukrainian scientific officinal center quality medical means ", 2014. - Vol . 2. – 724 s .
- State Pharmacopoeia of Ukraine / State enterprise " Ukrainian scientific officinal center quality medical means " - 2- e kind . - Kharkiv : State enterprise " Ukrainian scientific officinal center quality medical means ", 2015. - Vol . 3. – 732 p .
- About medicinal products: the law of Ukraine dated 04/04/96 No. 123/96 // Bulletin of the Verkhovna Rada of Ukraine. - 1996. - No. 123.
- Zujkina SS The pharmacotechnological studies of the phytospecies composition for the complex therapy of mastopathy / SS Zujkina, LI Vishnevska // Visnyk pharmacy . – 2017. – No. 2 (90). - WITH . 43-47.
- Bogutska , O. _ IS . The main ones directions solution problems pharmaceutical of incompatibilities / O . IS . Bogutska // Contemporary achievement pharmaceutical technologies and biotechnology : collection scientific works _ – issue 2. – Kharkiv . : Type - in NFaU , 2017. - S. 29–31.

- Polovka N . P. _ Rating biopharmaceuticals factors at developers and production new ones medical means / N. _ P. _ Polovko , L. _ And . Vishnevska , O. _ WITH . Shpychak // Modern achievement pharmaceutical technologies and biotechnology : collection scientific works , issue 2. – X .: Ed NFaU , 2017. - S. 155-160.
- Prospects for the creation of new original drugs based on substances of plant origin / O.A. Ruban, S.A. Malinovska, Murad Al-Tawaiti, S.I. Mazurets // Phytotherapy. – 2012. – No. 2. - pp. 63–65.
- The current state of creation, production and quality control of capsules / M.B. Chubka, L.V. Vronska, N.O. Zarivna et al. // Pharmaceutical journal. 2012. No. 2. P. 165168.
- Murachanian, D. Two-Piece Hard Capsules for Pharmaceutical Formulations / D. Murachanian // Journal of GXP Compliance. 2010. Vol. 14. P. 3142.
- Patel H. New pharmaceutical excipients in solid dosage forms – A review / H. Patel, V. Shah, U. Upadhyay // Int. J. of Pharm. & Life Sci. - 2011. - Vol. 2. – P. 1006–1019.
- Recent Trends of Treatment and Medication Peptic Ulcerative Disorder / D. Bhowmik, Chiranjib, KK Tripathi [et al.] // International Journal of PharmTech Research. - 2010. - Vol. 2. – P. 970–980
- The effects of powder compressibility, speed of capsule filling and pre-compression on plug densification / M. Llusa , E. Faulhammer , S. Biserni [et al.] // Int. J. Pharm. – 2014. – Vol. 471. – P. 182–188.

Electronic information resources

- Lecture materials, methodological developments for seminar classes and independent work at the Department of Social Pharmacy: Access mode: http://socpharm.nuph.edu.ua.
- Scientific library of the National Academy of Sciences: Access mode: http://dspace.ukrfa.kharkov.ua; http://lib.nuph.edu.ua
- www.moz.gov.ua is the official website of the Ministry of Health of Ukraine
- nuph.edu.ua is the official website of the National Pharmaceutical University

- library@nuph.edu.ua - website of the library of the National Academy of Sciences of Ukraine
- The website of the Department of Scientific Research of the National Academy of Sciences of the Russian Academy of Sciences. – Access mode: ztl.nuph.edu.ua.
- The website of the Department of Drug Technologies of ONMedU http://info.odmu.edu.ua/chair/drugs/files/195/ua
- The site of distance learning of the National Academy of Sciences: the page of the ZTL department - [Electronic resource]. – Access mode: http://pharmel.kharkiv.edu/moodle/course/index.php?categoryid=154
- fp.com.ua - website of the magazine "Pharmacist Praktik"
- www.provisor.com.ua – the official website of the magazine "Provisor"
- Compendium: drugs. - [Electronic resource]. - Access mode: http://compendium.com.ua/ - as of October 10, 2016.
- State Register of Medicinal Products of Ukraine. - [Electronic resource]. - Access mode: http://www.drlz.com.ua/ - as of January 10, 2017.

Database "Equalizer" LLC "Business Credit" - [Electronic resource]. - Access mode: http://eq.bck.com.ua/ - as of September 20, 2016.

Lecture No. 6

Topic: " Production of tablets by the method of direct pressing and with preliminary granulation. Industrial production of coated tablets. Quality control. Production of medical capsules » - 2 hours.

Relevance of the topic: Drug technology (industrial technology of drugs) is one of the fundamental technological sciences. It consists of several key aspects that are important for modern medicine and patients: Effectiveness and safety - Modern technologies make it possible to produce drugs with high efficiency and safety for patients. Exact dosage, quality control and the absence of impurities make medicines more effective and safer. Innovations in medicine: New technologies allow the creation of innovative drugs that can be more targeted and effective drug therapy. For example,

drugs designed to precisely affect specific cells or genes provide more effective treatments. Minimization of side effects: Technologies make it possible to develop medicinal formulas that minimize side effects and negative effects on the body. This provides a more comfortable and safe treatment for patients. Fast production and delivery process: The use of modern technologies allows to speed up the production process of medicines, which is especially important in the conditions of a rapidly changing medical environment, such as the spread of diseases or epidemics. Individual approach to treatment: Technologies make it possible to develop medicines that take into account the individual characteristics of the patient, which leads to a personalized approach to treatment and increases its effectiveness. Cost-effectiveness and availability Improved manufacturing technologies can reduce production costs, making drugs more accessible to a wide range of patients, providing cost-effectiveness in healthcare.

Thus, the use of modern technologies for the production of medicines is an important factor for improving the effectiveness of treatment, patient safety and the general state of public health.

Goal: get acquainted with the main stages of the industrial production of dosage forms and the discipline "Drug Technology", give a description the production of tablets by the method of direct pressing and with preliminary granulation and to describe the current state of the pharmaceutical industry of coated tablets and medical capsules .

Basic concepts:

Pressing **(** actual tableting) **is** the process of forming tablets from granular or powdery material under pressure.

Direct pressing **-** it is a pressing process of NOT granulated powders. Direct pressing allows you to eliminate 3-4 technological operations and thus has an advantage over tableting with preliminary granulation of powders.

Dedusting **is** the process of removing dust fractions from the surface of tablets coming out of the press.

Granulation - directed agglomeration of particles, i.e. the process of transformation of powdery material into grains of a certain size, which is necessary to improve the flowability of the tablet mixture and prevent its delamination.

Plan and organizational structure of the lecture:

No p.p.	**The main stages of the lecture and their content.**	**Goals in levels of abstraction.**	**Type of lecture, lecture equipment.**	**Time allocation.**
1	**2**	**3**	**4**	**5**
I	***Preparatory stage***			
1.	Determination of educational goals.		The lecture is combined	1%
2.	Providing positive motivation.			2%
	The main stage			
	Presentation of lecture material.			90%
II	Plan:		Slides	
3.	1. Characteristics of tablets as a dosage form. Types and groups of tablets.	I		
	2. Properties of powdered medicinal substances.	II		
	3. The main groups of auxiliary substances in the production of tablets.	III		
	4. Purposes and main		List of	

	types of granulation in the production of tablets. 5. Covering tablets with shells. 6. Ways of improving tablets as a dosage form.		references, questions, assignments.	
III	***The final stage***			
4.	Summary of the lecture, general conclusions.			2%
5.	Lecturer's answers to possible questions.			3%
6.	Tasks for self-training of students.			2%

Structural and logical scheme of the content of the lecture

1. Characteristics of tablets as a dosage form. Types and groups of tablets.
2. Properties of powdered medicinal substances.
3. The main groups of auxiliary substances in the production of tablets.
4. Purposes and main types of granulation in the production of tablets.
5. Covering tablets with shells.
6. Ways of improving tablets as a dosage form.

Content of lecture material (lecture text)

1. Characteristics of tablets as a dosage form. Types and groups of tablets.

Tablets (*Tabulettae* , from the Latin *tabula* — a board, *tabella* — a board, a tile) - a dosed medicinal form obtained by pressing drugs or a mixture of drugs and auxiliary substances, intended for internal, external, sublingual, implantation or parenteral use.

Tablets produced by the chemical and pharmaceutical industry make up approximately 40% of the production of finished medicines. Production of tablets

worldwide is growing by 10-15% annually. According to the WHO, such rates will remain until the end of the 20th century.

Characteristics of tablets

Tablets as a medicinal form have become widely used all over the world. Currently, tableted preparations make up about 80% of the total volume of finished medicines.

The positive qualities of the tablets provide:

— the appropriate level of mechanization of the main stages and operations and production, which contributes to high productivity and hygiene;

- the accuracy of the dosage is introduced into the medicinal tablets substances;

- portability of tablets, convenient for dispensing and storing them and transportation;

- long-term preservation of medicinal substances in stressed state;

- for substances that are not stable enough - a possibility application of protective coatings;

- possibility of masking unpleasant organoleptics

properties (taste, smell, color ability), which is achieved by

coating;

- a combination of medicinal properties incompatible with physical and chemical properties in other dosage forms;

- localization of the action of the medicinal substance in to a certain part of the gastrointestinal tract - by application of shells soluble in an acidic or alkaline environment;

- prolonging the action of medicinal substances (by coating, using special technologies and composition of core tablets);

- regulation of sequential suction of several medicinal substances from pills into the body in defined intervals (multilayer tablets);

- prevention of errors during vacation and taking medication - putting on the surface of tablets with corresponding inscriptions.

However, tablets have some disadvantages:

— the action of medicines in tablets develops relatively slowly;

- tablets cannot be entered into the body during vomiting;

- during storage, the tablets may become cemented, at the same time the decay time increases;

- tablets may include excipients, do not have therapeutic value, and sometimes cause some side effects (eg talcum powder is irritating gastric mucosa);

- certain medicinal products (for example, sodium or potassium bromide) form highly concentrated solutions in the dissolution zone that can cause severe irritation mucous membranes (this deficiency is eliminated by dissolving tablets in a certain amount of water);

- not all patients, especially children, can swallow freely pills

Classification of tablets

1. According to the method of obtaining, two classes of tablets are distinguished:

Pressed, obtained by pressing powders on tablet machines with different productivity. This method is the main one.

Formed or triturated tablets obtained by forming a tablet mass. They make up approximately 1-2% of the total volume of tablet production. Trituration tablets contain small doses of drugs and diluents: their mass can be up to 0.05 g.

Classification of tablets according to the structural feature:

1. By composition; simple (one-component \ and complex (multi-component).

2. According to the structure of the building: frame, single-layer and multi-layer (at least 2 layers), with or without coating.

Frame or skeleton tablets have an insoluble frame, the voids of which are filled with a medicinal substance. The tablet is like a sponge soaked in medicine. When taken, its frame does not dissolve, keeping its geometric shape, and the medicinal substance diffuses into the gastrointestinal tract.

Single-layer tablets consist of a pressed mixture of drugs and auxiliary substances and are uniform throughout the volume of the dosage form.

Medicinal substances are arranged in layers in multilayer tablets. The use of chemically incompatible substances causes their minimal interaction.

3. Tablet coatings are classified into: coated,

film and pressed dry.

The forms of tablets produced by the chemical and pharmaceutical industry are very diverse: cylinders, spheres, cubes, triangles, quadrilaterals, etc. The most common is a flat-cylindrical shape with a chamfer and a biconvex shape that is convenient for swallowing. In addition, punches and matrices for the production of tablets are easier to manufacture and do not cause particular difficulties when they are installed on tablet machines.

The size of tablets varies from 4 to 25 mm in diameter, the most common are from 4 to 12 mm, tablets with a diameter of more than 25 mm are called briquettes. Tablets with a diameter of more than 9 mm have one or two risks, applied perpendicularly, which allow dividing the tablet into two or four parts and thus varying the dosage of the medicinal substance.

The weight of the tablets is mainly 0.05-0.8 m, which is determined by the dosage of the medicinal substance and the amount of auxiliary substances included in their composition.

Tablets should have the correct shape, without jagged edges, a smooth and uniform surface, have sufficient strength and not crumble. The geometric shape and dimensions of tablets are determined by the standard - OST 64-072-89 "Medical Means. Tablets. Types and sizes". It provides for the production of two types of tablets: flat-cylindrical without a bevel and with a bevel, biconvex without a coating and with a coating: film, pressed and coated. Flat-cylindrical tablets are produced in 14 standard sizes with a diameter ranging from 4.0 to 20.0 mm; biconvex uncoated tablets — 10 standard sizes — from 4.0 to 13.0 mm, coated tablets — from 5.0 to 10.0 mm (Table 14.2). The diameter of the tablets is determined depending on their weight (Table 14.3).

The height of flat-cylindrical tablets should be within 30-40% of the diameter. Some tablets (in the CIS countries - these are tablets containing drugs) have inscriptions with the name of the drug in the form of concave impressions on the surface, since the convex letters on the end of the tablets are much more prone to abrasion and destruction.

Depending on the purpose and method of use of tablets, the following groups are distinguished:

Oriblettae — tablets that are used orally. Medicinal substances are absorbed through the mucous membrane of the stomach or intestines. These tablets are taken orally with water. The oral group of tablets is the main one.

Resoriblettae - tablets that are used sublingually; Medicinal substances are absorbed through the mucous membrane of the oral cavity.

Implantabulettae - tablets, aseptically produced, are used for implantation. Designed for slow absorption of medicinal substances in order to prolong the therapeutic effect.

Injectabulettae — aseptically produced tablets are used to obtain injection solutions of medicinal substances.

Solublettae - tablets that are used to prepare solutions for various pharmaceutical purposes.

Dulciblettae bacilli, boli, urethratoria, vagitoria — pressed urethral, vaginal and rectal dosage forms.

Scale: mass-diameter "medicines. Tablets. Types and sizes" (OST 64-072-89)

Tablet mass, g	**Tablet diameter, mm**
From 0.02 to 0.04	4
From 0.04 to 0.08	5
From 0.08 to 0.15	6
From 0.15 to 0.20	7
From 0.20 to 0.30	8
From 0.30 to 0.40	9
From 0.40 to 0.65	10-11
From 0.65 to 0.85	12
From 0.50 to 1.10	13
From 0.65 to 1.35	14

From 0.80 to 1.65	15
From 0.95 to 2.00	16
More than 1.8	20

2. Properties of powdered medicinal substances

The properties of the original medicinal substances largely determine the rational method of tableting. As raw materials, loose substances in the form of powder (particle size 0.2 mm) or granular (particle size from 0.2 to 3 mm) forms are used, which have the following properties:

— physical - density, shape, size and character

surface of particles, specific surface of particles, adhesion forces (gluing on the surface) and cohesion (gluing of particles inside bodies), surface activity, melting point, etc.;

— chemical — solubility, reactivity, etc .;

— technological — volume density, degree of compaction, flowability, moisture, fractional composition, dispersity, porosity, pressed, etc.;

- structural and mechanical - plasticity, strength, elasticity, viscosity of the crystal lattice, etc.

These properties are often divided into two large groups:

physico-chemical and technological.

Physico-chemical properties

Shape and size of particles . Powder medicinal substances are coarsely dispersed systems and have particles of various shapes and sizes. Most of them are crystalline systems; the amorphous state is less common.

In many drugs, the particles are anisodiametric (asymmetric, multi-axial). They can be elongated, when the length significantly exceeds the transverse dimensions (sticks, needles, etc.), or lamellar, when the length and width are significantly greater than the thickness (plates, scales, tablets, leaves, etc.). A smaller part of powdery substances has isodiametric (symmetrical, equiaxed) particles - these are spherical formations, blocks, polyhedra, etc.

The shape and size of powder particles depends: in the case of crystalline substances (chemical and pharmaceutical preparations) — on the structure of the

crystal lattice and the conditions of growth of particles in the process of crystallization, in crushed plant materials — on the anatomical and morphological features of crushed plant organs and the type of grinding machine.

The size of powder particles is determined by their length and width, measured using a microscope supplied with a micrometer grid, at a magnification of 400 or 600 times.

The shape of the particles is determined by the ratio of the average length of the particles to the average width. With this method, particles are conventionally divided into three main types: elongated — the ratio of length to width is 3:1; lamellar - the length exceeds the width and thickness, but not more than 3 times; equally springy - have a spherical, multifaceted shape, close to isodiametric .

There are 6 crystal systems: cubic, hexagonal, tetragonal, rhombic, monoclinic , triclinic .

Among the crystalline products, the largest amount consists of substances: monoclinic system -40, cubic -10, hexagonal -7, tetragonal -5, rhombic -28, triclinic - 10%.

It is known that only substances belonging to the cubic system are pressed into tablets directly, that is, by direct pressing, without granulation and auxiliary substances (sodium chloride, potassium bromide).

Usually, powders that have the form of particles in the form of sticks are characterized by fine dispersion, good compactability and sufficient porosity (analgin, norsulfasol, acrichin, etc.).

Powders with an equiaxed particle shape are coarsely dispersed, with a low degree of compaction, low porosity (lactose, hexamethylenetetramine, salol). The more complex the surface of the powder particles, the greater the adhesion and the less fluidity, and vice versa.

The physical properties of powders are determined by the specific and contact surface and true density.

The specific surface is the total surface occupied by the powdery substance, and the contact surface is the surface formed by the collision of powder particles.

For tableting, the chemical properties of the starting substances are important, such as: the presence of water of crystallization, solubility, wettability and hygroscopicity.

The wettability of powdered medicinal substances is their ability to interact with various liquids (lyophilicity) and, above all, with water (hydrophilicity). On the surface of solid particles of medicinal substances there is a different amount of hydrophilic groups (-OH, -COH, -COOH, etc.) or oxygen atoms, which are structural elements of their crystal lattice, therefore the wettability of the surface of powders has a different value, depending on the intensity of intermolecular interaction forces

Visually, the tendency of the surface of the powders to be wetted by water is manifested:

a) complete wetting - the liquid completely spreads over the surface of the powder;

b) partial wetting — water partially spreads on the surface;

c) complete non-wetting - the drop of water does not spread, maintaining a shape close to spherical.

Hydrophobic (not wetted by water) substances can be perfectly wetted by other liquids, for example, organic solvents.

The lyophilicity of tableted powdery substances is determined by the philicity coefficient i , which is the ratio of the specific heat of wetting by a polar liquid. (water) to the specific heat of wetting by a nonpolar liquid. It is known that the formation of a monomolecular layer of wetting liquid on the surface of a solid particle is always accompanied by the release of the so-called heat of wetting.

The practical meaning of wettability is that water easily penetrates the tablet obtained by pressing well-wetted substances, which accelerates the disintegration of the tablet.

Hygroscopicity . If the elasticity of vapors in the air is greater than their elasticity on the surface of solid particles, then the powdery mass prepared for tableting will begin to absorb vapors from the air and dissolve in the absorbed water. The kinetics of moisture absorption is determined by the weight method under (normal) normal

conditions, extreme conditions (desiccators over water - 100% relative humidity), or in a climatic chamber.

If the substance is highly hygroscopic, this leads to the use of auxiliary substances - in ologos stimulator and in.

Crystallization water . Crystallization water molecules determine the mechanical (strength, plasticity) and thermal (attitude to the temperature of the air environment) properties of the crystal and have a significant impact on the behavior of the crystal under pressure. The phenomenon of "cementation" is also closely related to the presence of crystallization water in tabletable substances.

Electrical properties . The phenomenon of electrification of powdered medicinal substances during their processing and pressing gives reason to draw a conclusion: when considering the nature of the connection of particles in tablets, along with the deformation ones, it is necessary to take into account the dielectric characteristics. Under mechanical influence, all asymmetric crystals containing polar groups in their structure or in the adsorption water film will be prone to polarization. For non-polar substances, the formation of surface charges is excluded.

Technological properties

The technological properties of powdered medicinal substances depend on their physical and chemical properties.

The fractional (granulometric) composition, or the distribution of powder particles by size, has a certain influence on the degree of flowability, and therefore on the rhythmic operation of tablet machines, the stability of the mass of the received tablets, the accuracy of the dosage of the medicinal substance, as well as on the quality characteristics of the tablets (appearance, disintegration , strength, etc.).

The fastest and most convenient method of determining dispersion is **sieve analysis.** Its technique consists in the fact that 100.0 g of the studied powder is sifted through a set of sieves (hole diameter 2.0, 1.0, 0.5, 0.25 and OD mm). The weight of the material is placed on the largest (upper) sieve and the entire set of sieves is shaken by hand or on a vibrating device) for 5 minutes, and then the mass of each fraction and its percentage content are found.

Studies of the fractional composition of pharmaceutical powders to be tableted have shown that most of them contain a large amount of fine fraction (less than 0.2 mm) and therefore have poor flowability. They are poorly dosed by volume on tablet machines, the tablets are of different weight and strength. The fractional composition of powders can be changed using directional granulation, which allows obtaining a certain number of large fractions.

It is very important to determine such volumetric indicators of powders as bulk and relative density and porosity.

Bulk (bulk) density is the mass of a unit volume of loosely packed powdery material. Bulk density depends on the shape, size, density of powder particles (granules), and their moisture content. The volume of the matrix channel can be predicted by the value of the bulk density.

Determination of the bulk density of the powder is carried out on the device model 545R-AK-3 of the Mariupol (former Zhdanivska) plant of technological equipment.

Weigh 5.0 g of powder to the nearest 0.001 g and pour it into the measuring cylinder. Set the amplitude of oscillations (35-40 mm) with the help of an adjusting screw, and after marking on the scale, fix the position with a lock nut. The frequency of oscillations is set using a transformer in the range of 100-120 cycles/min on the counter. Next, turn on the device with a toggle switch and monitor the powder level mark in the cylinder. When the powder level becomes constant (usually up to 10 min), the device is turned off.

The compressibility of powder preparations is influenced by the shape of the particles, their ability to move and deform under pressure. The compaction factor is an important technological factor; in particular, the larger it is, the more time is spent on pressing. At the same time, more effort is spent on pushing the tablet out of the depth of the matrix channel.

When tableting, the most important technological properties are flowability, pressed and sliding properties, which allow the tablet to be easily pushed out of the matrix.

Fluidity (flowability) - the ability of the powdery system to pour out of the funnel capacity or "flow" under its own weight and ensure uniform filling of the matrix channel. Material that has poor flowability in the funnel sticks to its walls, which disrupts the rhythm of its entry into the matrix. This leads to the fact that the given mass and density of tablets will fluctuate.

When determining the flowability of powders with a low bulk density, it is allowed to use a weight of 30.0 g. The angle of natural slope is also determined with the help of the VP-12A device - the angle between the base of the cone of the loose material and the horizontal plane. The angle of the natural slope varies widely - from 25 to 30°C for loose materials and 60-70°C for bound materials.

The flowability of powders is a complex characteristic that is determined by the dispersion and shape of the particles, the moisture content of the masses, and the granulometric composition. This technological characteristic can be used when choosing tableting technology. Powdery mixtures containing 80-100% of fine fraction (particle size less than 0.2 mm) are poorly dosed, so it is necessary to carry out directed particle agglomeration of such masses, i.e. granulation. If the fine fraction contains up to 15%, it is possible to use the pressing method.

Compressibility is the ability of powder particles to be cohesive under pressure, i.e. the ability of particles under the influence of electromagnetic forces (molecular, adsorption, electrical) and mechanical interlocking to mutual attraction and adhesion with the formation of stable, strong pressing.

There are no direct methods for determining compressibility.

Compressibility is characterized by the strength of the model tablet after the pressure is removed. The better the pressed powder, the higher the strength of the tablet. If the compressibility is low, the tablet turns out to be weak, and sometimes it completely collapses when pushed out of the matrix.

Compressibility can be evaluated by tablet compressive strength. The strength is determined on the devices of Khnykhfy or TVT of the company "Erveka" and is expressed in kilograms or newtons. The higher the strength of the tablet, the better the compressibility and formability of the tablet mass.

It is established that for substances with the strength of tablets:

— above 7 kg/cm2, pure solvents are used for the granulation process; if these are coarsely dispersed powders with good flowability, they are pressed directly, that is, by direct pressing;

- 4-7 kg/cm2 is enough to use ordinary binders

substances:

- 1-4 kg/cm2, it is necessary to use highly effective

binders.

Based on the results of determining the compressibility of tablet masses, a conclusion is drawn about tableting technologies.

Compressibility of the powder is the ability of its particles to cohesion and adhesion under pressure, that is, the ability of the particles of a substance under the influence of forces of various nature and mechanical engagement to mutual attraction and adhesion to form a strong compact tablet. Under pressure, the powder particles seem to fuse, stick together, and stick together, and the weakly structured dispersed system turns into a homogeneous solid.

Three theories of pressing (or tableting) are proposed: mechanical, capillary-colloid and electrostatic.

Mechanical theory . Pressing is a defining operation in the production of tablets. In modern industrial presses, powder is compressed bilaterally by upper and lower punches. When the punches move in the matrix, there is a gradual change in the state of the powder.

The whole process is divided into three stages :

1) sealing (pressing);

2) formation of a compact body;

3) volumetric compression of the formed compact body.

Capillary-colloidal theory. According to P. A. Rebinder's theory, the forces of interfacial interaction are largely determined by the nature of solid and the presence of liquid phases. The strength of structured systems depends on the amount of water and its location.

3. The main groups of auxiliary substances in the production of tablets

Excipients in tablet production are designed to give the tablet mass the necessary technological properties that ensure dosage accuracy, mechanical strength, disintegration and stability of tablets during storage.

Excipients used in the production of tablets are divided into groups depending on the purpose. The main groups and nomenclature of auxiliary substances are given in the table.

Requirements for excipients:

- they must be chemically indifferent ;

— should not have a negative impact on the patient's body, as well as on the quality of tablets during their preparation, transportation and storage.

Fillers (diluents) are added to obtain a certain mass of tablets. With a small dosage of the medicinal substance (usually 0.01 — 0.001 g) or when tableting potent, poisonous and other substances, they can be used to regulate certain technological indicators (strength, disintegration, etc.). Fillers determine the technological properties of the mass for tableting and the physical and mechanical properties of the finished tablets.

Binders . The particles of most medicinal substances have a small force of adhesion between themselves, so their tableting requires high pressure, which is often the cause of untimely wear of the press tool of tablet machines and obtaining low-quality tablets. In order to achieve the necessary adhesion force at relatively low pressures, binders are added to tabletable substances. By filling the interparticle space, they increase the contact surface of the particles and their cohesive ability.

Excipients used in the production of tablets

Group	Substance	Amount,% (of the total mass
Fillers (diluents)	Starch, glucose, sucrose, lactose (milk sugar), basic magnesium carbonate, magnesium oxide, sodium chloride, sodium hydrocarbonate, white clay (kaolin), gelatin, microcrystalline cellulose (MCC), methyl cellulose (MC), sodium salt carboxyl-methyl cellulose (Na KMC), calcium carbonate, calcium phosphate, glycine (aminoacetic acid), dextrin, amylopectin, ultraamylpectin, sorbitol, mannitol, pectin, etc.	Not normalized
Binding	Purified water, ethyl alcohol, crumb paste, sugar syrup, solutions: carboxymethyl cellulose (KMC), oxyethyl cellulose (OEC), oxypropyl methyl cellulose (OPMC); polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), alginic acid, sodium alginate, gelatin, etc.	Not normalized. 1-5% is recommend ed
Loosening: swelling gas-forming improve wettability and water penetration	Wheat, potato, corn, rice starch, pectin, gelatin, MC, N αCMC, amylopectin, ultraamylopectin, agar agar, alginic acid, potassium and sodium alginate, etc. A mixture of sodium hydrogen carbonate from citric or tartaric acid, etc Wheat, potato, corn, rice starch, sugar, glucose, tween-80 and up. Aerosil, etc.	Not normalized Not normalized Not normalized. Tween-80 no more than 1%

Anti- friction : sliding lubricating	Starch, talc, polyethylene oxide-4000, Aerosil, etc Stearic acid, calcium and magnesium stearate, etc. Starch, talc, polyethylene oxide-4000, stearic acid, calcium and magnesium stearate, etc.	Talc no more than 3%, aerosol no more than 10%, stearic acid, calcium and magnesium stearate no more than 1%
Film formers	Acetylphthalyl cellulose (AFC), MC, OPMC, PVP, PVA, ethyl cellulose	They are not normalized
Corrigents: to taste smell colors: dyes pigments	Sugar, glucose, fructose, sucrose, xylitol, mannitol, sorbitol, asparkam, glycine, dulcin, etc. Essential oils, fruit juice concentrates, citral, menthol, vanillin, ethyl vanillin, fruit essences, etc. Indigo carmine, acid red 2C, tropeolin 00, tartrazine, eosin, ruberozum, cerulezum, flavazom, chlorophyll, carotene, etc. Titanium dioxide, calcium carbonate, iron hydroxide, iron oxide, activated carbon, white clay, etc.	Not normalized
Plasticizers	Glycerin, Tween-80, petroleum jelly, oleic acid, polyethylene oxide-400, propylene glycol, etc.	Tween-80 no more than 1%
Prolongers and substances to create a hydrophobic	wax , sunflower oil, cottonseed oil, monopalmitin, trilaurin, paraffin, etc.	They are not normalized

Solvents	water , ethyl alcohol, acetone, chloroform, ammonia, hydrochloric acid, etc.	They are not normalized

Binders are of particular importance when pressing complex powders. During the operation of the tablet machine, they can be delaminated, which leads to the receipt of tablets with different contents of incoming ingredients. The use of the type of binders, their quantity depends on the physical and chemical properties of the pressed substances.

Functions of binders can be performed by various substances.

Water is used in all cases when simple moistening ensures normal granulation of the powdered mass.

Ethyl alcohol is used for granulation of hygroscopic powders, most often when the composition of the mass for tableting includes dry extracts from plant raw materials - these substances with water and aqueous solutions form a sticky, floating, poorly granulated mass. The concentration of the alcohol used is usually higher, the more hygroscopic the powder.

For powders that form, with water and alcohol, crumbling, non-granular masses, solutions of the Navy are used, the mechanism of action of which has been established and theoretically solved by E.E. Borzunov. In this case, the binding capacity of high-molecular compounds is determined not only by their concentration and viscosity, but also by the size of the molecule.

Dissolving substances. When medicinal substances are pressed, the porosity is sharply reduced, thereby making it difficult for liquid to penetrate inside the tablet. To improve disintegration or dissolution, disintegrants are used, which ensure the mechanical destruction of tablets in a liquid medium, which is necessary for the rapid release of the active substance. Disintegrants are added to the composition of tablets also if the drug does not dissolve in water or if the tablet is capable of cementing during storage. In the case of using a mixture of sodium bicarbonate from citric or tartaric acid as a disintegrant, it is necessary to take into account their interaction in a wet

environment, and therefore, correctly choose the order of their introduction during wet granulation into the tablet mass.

The effectiveness of the action of disintegrants is determined in three ways:

- by determining the absorption rate and quantity water absorbed by the powdery mass;

- sometimes the disintegration of tablets containing different concentration of loosening substances;

- by determining the rate of swelling and the maximum of the water capacity of disintegrants, by high-speed photographing under a microscope.

In general, all disintegrants ensure the destruction of tablets into small particles when they come into contact with liquid, as a result of which there is a sharp increase in the total surface of the particles, which promotes the release and absorption of active substances.

Antifriction substances. One of the problems of tablet production is obtaining good fluidity of granulate in feeding devices (funnels, hoppers). The obtained granules or powders have a rough surface, which makes it difficult to suck them from the loading funnel into the matrix nests. In addition, granules can stick to the walls of the matrix and punches due to the friction that develops in the contact zones of the particles with the press tool of the tablet machine. To remove or reduce these undesirable phenomena, antifriction substances, represented by the group of sliding and lubricating substances, are used.

Lubricants, adsorbing on the surface of particles (granules), eliminate or reduce their roughness, increasing their fluidity (flowability). Particles with a spherical shape have the greatest gliding efficiency.

4. Purposes and main types of granulation in the production of tablets.

Granulation - directed agglomeration of particles, i.e. the process of transformation of powdery material of grains of a certain size.

Granulation is necessary to improve the flowability of the tableted mass, which occurs as a result of a significant decrease in the total surface area of the particles when they coalesce into granules and, therefore, a corresponding decrease in the friction that occurs between the particles during movement.

Currently existing methods of granulation are divided into the main types: 1) dry granulation, or grain granulation; 2) wet granulation, or extrusion granulation; 3) structural granulation.

Dry granulation method. It consists in mixing powders and moistening them with solutions of adhesive substances in enameled mixers, followed by drying them to a viscous mass. Then the mass is turned into a coarse powder using rollers or an Excelsior mill. Grinding granulation is used in those cases where the moistened material reacts with the material during wiping. In some cases, if medicinal substances decompose in the presence of water, enter into chemical reactions during drying, or undergo physical changes (melting, softening, color change), they are briquetted.

Currently, using the dry granulation method, dry adhesives (for example, microcrystalline cellulose, polyethylene oxide) are added to the tablet mass of powders, which ensure the adhesion of particles, both hydrophilic and hydrophobic substances, under pressure.

Wet granulation method. In production, wet granulation is often carried out in granulators of type 3027 (Mariupol ZTO). Granulation, or wet wiping of the mass, is carried out with the aim of compacting the powder and obtaining uniform grains — granules with good flowability.

Powders with poor flowability and insufficient adhesion between particles are subjected to this method of granulation.

In both cases, adhesive solutions are added to the mass, which improve the adhesion between the particles.

The method of wet granulation includes the following operations:

1) mixing of powders;

2) wetting the powder with a solution of binders and

mixing;

3) granulation of wet mass;

4) drying of wet granules;

5) processing of dry granules.

Mixing of powders . It is carried out in order to achieve a homogeneous mass and even distribution of the active substance of the tablets.

Mixers of various designs are used for mixing and moistening powdery substances:

1) with rotating blades;

2) screw;

3) mixed drums.

When mixing powders, it is necessary:

- add less to a larger quantity;

- poisonous and potent substances used in

in small quantities, pre-sifted through a sieve, add to the mass in separate portions in the form of triturations, i.e. diluted with filler at a concentration of 1:100;

- colored substances and substances with a high specific gravity

mass load into the mixer last;

- introduce volatile essential oils into a dry granule

bath mass before pressing at the powdering stage, u

avoid reporting them.

The practice of tablet production shows that the time required for mixing a simple recipe (two- and three-component) in a dry state is 5-7 minutes, for a more complex one - 10-12 minutes.

After mixing the dry powders, a moisturizer is added to the mass in separate portions, which is necessary to prevent it from clumping.

With wet mixing of powders, the uniformity of their distribution is significantly improved, there is no separation of particles and delamination of the mass, and its plasticity is improved . Mixing of wet powders is accompanied by some compaction of the mass due to the displacement of air, which makes it possible to obtain denser solid granules. The time of mixing the wet mass: for simple mixtures 7-10 minutes, for complex mixtures - 15-20 minutes. The optimal amount of moisturizer is determined experimentally (based on the physical and chemical properties of the powders) and is specified in the regulations. A mistake can lead to marriage: if the moisturizer is not enough, the granules will fall apart after drying, if there is too much, the mass will be viscous, sticky and poorly granulated. The mass with optimal moisture is a moist, dense

mixture, does not stick to the hands, but crumbles when squeezed into individual lumps.

Granulation of wet mass . The wet mass is granulated on special granulator machines, the principle of operation of which is that the material is rubbed with blades, elastic rollers or other devices through a perforated cylinder or mesh. Granulators are vertical and horizontal.

Currently, wet granulation is the main type of granulation in the production of tablets, but it has a number of disadvantages:

— long-term effect of moisture on medicinal and auxiliary products

gatelnye substances;

— deterioration of the disintegration (solubility) of tablets;

- the need to use special equipment;

- duration and complexity of the process.

Drying of wet granules. Different types of dryers are used:

1) shelf dryers with forced air circulation;

2) dryers with a silica gel column.

If it is necessary to regenerate liquids contained in dried materials, dryers are used in which air is passed through silica gel. At the same time, valuable steam is adsorbed, and warm air is used again for drying the material.

Infrared rational dryers. Special mirror lamps, nichrome spirals placed in the focus of parabolic reflectors, metal and ceramic panel radiators with electric, steam or gas heating are used as heat emitters in such dryers.

Sublimation dryers . In recent years, the method of drying materials in a frozen state under deep vacuum conditions has been widely used in industry. It was called sublimation drying, or molecular drying. The method allows you to preserve the basic biological qualities of the dried material, when evaporation of the solid body occurs without melting, bypassing the liquid phase.

The main advantage of dryers is high productivity: the drying time of the material, depending on its physical properties and shape, lasts from 20 to 50 minutes; they consume little energy and occupy a small working area.

The dried granules must have some residual moisture before pressing.

The residual moisture for each tableted drug is individual and should be optimal, that is, the one at which the process proceeds in the best way, the quality of the tablets meets the requirements of HF, and the strength is the highest compared to tablets obtained from granules of the same drug with a different degree of moisture.

Undried granules stick to the punches, unevenly fill the matrix and require an increased amount of antifriction substances. Overdried granules are difficult to compress, and tablets may have broken edges.

Processing of granules . In the process of drying the granules, it is possible for them to stick together in separate lumps. In order to ensure a uniform fractional composition, dried granules are passed through granulators with meshes with a hole size of 1.5 mm, which largely ensures a constant mass of tablets. Then the granules are powdered, adding antifriction substances, and transferred to the tableting stage.

Structural granulation. It has a characteristic effect on the moistened material, which leads to the formation of rounded, and if certain conditions are met, rather homogeneous granules.

At present, there are three methods of granulation of this type used in pharmaceutical production: granulation in a drazirovochno boiler; spray drying granulation and structural granulation.

For granulation, a mixture of powders is loaded into the boiler in the dredging machine , and while the boiler is rotating at a speed of 30 rpm, it is moistened by feeding the binder solution through the nozzle. The powder particles stick together, are dried by warm air and, as a result of friction, acquire approximately the same shape. At the end of the process, sliding substances are added to the dried granulate.

Types of tablet machines

Pressing on tablet machines is carried out by a press tool consisting of a matrix and two punches.

The main types of tablet machines are eccentric, or impact, and rotary.

Eccentric machines are sliding and intermediate .

No car sledding . In this type of machine, the loading funnel moves during operation on special slides. The material coming from the loading funnel enters the

channel of the matrix attached to the matrix table. After that, the funnel with the material is removed, the upper punch goes down, compresses the material and rises.

Intermediate machines . Tablet machines of the intermediate type are similar in design and principle of operation to sleds , but differ from them in the immobility of the loading funnel and matrix.

Rotary tablet machines. They are widely used, have a large number of matrices and punches.

Factors affecting the main qualities of tablets - mechanical strength, disintegration and average weight

The mechanical strength of tablets depends on many factors. In the case of using the direct pressing method, the strength of the tablets will depend on the physical and chemical properties of the pressed substances.

The strength of tablets obtained by the method of wet granulation depends on the amount and nature of binding (gluing) substances, the amount of pressing pressure and the moisture content of the tableted material.

The amount of adhesives and the optimal humidity are usually specified in industrial regulations. The pressing pressure is selected for each drug and is controlled by measuring the strength of the tablets and their disintegration time. Excessive pressing pressure often leads to delamination of tablets. In addition, there is a sharp decrease in time, which reduces the penetration of liquid into the tablet and increases the time of its disintegration.

The moisture content above the optimum leads to sticking of the tablet mass to the press tool. Insufficient moisture content, that is, overdrying of the material, leads to delamination at the time of pressing or to insufficient mechanical strength.

The dissolution and solubility of tablets also depends on many factors:

- quantity and nature of binders;

- the amount and nature of disintegrants , which allows the tablet to disintegrate.

- pressing pressure;

— physico-chemical properties of the substances included in the tablet — primarily from their wettability, swelling and solubility.

The average weight of tablets also depends on a number of components:

- flowability of the material;

- fractional composition;

- the shape of the loading funnel and the angle of the slope;

- rotation speed of the matrix table, that is, from the speed

pressing.

Effect of excipients and species granulation on the bioavailability of drugs substances from tablets

No pharmaceutical factor has such a significant and complex effect on the effect of the drug, excipients.

In the pre-biopharmaceutics and drug era, the introduction of excipients was considered only as the introduction of indifferent fillers and form formers, without which it is impossible to do when obtaining the appropriate dosage forms.

It has been proven that the method of obtaining dosage forms largely determines the stability of the drug, the speed of its release from the dosage form, the intensity of absorption, and ultimately, the therapeutic effectiveness. For example, the degree of preservation of a number of medicinal substances in ready-made dosage forms depends on the choice of granulation method when obtaining tablets. It is especially undesirable to use wet granulation when receiving tablets containing reserpine, antibiotics and other substances, as the drugs may decompose.

1. Granulation conditions have a great influence on the disintegration of tablets. The most commonly used humectants in the industry - starch paste and gelatin solutions - are not optimal for many drugs, as they increase the time of their disintegration. Increasing the strength of tablets with the help of highly viscous granulating liquids, other things being equal, leads to an increase in the time of disintegration; better disintegration among highly viscous liquids is usually provided by solutions of polymers: MC, OPMC, PVP, NaKMU,.

The harmful effect of hydrophobic slippery substances (talc, magnesium and calcium stearate), which worsen the disintegration of tablets due to the difficult penetration of digestive fluids into the porous structure of the tablet, is significantly reduced or completely eliminated if the tablet masses contain highly swelling substances (CMC, MC).

2. Pressing affects the release rate the drug, which, in its queue, can disrupt its process absorption in places of absorption.

3. One of the methods of improving the pharmaceutical properties of tablets is to create them based on inclusion complexes of cyclodextrins with drugs

substances Yes, the use of a-cyclodextrin complex significantly improves dissolution of digoxin, cavinton; an increase is observed speed dissolution of salicylic acid in a complex with (3-cyclodextrin.

In order to maintain the concentration of a medicinal substance in the body at a certain constant level, in the manufacture of some tablets, auxiliary substances are used that slow down the rate of release of medicinal substances. For example, long-acting tablets of salbutamol, containing an auxiliary substance - acrylic resin, have been developed.

5. Covering tablets with shells

Covering tablets with shells has a multifaceted meaning and the following goals:

1) protection of tablets from extreme environmental factors

(impacts, abrasions, etc.);

2) protection from environmental influences (light, moisture, oxygen and carbon dioxide of the air);

3) masking of unpleasant taste and smell, contained in tablets of medicinal substances;

4) protection against the coloring ability of drugs substances contained in tablets (for example, tablets activated carbon);

5) protection contained in tablets of medicinal substances from the acidic reaction of gastric juice;

6) protection of the mucous membrane of the mouth, esophagus and stomach from irritation effect of medicinal substances;

7) localization of the therapeutic effect of drugs substances in a certain department of the gastrointestinal tract;

8) prevention of digestive disorders stomach, possible with neutralization of gastric juice medicinal substances of a basic nature;

9) prolonging the therapeutic effect of drugs substances in tablets;

10) overcoming the incompatibility of various substances, are in one tablet, by introducing them into the composition shell and core;

11) improvement of the marketable appearance of tablets and their convenience application.

When coating tablets with shells, various auxiliary substances are used, conditionally divided into the following groups: adhesives that ensure adhesion of the coating materials to the core and to each other (sugar syrup, PVP, KMC, MC, AFC, OPMC, EC, PEG, etc.); structural substances that create frameworks (sugar, magnesium oxide, calcium oxide, talc, basic magnesium carbonate); plasticizers that give the coating properties of plasticity (vegetable oils, MC, PVP, CM, tweens, etc.); hydrophobizers that give the coating properties of moisture resistance (aerosil, shellac, polyacrylic resins, zein); dyes used to improve appearance or to indicate a therapeutic group of substances: (tropeolin 00, tartrazine, acid red 2C, indigo carmine, etc.); spices that give the coating a pleasant taste (sugar, citric acid, cocoa, vanillin, etc.).

More than 50 names of film formers are used.

Depending on their composition and method of application, tablet coatings are divided into the following groups:

1. Pressed (or dry) coatings.
2. Film coatings.
3. Dragee coating (applying a sugar coating).

Pressed coatings

The application of shells by pressing ("dry" coating) is carried out with the help of tablet machines of the "Draykota" type of the English company "Zavdaty" or domestic RTM-24 D. The machine is a double unit consisting of two rotors.

On the first rotor, tablets are pressed in the usual way - biconvex cores, which are transferred using a special transport device to the second rotor, where the coating is applied.

The main advantage of this coating method is the exclusion of the use of solvents in the technology. Therefore, pressed coatings are rational for tablets of hygroscopic and moisture-sensitive substances (antibiotics).

In order to prolong the effect, the active substance is introduced into the composition of both the core and the coating. The coating quickly disintegrates in the stomach (initial dose), and the core (tablet) disintegrates gradually, maintaining a certain constant concentration of the substance in the body. This method allows you to overcome the incompatibility of different substances found in one tablet by introducing them into the composition of the shell and core.

Film coatings

A film coating is a thin (approximately 0.05-0.2 mm) shell that forms on a tablet after drying of the film-forming substance solution applied to its surface.

They have the following advantages:

1. The possibility of selective solubility of tablets in the stomach or intestines.
2. Regulation of the rate of adsorption of medicinal substances.
3. Possibility of combination in one dosage form
incompatible medicinal "substances.
4. Physical, chemical and mechanical preservation
properties of tablet cores when film coatings are applied.
5. Preservation of original geometric parameters
tablets, their form, marking, brand names.
6. Reduction of the mass of the volume of the film coating with
compared to the drugstore ones .
7. The possibility of automation of the coating process, intensifiers
cations of production and reduction of production areas.

Depending on solubility, film coatings are divided into the following groups:

a) water-soluble;
b) soluble in gastric juice;
c) enteric soluble;
d) insoluble.

Water soluble and gastric soluble coatings. Water-soluble coatings improve the appearance of tablets, adjust their taste and smell, and protect against mechanical damage. Coatings, soluble in the stomach, protect tablets from exposure to air moisture; they break down in the body within 10-30 minutes. To obtain water-soluble

coatings, polyethylene oxide and polyvinylpyrrolidone are applied to tablets in the form of 20-30% solutions in 50-90% ethyl or isopropyl alcohol, methylcellulose and sodium salt of carboxymethylcellulose - in the form of 4-7% aqueous solutions.

Coatings soluble in gastric juice are benzylamino and diethylaminobenzylcellulose, d-aminobenzoate, sucrose, glucose, fructose, mannitol, vinylpyridine, zein and gelatin.

Enteric coatings

Enteric-dissolving coatings protect the medicinal substance contained in the tablet from the action of the acidic reaction of gastric juice, protect the gastric mucosa from the irritating effect of some drugs, localize the medicinal substance in the intestine, prolonging its effect to a certain extent. Enteric-dissolving coatings also have a more pronounced moisture-protective effect than the groups of coatings listed above.

The process of dissolution of enteric membranes in the body is due to the effect on them of a complex of enzymes and various solubilizing substances contained in the intestinal juice.

High molecular weight compounds with the properties of polyelectrolytes with a large number of carboxyl groups are used as film formers **to obtain enteric-soluble coatings .** They dissociate in a neutral or alkaline environment with the formation of insoluble salts. Natural substances are used: shellac, carnauba wax, casein, keratin, paraffin, ceresin, spermaceti, cetyl alcohol, as well as synthetic products, stearic acid combined with fats and bile acids, butyl stearate, dextrin phthalates, acetyl-, methylphthalylcellulose monosuccinates.

Acetylphthalylcellulose is most often used to obtain enteric-soluble coatings, as a substance most resistant to the influence of gastric juice. The listed film formers are applied to the tablets in the form of solutions in ethyl, isopropyl alcohol, acetone or in mixtures of the specified solvents. To obtain colored shells, pigments and dyes are added to the solutions.

Enteric-dissolving coatings withstand (2-4 hours or more) the influence of gastric juice, which allows such tablets to pass through the stomach unchanged; in the intestinal juice, they disintegrate within 1 hour, ensuring the release of the medicinal substance in the intestines.

Insoluble coatings.

The main purpose of coatings of this type is to protect the tablet from mechanical damage and from the influence of atmospheric moisture, to eliminate the unpleasant smell and taste of the medicinal substance, and to prolong its action. Coatings include ethyl cellulose, polyethylene sorbitol monolaurate, surfactants, etc. The mechanism of drug release from tablets with insoluble shells is as follows. After the tablet enters the gastrointestinal tract, digestive juices penetrate into it through the micropores of the shell and cause either the dissolution of the tablet's contents or its swelling. In the first case, the dissolved substances diffuse through the film in the opposite direction - towards the gastrointestinal tract under the influence of the concentration difference, in the second case, the shell ruptures due to the increase in the volume of the tablet, after which the medicinal substance is released in the usual way.

Requirements for film-forming substances:

1. Complete harmlessness for the body.
2. Good solubility in widely available organic compounds
solvents.
3. Good film-forming properties.
4. Chemical indifference.
5. Stability during long-term storage (storage
strength, elasticity and solubility).
6. Availability.

Methods of applying film coatings

There are 3 ways of applying film coatings to tablets:

1. Immersion in a solution of a film-forming substance.
2. Layering in the fermentation boiler.
3. Obtaining a coating in a suspended layer.

The first method is based on immersing the tablets alternately, covering the solution with one side and then the other. This method is quite complicated and suitable only for applying viscous, but not too sticky solutions to tablets. Currently, due to insufficient productivity, it is rarely used.

The most widely used method of applying film coatings in the priming boiler. This method is inexpensive, suitable for solutions of almost any viscosity, and has high productivity. To apply the coating, biconvex tablets are placed in a drying boiler, during operation it rotates at a speed of 20-25 rpm.

The film coating slightly increases the weight of the tablets. Due to the use of volatile organic solvents, the long stage of drying the shells is excluded. The duration of the film coating process is 2-4 hours.

Film coatings can be applied not only to tablets, but also to granules or particles of powdery material.

The main disadvantage of applying film coatings on an industrial scale is a significant increase in the concentration of vapors, often poisonous and flammable organic solvents in the premises of workshops, which requires the adoption of appropriate fire safety measures, the installation of powerful supply and exhaust ventilation and the safety of workers.

The UZC-25 closed cycle installation is capable of capturing solvent vapors, regenerating them and putting them back into production. This plant produces tablets PASK - Sodium (sodium salt of para-aminosalicylic acid) with a film enteric coating.

Coated coating

Drazhirovane (from the French dragee — application of a sugar coating) coating is the oldest type of tablet coating, used since the beginning of the 20th century. **The main purpose of the shells** is to protect the tablets from external influences, mask the unpleasant taste and smell of the medicinal substance, and improve the appearance of the tablets. Sometimes substances are added to the shell to protect the tablet from the effects of gastric juice.

The core tablet must be mechanically strong.

This is due to the action of four factors on the tablet during drugging:

- the total weight of tablets, which depends on the amount of loading of the boiler (with an increase in the load and speed of rotation of the boiler the possibility of pill destruction increases);

- free fall of tablets from the upper point of the rotating one boiler to the bottom (this force directly proportional to the mass of tablets and the height from which they fall);

- kinetic energy of rotating tablets in the boiler (the tablet does not just fall arbitrarily, but a rotating one is created moment, the strength of which depends on the mass of the tablet and speed rotation of the boiler);

- wedging effect of liquids used in drugged no .

Tablets to be coated should not have a flat shape to avoid sticking together.

Two types of tablets are recommended for teasing:

- with an average surface oval, depth of curvature is about 15% of the diameter, the height in the center is 25-30% diameter (p = 0.75 d);

- with standard surface curvature (small oval), the depth of curvature is 10% of the diameter, height in the center - not less than 25% of the tablet diameter (p = l,ld).

Until 1975, domestic chemical and pharmaceutical factories had the technology of coating tablets using the sugar-flour coating method.

Stages of the technological process of pill irritation:

1. Covering, or primer.
2. Layering, or knurling.
3. Smoothing or polishing.
4. Gloss.

The coating, or primer , consists in the fact that the mobile tablets in the fermentation boiler are moistened with sugar syrup of 64-70% concentration and sprinkled with wheat flour or its mixture with basic magnesium carbonate. After sprinkling, the tablets are rotated for 25-30 minutes, after which they are dried with warm air (40-50 °C) for 30-40 minutes. The operations of moistening tablets, sprinkling, free rotation and drying are repeated 2-3 times. The wrapping stage, if necessary, is used to isolate the tablet-core from moisture penetration, especially in the first moments of tablet hydration.

The stage of enveloping is followed by the stage of layering, or knurling. In the entire technological cycle, teasing is the most important stage, since it is here that the formation of the entire shell takes place.

At this stage, some factories use sugar-flour dough for **layering** , others - tablets are moistened with sugar syrup and sprinkled with basic magnesium carbonate or a mixture of it with wheat flour in equal quantities. After a single serving of sugar-flour dough, the tablets are given free rotation, stirring them in the boiler for 30-40 minutes. Then the tablets are dried with warm air for 20-30 minutes. The operations of feeding the dough, free rotation, and drying the tablets are repeated many times until a certain mass of tablets is obtained.

The stage of layering is followed by the stage of smoothing, or polishing, which is carried out with the help of sugar syrup with the addition of small amounts of gelatin (up to 1%) and dyes. At this stage, **unevenness** and **roughness are removed.**

The last stage of the irritation process is **the glossing stage** , i.e. giving the tablets a shine and a commercial appearance. **It is carried out in two ways.**

- Using the first method, glossy mastic is prepared.

Glossy mastic in the amount of 0.05-0.06% is applied by hand to rotating warm tablets and the tablets are allowed to rotate freely for 30-40 minutes. Then the tablets are sprinkled with a small amount of talc to speed up the gloss.

Stages of the suspension method of pill irritation.

1. Coating tablets from an uncolored suspension.
2. Coating tablets from a colored suspension

or colored syrup.

3. Polishing of tablets.

Suspension coating of tablets is carried out both on conventional coating boilers and on automatic lines of the companies "Stenberg" (Germany) and "Pellegrini (Italy).

The technological mode of teasing is as follows.

Pellets-cores in the amount of 25-30% of the volume of the boiler, pre-run-in and dust-free, are loaded into the drizzling boiler. Turn on the boiler drive and apply 2-2.5% suspension to the rotating tablets by watering or spraying with a nozzle. Tablets are allowed to "roll" for 4-5 minutes. The angle of inclination of the boiler to the horizontal is 45°, the speed of rotation is 20-25 rpm. After that, the tablets are dried with warm air at 40-45 °C for 3-4 minutes.

The suspension feeding, running-in and drying operations are repeated many times until a certain mass of tablets is obtained.

The procedure for applying a colored coating based on a colored suspension or colored syrup and polishing tablets was discussed above.

The suspension method of coating tablets with shells made it possible to automate the process, reduce costs, and increase labor productivity by 3-5 times.

New technology has improved the quality of coated tablets :

a) their average mass decreased;

b) to improve the product appearance;

c) the stability of coated tablets increased —

the shelf life of drugs increased from 1 year to 4 years;

d) excluded food product - flour, which led to

cracking of the coating.

Trituration tablets

Tablets obtained by the formation of moistened masses are called trituration tablets (Tabulettae friables). Unlike pressed tablets, trituration tablets are not subjected to pressure; the adhesion of the particles of these tablets is carried out as a result of autohesion during drying, therefore the tablets have low strength.

Trituration tablets are made in cases where the use of pressure is undesirable for some reason (for example, nitroglycerin tablets, when an explosion may occur when pressure is used), or the dosage of medicinal substances is small, and the addition of a large amount of excipients is impractical. Due to the small size (1-4 mm) and mass of the medicinal substance (20-40 mg), it is technically difficult to produce such tablets on serial tablet presses, and in most cases it is impossible. It is advisable to make trituration tablets in cases where the necessary tablets dissolve quickly and easily in water (tablets for the preparation of eye drops and injection solutions), since they do not require antifriction substances, which are, as a rule, insoluble compounds in water.

Trituration tablets are obtained from crushed medicinal and auxiliary substances. They use lactose, sucrose, glucose, starch and their mixtures. The powdery mixture is moistened most often with ethanol (40-95%), it is taken in a precisely determined amount until a plastic, but not viscous mass is obtained.

For the formation of trituration tablets, special rather complex machines with a capacity of up to 200,000 tablets per shift have been created. The loading funnel of the machines is filled with a paste-like mass, which is rubbed into the perforated plates with the help of a winged stirrer - through, cylindrical holes made of chemically resistant material (plastic, ebonite, stainless steel). Next, the rubbed mass is pushed out of the plates by a system of small punches, and the formed tablets are dried directly in the matrix, in the air or on a conveyor belt for drying in drying cabinets (drying temperature 30-40 °C).

Trituration tablets are standardized according to the content of active substances and physicochemical indicators in accordance with the pharmacopoeial article "Tablets". Trituration tablets are not affected by mechanical strength, and the definition of disintegration and solubility have some differences.

Packaging, packaging and labeling of tablets

Tablets are produced in different packaging designed for purchase by patients or medical institutions. The use of optimal packaging is the main way to prevent a decrease in the quality of tableted drugs during storage. Therefore, the choice of the type of packaging and packaging materials is decided in each specific case individually, depending on the physical and chemical properties of the substances included in the tablets.

One of the most important requirements for packaging materials is protection of tablets from exposure to light, atmospheric moisture, air oxygen, and microbial contamination.

Currently, such traditional packaging materials as paper, cardboard, metal, glass are used for packaging tablets (cardboard convalutes, glass test tubes, metal pencil cases, glasses for 50, 100, 200 and 500 tablets, iron cans with pressed lids for 100-500 tablets).

Along with traditional materials, film packages made of cellophane, polyethylene, polystyrene, polypropylene, polyvinyl chloride and various combined films based on them are widely used. The most promising film contour packaging, obtained on the basis of combined materials by the method of heat welding: cellless (strip) and cell (blister).

For tape packaging, the following are widely used in various combinations: laminated cellophane tape, aluminum foil, laminated paper, polymer film laminated with polyester or nylon. The packaging is made using heat welding of two combined materials. Packaging is carried out on special machines (A1-AUZ-T and A1-AU4-T). Cellular packaging consists of two main elements: a film from which cells are obtained by thermoforming, and a heat-sealing or self-adhesive film for gluing the packaging cells after filling them with tablets. Hard (unplasticized) or weakly plasticized polyvinyl chloride (PVC) with a thickness of 0.2-0.35 mm or more is most often used as a thermoforming film. The PVC film forms well and is thermally bonded to various materials (foil, paper, cardboard covered with a thermal lacquer layer). This is the most common material used for packaging non-hygroscopic tablets.

Polypropylene is recommended for hygroscopic medicinal products, but it is more difficult to mold and, in addition, it is more rigid than PVC. Polystyrene is also well formed, but due to its high moisture permeability, it is rarely used.

As a film intended for closing the cells, aluminum foil is often used. From the inside, it is covered with glue or a thermal adhesive film, with an external varnish. Aluminum foil is impermeable to water vapor and gases, well protects drugs from the penetration of odors. The packaging, which has aluminum foil as one of the layers, is characterized by lower permeability, and consists entirely of aluminum foil - will ensure high tightness.

The thermoforming film from the roll is continuously wound and enters the rotating forming drum, where it is heated by infrared emitters to a plastic state and then is sucked to the cells of the drum with the help of a vacuum, taking the required shape. Next, the film enters the guide table, where the film cells are loaded with tablets. Then the film is covered from above with aluminum foil or paper, which is unwound from the roll and with the help of two thermogluing drums - cold, driven and hot, rotates freely and is glued to it. A strip of tablets is cut out on a die. Ready packages are lowered from the machine on a tray, and the remaining cut tape is wound into a roll, then removed from the machine.

The productivity of the machines is 3600-9600 packages per hour.

All types of packages are marked with the following information: ministry, manufacturing plant, name of the tableted drug in Russian and Latin, number of tablets, composition, batch number and price.

The box is glued with a wrapping paper or tape. A label made of label paper or writing paper is pasted on the box indicating the product, the manufacturer, the serial number, and the number of packages.

The boxes are placed in a container or packed in a plywood or board box. The bottom and walls of the box are lined with wrapping paper, the free space is filled with lignin. A packing slip is placed in the box.

Storage conditions for tablets

storage conditions affect the stability of medicinal substances in tablets and their physicochemical parameters (strength, disintegration).

When stored in excessively dry air, tablets lose moisture, which is one of the main reasons for their cementation and, as a result, almost complete loss of the ability to disintegrate. With high air humidity, the strength of the tablets usually decreases, and the disintegration time can either increase or decrease.

An increase in air temperature and the effect of direct sunlight also have a negative effect on the quality of tablets.

Therefore, the tablets are stored at room temperature in a dry place protected from light.

After a year of storage, the disintegration of the tablets is checked in accordance with the requirements of HF.

6. Ways of improving tablets as a dosage form

The development of methods of coating tablets by pressing, as well as the use of a number of other technological principles, significantly expanded the problem of tableting and opened ways to improve tablets as a dosage form and create new drugs with prolonged action.

Multilayer tablets

Multi-layered (layered) tablets make it possible to combine medicinal substances incompatible in terms of physico-chemical properties in other medicinal forms, to

prolong the effect of medicinal substances in certain time intervals and to regulate the sequence of their absorption.

With the help of multilayer tablets, it is possible to achieve a prolongation of the action of the medicinal substance. It is obvious that the dose of the substance contained in the shell will first have an effect, and then (let's say after 3 hours) the dose of the same medicinal substance contained in the middle of the tablet will begin to have an effect. If there will be different medicinal substances in the layers of the tablet , then their effect will be manifested differentially, sequentially, in the order of dissolution of the layers.

Tablets with an insoluble skeleton

Tablets with an insoluble skeleton are also promising. The medicinal substance is gradually released from it by leaching. Such a tablet is compared to a sponge, the pores of which are filled with a soluble substance (a mixture of a medicinal substance with a soluble filler - sugar, lactose, polyethylene glycol, etc.). Tablets do not disintegrate in the digestive tract and retain their geometric shape. Some inorganic (barium sulfate, gypsum, di- and tri-substituted calcium phosphate, titanium dioxide) and organic (polyethylene, polyvinyl chloride, refractory waxes, aluminum soap, etc.) substances serve as material for the skeleton. Skeletal tablets can be obtained by simply pressing medicinal substances that form a skeleton. They can also be multi-layered, for example three-layered, and the medicinal substance is mainly in the middle layer. Its dissolution begins from the side surface of the tablet, while from the large surfaces (top and bottom) initially only auxiliary substances from the middle layer diffuse through the capillaries formed in the outer layers.

Tablets with ionites

Continuation of the action of the medicinal substance is possible by increasing the molecule of the medicinal substance by depositing it on an ion-exchange resin. Substances associated with the ion exchange resin become insoluble and their release from tablets in the digestive tract is based solely on ion exchange. The rate of release of the medicinal substance varies depending on the degree of crushing of the ionite (grains with a size of 300-400 μm are more often used), as well as on the number of branched ego chains.

Materials on the activation of students of higher education during the lecture: questions, situational tasks, etc.:

Question:

1. What are tablets as a dosage form?

2. Specify the main groups of excipients used in the production of tablets.

3. In what cases are thinners used in the production of tablets?

4. Explain the purpose of binders. In what cases are dry binders used?

5. What are leavening agents? What groups are they divided into according to the mechanism of action?

6. Give examples of auxiliary substances that cause the destruction of tablets due to their swelling.

7. Specify the purpose of lubricants. What conditional groups are they divided into?

8. For what purpose is starch used in tablet production and to which groups of auxiliary substances can it be classified?

9. For what purpose is sugar used in tablet production?

10. What is the essence of the granulation process and for what purpose do powdery substances undergo the granulation stage?

General material and bulk-methodological support of the lecture:

- educational premises - the auditorium of the department;
- equipment - computer, tables;
- equipment – multimedia projector;
- illustrative materials - presentation, slides.

Questions for self-control:

1. Name the methods of granulation used in tablet production and their distinctive features.

2. Explain the principle of wet granulation. What kind

ways is it carried out?

3. What is dry granulation, how is it carried out and in what cases is it used?

4. Which granulation methods are technically more advanced and promising. How can this be explained?

5. What is pellet running-in and for what purpose is it carried out?

6. What medicinal substances can be tableted without granulation?

7. How to improve the technological properties of powders

and perform direct pressing?

8. Name the main nodes of RTM and explain the principle of its operation.

9. What is a double press tablet machine?

10. Explain the purpose of coatings applied to tablets.

11. Specify the coating that is applied to tablets by the method of

ращивания (teasing) and list the stages of this process.

12. What are the essence and advantages of the drugging method using suspensions?

13. What is a film coating? How are they divided depending on solubility?

14. Give examples of substances that form film coatings that are soluble in intestinal juice.

15. In what ways are film coatings applied to tablets?

16. What is pressed coating?

17. How are multilayer tablets obtained?

18. What are frame tablets and in what ways are they obtained?

19. What are trituration tablets and what stages does the process of obtaining them consist of?

20. Specify the main indicators that determine quality

tablets

21. How is the average weight of a tablet determined and what deviations from the average weight are allowed in individual tablets?

22. Specify the limits of permissible deviations in the content of active substances in tablets.

23. What should be the strength of tablets? How to evaluate it?

24. How is the disintegration of tablets determined? What are the disintegration requirements of HF for uncoated and coated tablets?

25. What disintegration requirements does GF apply to enteric-coated tablets?

26. Name the factors affecting the bioavailability of active substances in tablets.

27. State the requirements for HF to dissolve active substances from tablets. Describe the method of determination.

28. What are dragees and granules as dosage forms? Evaluate their prospects. Give a definition.

29. What does the process of obtaining dragees and granules consist of?

30. What auxiliary substances are used in the production of dragees and granules?

31. What indicators are used to control the quality of dragees and granules?

32. Name the drugs produced in the form of dragees and granules.

References:

1. Study guide for independent work of students of the Faculty of Pharmacy for the licensing exam "Step 2. Pharmacy" / V.Yu. Anisimov, O.I. Belyaeva, H.G. Vidavska, V.O. Helmboldt, A.V. Zamkova, I.V. Lytvynchuk, A.V. Nikitin, B.V. Pristupa, I.B. Petkova, Ya.V. Rozhkovskyi, S.B. Strechen, L.M. Unguryan, N.C. Fizor Odesa: Odesa.nats.med. Univ. 2020. - 240 p.

Mode of access to lecture texts for students of the Faculty of Pharmacy: https://info.odmu.edu.ua/chair/drugs/files/390/ua

Literature used by the lecturer to prepare the lecture.

Main:

1. Industrial technology of medicines: a basic textbook for students. Higher. student pharmacy institutions (pharmacological institutions) / E.V. Gladukh, O.A. Ruban, I.V. Saiko et al. - Kh.: NFaU: Original, 2016. - 632p. : Name - (National textbook series)

2. Workshop on industrial technology of medicinal products specialty "Pharmacy" / Ed. Ruban O.A. - Kh .: NFaU, 2015. - 374 p

3 . INDUSTRIAL technology of medicines : education. manual for students' independent work / O. A. RUBAN , V. D. RYBACHUK , L. M. Khohlova etc. - KH.: NATIONAL UNIVERSITY OF UKRAINE, 2015. - 120 p.

- Excipients in the production of drugs: training. manual for students higher pharmacy education closing / O. A. RUBAN , I. M. Pertsev, S. A. Kutsenko, Yu. S. Maslii; under the editorship I. M. Pertseva. – Kh.: Golden Pages, 2016. – 720 p.
- Technology of drugs for industrial production: tutorial. for university students education closing : in 2 parts / V. I. Chuyeshov, E. V. Gladukh, I. V. Saiko and others. – 2nd ed., revision. and additional - Kh.: National University of Applied Sciences: Original, 2012. - Part 1. - 694 p.
- Technology of drugs for industrial production: tutorial. for university students education closing : in 2 parts / V. I. Chuyeshov, E. V. Gladukh, I. V. Saiko and others. – 2nd ed., revision. and additional - Kh.: National Academy of Sciences: Original, 2013. - Part 2. - 638 p.
- Modern pharmaceutical technologies: education. manual to laboratory classes of full-time, evening and part-time master's students of the specialty 8.110201 "Pharmacy" / under the editorship. O. A. Ruban. - Kh.: Publishing House of the National Academy of Sciences, 2016. - 256 p.
- Encyclopedia of Pharmaceutical Technology: 3-d Ed. / ed. by J. Swarbrick. – New York; London: Informa Healthcare, 2007. – 4128 p.
- European Pharmacopoeia 8.0 [8th edition] / European Directorate for the Quality of Medicines & Healthcare. - Strasbourg, 2013. - 3638 p.
- Handbook of Pharmaceutical Excipients, 6th edition / RC Rowe, PJ Sheskey, ME Quinn. - Pharmaceutical Press and American Pharmacists Association, 2009. - 521 p.
- State Pharmacopoeia of Ukraine / State enterprise " Ukrainian scientific officinal center quality medical means " - 2- e kind . - Kharkiv : State enterprise " Ukrainian scientific officinal center quality medical means ", 2015. - Vol . 1. - 1128 p .
- State Pharmacopoeia of Ukraine / State enterprise " Ukrainian scientific officinal center quality medical means " - 2- e kind . - Kharkiv : State enterprise " Ukrainian scientific officinal center quality medical means ", 2014. - Vol . 2. – 724 s .

- State Pharmacopoeia of Ukraine / State enterprise " Ukrainian scientific officinal center quality medical means " - 2- e kind . - Kharkiv : State enterprise " Ukrainian scientific officinal center quality medical means ", 2015. - Vol . 3. – 732 p .
- About medicinal products: the law of Ukraine dated 04/04/96 No. 123/96 // Bulletin of the Verkhovna Rada of Ukraine. - 1996. - No. 123.
- Zujkina SS The pharmacotechnological studies of the phytospecies composition for the complex therapy of mastopathy / SS Zujkina, LI Vishnevska // Visnyk pharmacy . – 2017. – No. 2 (90). - WITH . 43-47.
- Bogutska , O. _ IS . The main ones directions solution problems pharmaceutical of incompatibilities / O . IS . Bogutska // Contemporary achievement pharmaceutical technologies and biotechnology : collection scientific works _ – issue 2. – Kharkiv . : Type - in NFaU , 2017. - S. 29–31.
- Polovka N . P. _ Rating biopharmaceuticals factors at developers and production new ones medical means / N. _ P. _ Polovko , L. _ And . Vishnevska , O. _ WITH . Shpychak // Modern achievement pharmaceutical technologies and biotechnology : collection scientific works , issue 2. – X .: Ed NFaU , 2017. - S. 155-160.
- Prospects for the creation of new original drugs based on substances of plant origin / O.A. Ruban, S.A. Malinovska, Murad Al-Tawaiti, S.I. Mazurets // Phytotherapy. – 2012. – No. 2. - pp. 63–65.
- The current state of creation, production and quality control of capsules / M.B. Chubka, L.V. Vronska, N.O. Zarivna et al. // Pharmaceutical journal. 2012. No. 2. P. 165168.
- Murachanian, D. Two-Piece Hard Capsules for Pharmaceutical Formulations / D. Murachanian // Journal of GXP Compliance. 2010. Vol. 14. P. 3142.
- Patel H. New pharmaceutical excipients in solid dosage forms – A review / H. Patel, V. Shah, U. Upadhyay // Int. J. of Pharm. & Life Sci. - 2011. - Vol. 2. – P. 1006–1019.
- Recent Trends of Treatment and Medication Peptic Ulcerative Disorder / D. Bhowmik, Chiranjib, KK Tripathi [et al.] // International Journal of PharmTech Research. - 2010. - Vol. 2. – P. 970–980

- The effects of powder compressibility, speed of capsule filling and pre-compression on plug densification / M. Llusa , E. Faulhammer , S. Biserni [et al.] // Int. J. Pharm. – 2014. – Vol. 471. – P. 182–188.

Electronic information resources

- Lecture materials, methodological developments for seminar classes and independent work at the Department of Social Pharmacy: Access mode: http://socpharm.nuph.edu.ua.
- Scientific library of the National Academy of Sciences: Access mode: http://dspace.ukrfa.kharkov.ua; http://lib.nuph.edu.ua
- www.moz.gov.ua is the official website of the Ministry of Health of Ukraine
- nuph.edu.ua is the official website of the National Pharmaceutical University
- library@nuph.edu.ua - website of the library of the National Academy of Sciences of Ukraine
- The website of the Department of Scientific Research of the National Academy of Sciences of the Russian Academy of Sciences. – Access mode: ztl.nuph.edu.ua.
- The website of the Department of Drug Technologies of ONMedU http://info.odmu.edu.ua/chair/drugs/files/195/ua
- The site of distance learning of the National Academy of Sciences: the page of the ZTL department - [Electronic resource]. – Access mode: http://pharmel.kharkiv.edu/moodle/course/index.php?categoryid=154
- fp.com.ua - website of the magazine "Pharmacist Praktik"
- www.provisor.com.ua – the official website of the magazine "Provisor"
- Compendium: drugs. - [Electronic resource]. - Access mode: http://compendium.com.ua/ - as of October 10, 2016.
- State Register of Medicinal Products of Ukraine. - [Electronic resource]. - Access mode: http://www.drlz.com.ua/ - as of January 10, 2017.

Database "Equalizer" LLC "Business Credit" - [Electronic resource]. - Access mode: http://eq.bck.com.ua/ - as of September 20, 2016.

Lecture No. 7

Topic: " Industrial production of soft dosage forms" - 2 hours.

Relevance of the topic: Drug technology (industrial technology of drugs) is one of the fundamental technological sciences. It consists of several key aspects that are important for modern medicine and patients: Effectiveness and safety - Modern technologies make it possible to produce drugs with high efficiency and safety for patients. Exact dosage, quality control and the absence of impurities make medicines more effective and safer. Innovations in medicine: New technologies allow the creation of innovative drugs that can be more targeted and effective drug therapy. For example, drugs designed to precisely affect specific cells or genes provide more effective treatments. Minimization of side effects: Technologies make it possible to develop medicinal formulas that minimize side effects and negative effects on the body. This provides a more comfortable and safe treatment for patients. Fast production and delivery process: The use of modern technologies allows to speed up the production process of medicines, which is especially important in the conditions of a rapidly changing medical environment, such as the spread of diseases or epidemics. Individual approach to treatment: Technologies make it possible to develop medicines that take into account the individual characteristics of the patient, which leads to a personalized approach to treatment and increases its effectiveness. Cost-effectiveness and availability Improved manufacturing technologies can reduce production costs, making drugs more accessible to a wide range of patients, providing cost-effectiveness in healthcare.

Thus, the use of modern technologies for the production of medicines is an important factor for improving the effectiveness of treatment, patient safety and the general state of public health.

Goal: to get acquainted with the main stages of the industrial production of soft dosage forms and the discipline "Drug Technology", to describe the pharmaceutical development of soft dosage forms, and to describe the current state of the pharmaceutical industry.

Basic concepts:

Ointment is a soft medicinal form for external use. The ointment consists of a medicinal substance and the so-called medicinal base (vaseline, lanolin, naphthalene, etc.). In their basis, ointments contain fats (pork, beef).

Cream is an emulsion containing half water and half oil. Creams also contain solid particles of drugs intended for absorption by the skin.

Gel is a structured system consisting of high-molecular and low-molecular substances.

The paste is a suspension ointment with the amount of powdery substances, in accordance with the recommendations of the Federal State Administration of Ukraine, more than 20% (previously 25%).

Liniments - medicinal form for external use only (more often, by rubbing) is a liquid ointment or a mixture of various irritating substances with oils, oils with alkali solutions, soap-water or soap-alcohol solutions.

Homogeneity is one of the key properties of space in classical mechanics. It means that the parallel transfer of the closed frame of reference in it as a whole does not change the mechanical properties of the system, and, in particular, does not affect the result of measurements.

Sterility is the absence of viable microorganisms and their spores in the environment, organism, any material or product.

Homogeneous ointments are systems characterized by the absence of an interphase interface between medicinal substances and the base of the ointment.

Heterogeneous ointments are systems that have a phase separation with different boundary layers. These include suspension (or trituration), emulsion and combined ointments .

Plan and organizational structure of the lecture:

No p.p.	**The main stages of the lecture and their content.**	**Goals in levels of abstraction.**	**Type of lecture, lecture equipment.**	**Time allocation.**

1	2	3	4	5
I 1. 2. II 3.	***Preparatory stage*** Determination of educational goals. Providing positive motivation. ***The main stage*** Presentation of lecture material. Plan: 1. What are soft dosage forms and their classification 2. Definition of emulsion, suspension, as LF, scope of application. 3. Features of preparation of emulsion and suspension preparations. 3. Method of obtaining and equipment used in the production of soft dosage forms . 4. By what methods are suspensions and emulsions obtained at	 I II III	 The lecture is combined Slides List of references, questions, assignments.	 1% 2% 90%

	pharmaceutical factories? 5. What factors determine the stability of suspensions and emulsions? 6. What role do auxiliary substances play in the production of suspensions and emulsions 7. What stages does the process of obtaining dispersion preparations consist of? 8. What preparations are used in the production of suspensions and emulsions? 9. What is the principle of operation of turbine mixers and RPA? B. Tests for self-control with standard answers. B. Tasks for self-control with answers. 10. The current state of development of the pharmaceutical industry. ***The final stage*** Summary of the lecture,			

III 4. 5. 6.	general conclusions. Lecturer's answers to possible questions. Tasks for self-training of students.			2% 3% 2%

Structural and logical scheme of the content of the lecture

1. What are soft dosage forms and their classification

2. Definition of emulsion, suspension, as LF, scope of application.

3. Features of preparation of emulsion and suspension preparations.

3. Method of obtaining and equipment used in the production of soft dosage forms .

4. By what methods are suspensions and emulsions obtained at pharmaceutical plants?

5. What factors determine the stability of suspensions and emulsions?

6. What role do auxiliary substances play in the production of suspensions and emulsions

7. What stages does the process of obtaining dispersion preparations consist of?

8. What preparations are used in the production of suspensions and emulsions?

9. What is the principle of operation of turbine mixers and RPA? B. Tests for self-control with standard answers. B. Tasks for self-control with answers.

10. The current state of development of the pharmaceutical industry.

Content of lecture material (lecture text)

Ointment - soft LF, intended for application to the skin, wounds or mucous membranes. Ointments consist of a base and one or more medicinal substances evenly distributed in it. Ointments include stabilizers and preservatives.

Characteristics and classification. Ointments are widely used in various fields of medicine: in the treatment of dermatological diseases, in otolaryngology, surgical,

proctological, gynecological practice, as well as as a means of protecting the skin from adverse external influences (organic substances, acids, alkalis). Recently, ointments are also used to affect the internal organs and the whole body for the purpose of treatment, prevention and diagnosis of diseases.

Medicinal substances belonging to all pharmacological groups are used in the form of ointments: antiseptics, anesthetics, hormones, vitamins, antifungal agents, analgesics , etc.

Depending on the consistency, they distinguish: ointments, pastes, creams, gels, liniments.

Requirements for ointments:

1. They should have a soft consistency for the convenience of applying them to the skin and mucous membranes and forming an even continuous film on the surface.

2. Medicinal substances in ointments should be maximally dispersed and distributed throughout the ointment in order to achieve the necessary therapeutic effect and accuracy of dosage of the medicinal substance.

3. Should they be stable, not contain mechanical inclusions.

4. Their composition should not change during storage and use.

5. The concentration of medicinal substances and the weight of the ointment must correspond to the prescription.

There are several classifications: by place of application, nature of action and type of dispersion system.

At the place of application of the ointment:

- dermatologist
- for the nose
- the dentist of Ichni
- vaginal
- rectal; using special syringes
- urethral and
- rectal and

For example, ointments applied to the mucous membrane are sensitive to microorganisms, so they are prepared in aseptic conditions. In addition, the dispersion of eye ointments is much higher than that of a dermatologist.

According to the nature of the action:

1) ointments that have a local effect on the upper layer of the skin or the surface of the mucous membrane;

2) ointments of resorptive effect (resorption - absorption, absorption), the depth of penetration into the skin or mucous membrane reaches the blood. Beds and exerts an effect on the whole body ("Nitrong" ointment - contains a 2% oil solution of nitroglycerin and is taken for prof. Angina attacks. The effect occurs after 30 - 40 minutes and lasts for 3 - 5 hours).

From the point of view of technology, classification by type of dispersion system is more important:

- homogeneous ointments;
- heterogeneous ointments.

Homogeneous - in them, medicinal substances are distributed in the base according to the type of solution, that is, brought to molecular dispersion.

Heterogeneous - characterized by the presence of an interfacial surface between medicinal substances and the base.

Bases for ointments. The bases provide the necessary weight of the ointment and thus the proper concentration of medicinal substances, a soft consistency, and have a significant impact on the stability of the ointments. The degree of release of medicinal substances from ointments, the speed and completeness of their development largely depend on the nature and properties of the base. For example, boric acid ointment 2% on a consistent emulsion basis shows the same therapeutic activity as a similar ointment of 10% concentration prepared on petroleum jelly. In this way, the ointment should be considered as a whole, and the base as the active part of the ointment. A number of requirements are put forward to the foundations:

- structural and mechanical properties are also necessary ;
- not be exposed to microbial contamination;
- soft consistency

- biological safety ;
- neutral reaction ;
- ease of allocation from the application site ;
- pharmacologically indifferent , should not have an irritating or sensitizing effect, contribute to maintaining the initial pH value of the skin or mucous membrane;
- the properties of the base must correspond to the purpose of the ointment ;
- not change under the influence of environmental factors
- physical and chemical stability
- not to react with medicinal substances introduced into it
- required absorption capacity _ _

a) a soft consistency is necessary for ease of application to the skin and mucous membranes.

b) The chemical inertness of the bases guarantees the absence of interaction with medicinal substances, changes under the influence of external factors (air, light, moisture, temperature) and, therefore, the stability of the ointment is ensured.

c) absence of allergies. irritants and the sensitizing effect of ointments depends on harmless biological bases.

d) it is important that the bases do not disturb the physiological functions of the skin. The outer layer of the skin has an acidic reaction that prevents the reproduction of microorganisms. Therefore, maintaining the original pH value of the skin is of great importance.

e) the presence of microorganisms can be the cause of re-infection of the inflamed skin and mucous membrane, as well as a decrease in the activity of medicinal substances.

e) the issue of ease of removal of ointment residues from linen, skin surface, especially from their fibrous areas is of great importance.

g) the properties of the base must not correspond to the purpose of the ointments.

Bases for surface-acting ointments should not contribute to the deep absorption of medicinal substances. Bases for resorptive ointments, on the contrary, to ensure the absorption of medicinal substances through the skin layer. The bases of protective ointments should dry quickly and adhere tightly to the surface of the skin. Several

classifications of bases for ointments are known: by physical properties, by chemical composition, sources of production, etc.

The most expedient is the classification according to the degree of affinity of the properties of medicinal substances and bases, by the possibility of dissolution of medicinal substances and the base. According to this principle, all ointment bases are divided into 3 groups: lipophilic, hydrophilic, lipophilic-hydrophilic bases.

Classification of ointment bases.

The most progressive classification of ointment bases is a system that takes into account the ability of the base to absorb liquid, which is consistent with the technological principles of ointment production.

According to this classification, ointment bases are divided into four groups: hydrophobic, absorbent, water-washable, water-soluble.

Hydrophobic bases include individual substances and their mixtures with clearly visible hydrophobic properties (vaseline, petrolatum, animal fats, vegetable and mineral oils).

To class *absorption* bases belong to a group of bases capable of incorporating up to 50% or more of water or aqueous solutions of medicinal substances with the formation of emulsions of the w/m type (lanolin, hydrolin).

To the group *sinks* bases include emulsion bases of the m/w type, made with the use of surface-active substances (surfactants), highly hydrophilic inorganic (bentonites), organic (water-soluble cellulose esters) substances and their mixtures.

Water soluble ointment bases unite a large group of hydrophilic bases formed by water-soluble high-molecular compounds of synthetic or natural origin. They also include numerous hydrophilic colloid bases — starch, algin, pectin hydrogels.

:

Bases for ointments		
Lipophilic: 1. Fats and their derivatives (pork fat, vegetable oils, hydrogenated fats)	Hydrophilic: 1. Gels of high molecular weight carbohydrates and proteins (starch, ethers,	Lipophilic-hydrophilic: 1. Adsorption (lipophilic base + surfactant emulsifiers)

2. Waxes (beeswax, spermaceti, lanolin) 3. Hydrocarbon bases (vaseline, petrolatum, paraffin, petroleum jelly, ceresin) 4. Silicone bases (Esyrol - Aerosilna, etc.)	cellulose, gelatin, collagen) 2. Gels of synthetic IUDs (PEO-400, PEO-1500, PEO-4000, PVP, etc.) 3. Gels of inorganic compounds of clay minerals (bentonite bases)	2. Emulsion (lipophilic base + surfactant emulsifiers + water)

Lipophilic bases are chemically heterogeneous substances that have pronounced hydrophobicity.

This includes fats and their derivatives, waxes, hydrocarbons and silicone bases. (Hydrogenated fats are products obtained during the catalytic hydrogenation of vegetable oils. At the same time, unsaturated glycerides turn into marginal ones, and liquid oils change their consistency to soft and hard depending on the degree of hydrogenation. Hydrogenated fats are more stable during storage).

Hydrophilic bases - a characteristic feature is the ability to dissolve in water. Hydrophilic bases do not leave greasy marks, they are better washed off the skin and clothes.

disadvantage is low resistance to microbial contamination. This includes gels of BM of carbohydrates and proteins, synthetic BM, inorganic substances.

Lipophilicity - hydrophilic bases - both water- and fat-soluble substances, aqueous solutions of medicinal substances can be easily introduced into them. Emulsifier surfactant is included as mandatory components.

Technology of ointments.

The main task of the technology in the manufacture of ointments is to ensure that medicinal substances are maximally dispersed and evenly distributed throughout the mass of the base; the consistency of the ointment would ensure ease of application and uniform distribution on the skin or mucous membrane; the stability of the ointment would guarantee the invariance of its composition during application and storage.

The ointment technology consists of the following stages:

1. preparation of the basis for ointments and medicinal substances;

2. introduction of medicinal substances into the base;

3. homogenization of ointments;

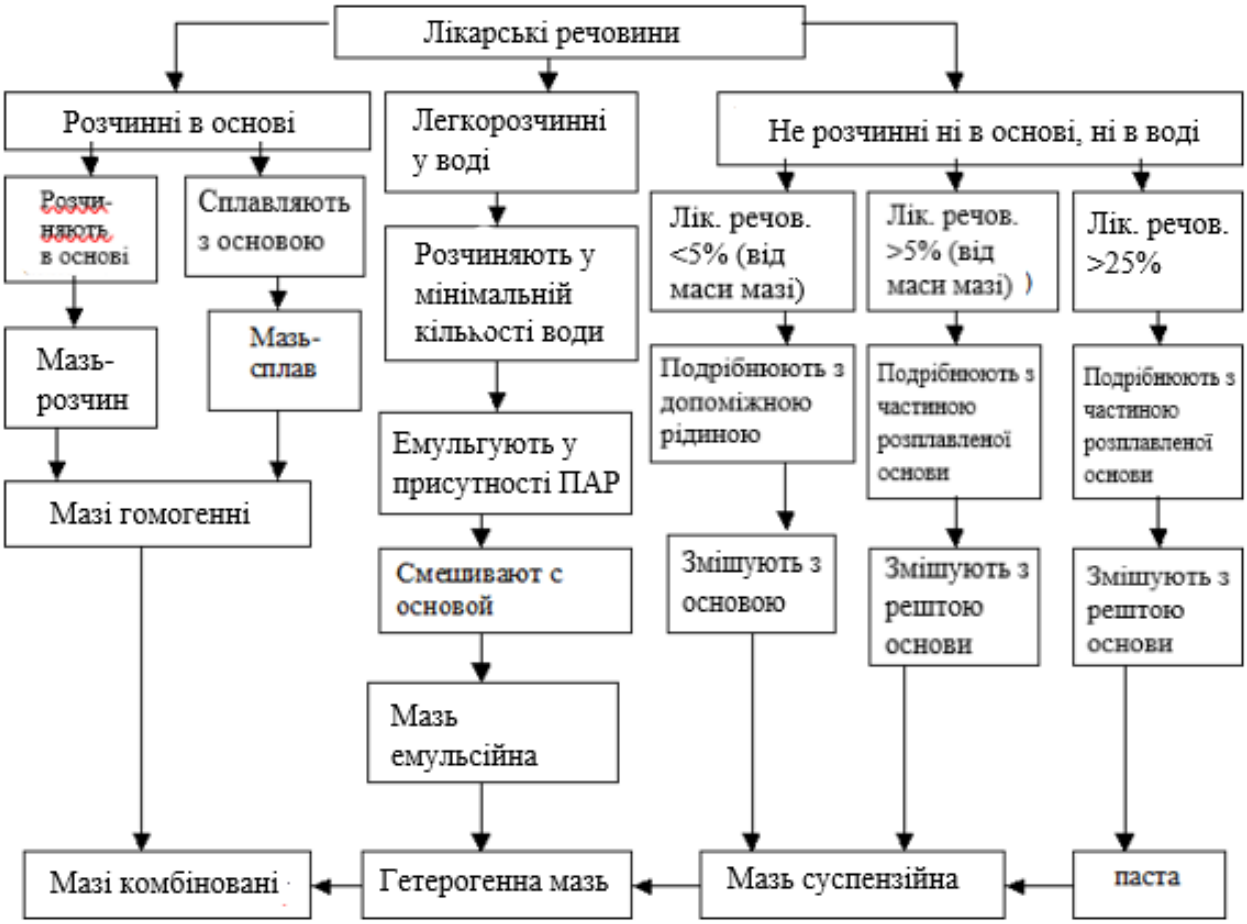
4. standardization;

5. packaging and storage.

1. Preparation of the base for ointments. The base is melted in a barrel or tank (in a ball) and moved to a boiler. If there are several components, melting begins with refractory substances. If necessary, filter the base through cloth or gauze. The medicinal substance is crushed by sifting through a sieve.

2. Introduction of medicinal substances into the base. Addition of medicinal substances to the base is carried out in 2 cylindrical mixers or in reactors with a steam jacket or electric heating, equipped with 3 powerful mixers: anchor, blade, turbine, which ensure good mixing and grinding of the ointment components.

Administration of medicinal substances to the ointment .



· Depending on the method of introduction of medicinal substances and the nature of their distribution in the basis of ointments are classified: homogeneous, suspension, emulsion and combined.

Ointments-alloys (combination of 2 or more solubility components)

homogeneous

Ointments-solutions (contain medicine). Substances dissolved in the base.

The preparation of ointments begins with the melting of the base, after which medicinal substances are dissolved in the obtained melt).

Suspension - ointments containing medicinal substances that are not soluble in water and the base, which are distributed in it in the form of a suspension.

Emulsion- are characterized by the presence of a liquid dispersion phase that does not dissolve in the base and is distributed in it according to the type of emulsion (dispersion phase - H_2O_2, linetol, glycerin, tar, Burov's liquid, as well as solutions of medicinal substances).

Combined - the most complex multicomponent systems contain a liquid and a solid ingredient, one of which dissolves in water, the other in the base, the third - neither there nor there.

3. homogenization of ointments - if it is not possible to obtain the necessary degree of dispersion of medicinal substances during mixing. It is carried out in millstones or roll maseterka, as well as the RPA apparatus.

4. Standardization - the ointment is standardized according to the content of medicinal substances, the pH value and the degree of solid dispersion. parts in suspension ointment.

5. Packaging and storage - in glass jars, p / e and aluminum tubes. Packaging in tubes - with the help of turbo filling machines. Store ointments in a cool place protected from light. The ointment prepared by the pharmacy is kept for 10 days.

The main directions of improving the quality and technology of ointments.

1) expansion of the range of ointment bases and their selection depending on the application of the ointment and the age of the patient.

2) Increased physical stability of suspension and emulsion ointments can be

achieved by adding thickeners, emulsifiers, etc. Excipients.

3) Chemical stability - use of antioxidants (butyloxyanisole, α-tocopherol, etc.)

4) Microbiological stability - with the help of preservatives (0.2% sorbic acid, 1:3 mixture of nipagin and nipazole, 0.9% benzyl alcohol).

5) The problem of packaging - in connection with modern requirements for the level of microbial contamination in non-sterile medicinal products. Combined (laminated) materials are created, combining the best properties of aluminum foil, polymers, and paper. Disposable packaging is created.

Materials on the activation of students of higher education during the lecture: questions, situational tasks, etc.:

Question:

1. What are soft dosage forms and their classification

2. Definition of emulsion, suspension, as LF, scope of application.

3. Features of preparation of emulsion and suspension preparations.

3. Method of obtaining and equipment used in the production of soft dosage forms

.

4. By what methods are suspensions and emulsions obtained at pharmaceutical plants?

5. What factors determine the stability of suspensions and emulsions?

General material and bulk-methodological support of the lecture:

- educational premises - the auditorium of the department;
- equipment - computer, tables;
- equipment – multimedia projector;
- illustrative materials - presentation, slides.

Questions for self-control:

1. Name the drugs produced in the form of MLF.

2. What role do auxiliary substances play in the production of suspensions and emulsions ?

3 . What are the stages of the process of obtaining dispersion preparations?

4 . What drugs are used in the production of suspensions and emulsions?

5. What is the principle of operation of turbine mixers and RPA? B. Tests for self-control with standard answers. B. Tasks for self-control with answers.

6. What are the features of the current state of the pharmaceutical industry?

References:

1. Study guide for independent work of students of the Faculty of Pharmacy for the licensing exam "Step 2. Pharmacy" / V.Yu. Anisimov, O.I. Belyaeva, H.G. Vidavska, V.O. Helmboldt, A.V. Zamkova, I.V. Lytvynchuk, A.V. Nikitin, B.V. Pristupa, I.B. Petkova, Ya.V. Rozhkovskyi, S.B. Strechen, L.M. Unguryan, N.C. Fizor Odesa: Odesa.nats.med. Univ. 2020. - 240 p.

Mode of access to lecture texts for students of the Faculty of Pharmacy: https://info.odmu.edu.ua/chair/drugs/files/390/ua

Literature used by the lecturer to prepare the lecture.

Main:

1. Industrial technology of medicines: a basic textbook for students. Higher. student pharmacy institutions (pharmacological institutions) / E.V. Gladukh, O.A. Ruban, I.V. Saiko et al. - Kh.: NFaU: Original, 2016. - 632p. : Name - (National textbook series)

2. Workshop on industrial technology of medicinal products specialty "Pharmacy" / Ed. Ruban O.A. - Kh .: NFaU, 2015. - 374 p

3 . INDUSTRIAL technology of medicines : education. manual for students' independent work / O. A. RUBAN , V. D. RYBACHUK , L. M. Khohlova etc. - KH.: NATIONAL UNIVERSITY OF UKRAINE, 2015. - 120 p.

- Excipients in the production of drugs: training. manual for students higher pharmacy education closing / O. A. RUBAN , I. M. Pertsev, S. A. Kutsenko, Yu. S. Maslii; under the editorship I. M. Pertseva. – Kh.: Golden Pages, 2016. – 720 p.
- Technology of drugs for industrial production: tutorial. for university students education closing : in 2 parts / V. I. Chuyeshov, E. V. Gladukh, I. V. Saiko and others. – 2nd ed., revision. and additional - Kh.: National University of Applied Sciences: Original, 2012. - Part 1. - 694 p.
- Technology of drugs for industrial production: tutorial. for university students education closing : in 2 parts / V. I. Chuyeshov, E. V. Gladukh, I. V. Saiko

and others. – 2nd ed., revision. and additional - Kh.: National Academy of Sciences: Original, 2013. - Part 2. - 638 p.

- Modern pharmaceutical technologies: education. manual to laboratory classes of full-time, evening and part-time master's students of the specialty 8.110201 "Pharmacy" / under the editorship. O. A. Ruban. - Kh.: Publishing House of the National Academy of Sciences, 2016. - 256 p.
- Encyclopedia of Pharmaceutical Technology: 3-d Ed. / ed. by J. Swarbrick. – New York; London: Informa Healthcare, 2007. – 4128 p.
- European Pharmacopoeia 8.0 [8th edition] / European Directorate for the Quality of Medicines & Healthcare. - Strasbourg, 2013. - 3638 p.
- Handbook of Pharmaceutical Excipients, 6th edition / RC Rowe, PJ Sheskey, ME Quinn. - Pharmaceutical Press and American Pharmacists Association, 2009. - 521 p.
- State Pharmacopoeia of Ukraine / State enterprise " Ukrainian scientific officinal center quality medical means " - 2- e kind . - Kharkiv : State enterprise " Ukrainian scientific officinal center quality medical means ", 2015. - Vol . 1. - 1128 p .
- State Pharmacopoeia of Ukraine / State enterprise " Ukrainian scientific officinal center quality medical means " - 2- e kind . - Kharkiv : State enterprise " Ukrainian scientific officinal center quality medical means ", 2014. - Vol . 2. – 724 s .
- State Pharmacopoeia of Ukraine / State enterprise " Ukrainian scientific officinal center quality medical means " - 2- e kind . - Kharkiv : State enterprise " Ukrainian scientific officinal center quality medical means ", 2015. - Vol . 3. – 732 p .
- About medicinal products: the law of Ukraine dated 04/04/96 No. 123/96 // Bulletin of the Verkhovna Rada of Ukraine. - 1996. - No. 123.
- Zujkina SS The pharmacotechnological studies of the phytospecies composition for the complex therapy of mastopathy / SS Zujkina, LI Vishnevska // Visnyk pharmacy . – 2017. – No. 2 (90). - WITH . 43-47.
- Bogutska , O. _ IS . The main ones directions solution problems pharmaceutical of incompatibilities / O . IS . Bogutska // Contemporary achievement

pharmaceutical technologies and biotechnology : collection scientific works _ – issue 2. – Kharkiv . : Type - in NFaU , 2017. - S. 29–31.

- Polovka N . P. _ Rating biopharmaceuticals factors at developers and production new ones medical means / N. _ P. _ Polovko , L. _ And . Vishnevska , O. _ WITH . Shpychak // Modern achievement pharmaceutical technologies and biotechnology : collection scientific works , issue 2. – X .: Ed NFaU , 2017. - S. 155-160.
- Prospects for the creation of new original drugs based on substances of plant origin / O.A. Ruban, S.A. Malinovska, Murad Al-Tawaiti, S.I. Mazurets // Phytotherapy. – 2012. – No. 2. - pp. 63–65.
- The current state of creation, production and quality control of capsules / M.B. Chubka, L.V. Vronska, N.O. Zarivna et al. // Pharmaceutical journal. 2012. No. 2. P. 165168.
- Murachanian, D. Two-Piece Hard Capsules for Pharmaceutical Formulations / D. Murachanian // Journal of GXP Compliance. 2010. Vol. 14. P. 3142.
- Patel H. New pharmaceutical excipients in solid dosage forms – A review / H. Patel, V. Shah, U. Upadhyay // Int. J. of Pharm. & Life Sci. - 2011. - Vol. 2. – P. 1006–1019.
- Recent Trends of Treatment and Medication Peptic Ulcerative Disorder / D. Bhowmik, Chiranjib, KK Tripathi [et al.] // International Journal of PharmTech Research. - 2010. - Vol. 2. – P. 970–980
- The effects of powder compressibility, speed of capsule filling and pre-compression on plug densification / M. Llusa , E. Faulhammer , S. Biserni [et al.] // Int. J. Pharm. – 2014. – Vol. 471. – P. 182–188.

Electronic information resources

- Lecture materials, methodological developments for seminar classes and independent work at the Department of Social Pharmacy: Access mode: http://socpharm.nuph.edu.ua.
- Scientific library of the National Academy of Sciences: Access mode: http://dspace.ukrfa.kharkov.ua; http://lib.nuph.edu.ua
- www.moz.gov.ua is the official website of the Ministry of Health of Ukraine

- nuph.edu.ua is the official website of the National Pharmaceutical University
- library@nuph.edu.ua - website of the library of the National Academy of Sciences of Ukraine
- The website of the Department of Scientific Research of the National Academy of Sciences of the Russian Academy of Sciences. – Access mode: ztl.nuph.edu.ua.
- The website of the Department of Drug Technologies of ONMedU http://info.odmu.edu.ua/chair/drugs/files/195/ua
- The site of distance learning of the National Academy of Sciences: the page of the ZTL department - [Electronic resource]. – Access mode: http://pharmel.kharkiv.edu/moodle/course/index.php?categoryid=154
- fp.com.ua - website of the magazine "Pharmacist Praktik"
- www.provisor.com.ua – the official website of the magazine "Provisor"
- Compendium: drugs. - [Electronic resource]. - Access mode: http://compendium.com.ua/ - as of October 10, 2016.
- State Register of Medicinal Products of Ukraine. - [Electronic resource]. - Access mode: http://www.drlz.com.ua/ - as of January 10, 2017.

Database "Equalizer" LLC "Business Credit" - [Electronic resource]. - Access mode: http://eq.bck.com.ua/ - as of September 20, 2016.

Lecture No. 8

Topic: " Industrial production of suppositories " - 2 hours.

Relevance of the topic: Drug technology (industrial technology of drugs) is one of the fundamental technological sciences. It consists of several key aspects that are important for modern medicine and patients: Effectiveness and safety - Modern technologies make it possible to produce drugs with high efficiency and safety for patients. Exact dosage, quality control and the absence of impurities make medicines more effective and safer. Innovations in medicine: New technologies allow the creation of innovative drugs that can be more targeted and effective drug therapy. For example,

drugs designed to precisely affect specific cells or genes provide more effective treatments. Minimization of side effects: Technologies make it possible to develop medicinal formulas that minimize side effects and negative effects on the body. This provides a more comfortable and safe treatment for patients. Fast production and delivery process: The use of modern technologies allows to speed up the production process of medicines, which is especially important in the conditions of a rapidly changing medical environment, such as the spread of diseases or epidemics. Individual approach to treatment: Technologies make it possible to develop medicines that take into account the individual characteristics of the patient, which leads to a personalized approach to treatment and increases its effectiveness. Cost-effectiveness and availability Improved manufacturing technologies can reduce production costs, making drugs more accessible to a wide range of patients, providing cost-effectiveness in healthcare.

Thus , the use of modern technologies for the production of medicines is an important factor for improving the effectiveness of treatment, patient safety and the general state of public health.

Goal: Study the general technological scheme of suppositories, familiarize yourself with the proper production rules. To study the industrial methods of manufacturing suppositories with various medicinal and auxiliary substances, to carry out step-by-step control and to be able to standardize the finished product in accordance with the requirements of regulatory and technical documentation, to be able to draw up technological production schemes.

Basic concepts:

Suppositories (from the Latin *Suppositoria* - to place, to place) - a medicinal form known to mankind for more than one millennium. Solid single-dose medicinal products

Rectal suppositories (*Suppositoria rectalia*) are intended for introduction into the rectum.

Vaginal suppositories (*Suppositoria vaginalia*) are used for introduction into the vagina.

Bacilli are intended for introduction into the urethra, cervical canal, fistula and wound passages, auditory hole .

Plan and organizational structure of the lecture:

No p.p.	**The main stages of the lecture and their content.**	**Goals in levels of abstraction.**	**Type of lecture, lecture equipment.**	**Time allocation.**
1	**2**	**3**	**4**	**5**
I	***Preparatory stage***			
1.	Determination of educational goals.		The lecture is combined	1%
2.	Providing positive motivation.			2%
II	***The main stage*** Presentation of lecture material.			90%
3.	Plan: 1. Concept of suppositories .		Slides	
	2. Methods of making suppositories at the factory. .	I		
	3. Storage suppositories **drugs _**	II		
III	***The final stage***			
4.	Summary of the lecture, general conclusions.	III		2%
5.	Lecturer's answers to possible questions.		List of references,	3%

6.	Tasks for self-training of students.		questions, assignments.	2%

Structural and logical scheme of the content of the lecture

1. Concept of suppositories .
2. Methods of making suppositories at the factory. .
3. Storage suppositories drugs _

Content of lecture material (lecture text)

Suppositories (from the Latin *Suppositoria* - to place, to place) - a medicinal form known to mankind for more than one millennium. For the first time, rectal suppositories were mentioned in the oldest papyri, which date back to 2600 BC. e. It is known from 3 written records that in ancient times the inhabitants of Mesopotamia and Egypt used suppositories for treatment, the composition of which included vegetable and animal fats, honey, incense, plant juices, resins, etc. These substances were used as bases until about the 18th century, then until the end of the second decade of the 20th century, only cocoa butter was used as a suppository base. Nowadays, a large number of suppository bases have been introduced, which are characterized by indisputable advantages over cocoa butter.

General properties

Suppositories are solid single-dose medicinal products. The shape, volume and consistency of suppositories should be suitable for rectal use. They contain one or more active substances dispersed or dissolved in a simple or complex base that can dissolve or disperse in water or melt at body temperature.

Rectal suppositories (candles), vaginal suppositories and sticks are distinguished.

Medicines for rectal use can be classified as:

- rectal suppositories;
- rectal capsules;
- rectal solutions and suspensions;
- powders and tablets for the preparation of rectal solutions or suspensions;
- soft drugs for rectal use;

- rectal foams;
- rectal tampons.

Rectal suppositories (*Suppositoria rectalia*) are intended for introduction into the rectum.

Vaginal suppositories (*Suppositoria vaginalia*) are used for insertion into the vagina.

Bacilli are intended for introduction into the urethra, cervical canal, fistula and wound passages, auditory hole .

The general property of suppositories is their ability to be solid at room temperature, and to turn into a liquid at body temperature. This property is important in the medical use of such dosage forms. The hardness of the suppositories makes it possible to overcome the reflex resistance of muscles and tissues, and the liquid consistency in the body cavities - to evenly distribute medicinal substances on the mucous membrane, which can have both local (local) and resorptive (systemic) effects on the body.

In recent years, the industrial production of such dosage forms has increased due to their significant advantages over other forms. Suppositories can be used during emergency care, because their pharmacological effect is revealed much earlier than in oral dosage forms. This is due to the rapid absorption of drugs in the large intestine and their penetration into the blood, bypassing the liver through the middle and lower hemorrhoidal veins. In terms of duration of action, suppositories are similar to injectable drugs, but their administration does not violate the integrity of the skin. In addition, rectal use of drugs very often makes it possible to reduce a single dose due to their prolonged release from suppositories. When administered orally, many drugs are inactivated by enzymes of digestive juices, have an adverse effect on the gastrointestinal tract and liver - rectal dosage forms are free of these defects.

The rate of absorption of drugs from suppositories is influenced by such physiological factors as the state of the rectum, blood circulation of the absorption surface, muscle tone and the layer of mucus on the surface of the walls of the rectum.

The most influential factor in the absorption of active substances from suppositories is the nature of the base, which accounts for up to 90% of the weight of

suppositories. Excipients are in close contact and interact with medicinal products to varying degrees. This determines the degree of their release from the rectal form and affects the completeness and speed of absorption.

Rectal suppositories can have the shape of a cone, a cylinder with a pointed end, or another shape; the maximum diameter usually does not exceed 1.5 cm.

The weight of one suppository should be between 1 and 4 g, length - 2.5-4 cm, with a width at the base of no more than 1.5 cm. The weight of a suppository for children should be from 0.5 to 1.5 g.

Vaginal suppositories can be spherical (balls - *globuli*), egg-shaped (ovules - *ovula*) or have the shape of a tongue - a flat body with a rounded end (pessaries - pessaria). The weight of these dosage forms ranges from 1.5 to b g.

Sticks have the shape of cylinders with a pointed end, 2-5 mm thick and up to 10 cm long.

CHARACTERISTICS OF BASES AND AUXILIARY SUBSTANCES

3 view of physical and chemical science, suppositories are considered as dispersed systems consisting of a dispersed medium, represented by the base, and a dispersed phase, the role of which is performed by medicinal substances. Depending on the properties of medicinal substances, suppositories can create different dispersion systems.

Homogeneous systems are formed in those cases when the medicinal substance is dissolved in the base, and *heterogeneous systems are formed* when medicinal substances are introduced into the base in the form of an emulsion or suspension.

In the structure of suppositories, main (medicinal substances) and auxiliary (carriers or base) components are distinguished.

A number of requirements are put forward to suppository bases:

- they must retain sufficient hardness at room temperature;
- the melting or dissolving temperature should be close to the temperature of the human body;
- should not irritate the mucous membrane of the rectum and cause other undesirable effects, i.e. should be physiologically indifferent;

- should not interfere with the release and therapeutic effect of the medicinal substance;
- should not interact with medicinal substances that are injected into the suppository mass.

The technological requirements for the foundations are closely related to the specified general requirements. These include:

- chemical and physical stability of the base during the manufacturing and storage of suppositories;
- the ability to be easily formed and maintain the required hardness during injection;
- the ability to emulsify the required amount of solutions;
- have a certain plasticity, viscosity, time of complete deformation, i.e. certain structural and mechanical properties.

These requirements are met by lipophilic and hydrophilic bases used in the pharmaceutical industry of various countries.

Lipophilic bases. As suppository bases, DFU suggests using cocoa butter, its alloys with paraffin and hydrogenated fats, vegetable and animal hydrogenated fats, solid fat, lanol, alloys of hydrogenated fats with wax, solid paraffin, and other bases approved for medical use.

Lyophilic bases must meet the following requirements:

- quickly melt in the rectum;
- the melting point should not exceed 37 °C;
- have sufficient hardness and a small interval between the melting and solidification temperatures;
- have sufficient viscosity;
- absorb liquids well;
- be stable during storage.

Nowadays, *cocoa butter remains the official basis in the pharmacopoeias of a number of countries.* It consists of a mixture of triglycerides: tristearin, tripalmetin, triolein, trilaurin, triarachin. The composition of cocoa butter explains the polymorphic modifications of this base with different physical properties.

When this base is melted at a temperature above 36 °C and further cooled under various conditions, as well as when stored at a temperature above 10 °C, cocoa butter changes into a modification with a low melting point (23-24 °C) and a low solidification temperature (17- 18 °C), which causes difficulties in the formation of suppositories. Cocoa butter also poorly emulsifies aqueous solutions, is capable of rancidity due to the high content of oleic acid (about 30%). In addition, it may contain viable pathogenic microorganisms.

To improve the structural and mechanical properties and the ability to release medicinal substances, various auxiliary substances are added to this base: lecithin, white wax, starch, microcrystalline cellulose, aerosol, palm oil.

Laurel petiole oil and coriander oil have approximately the same properties as cocoa butter.

Hydrogenated fats make it possible to create suppository bases free from the defects of cocoa butter. Back in 1934, A. G. Bosin developed the butyrol suppository base — an alloy of hydrogenated fats with paraffin. As a substitute for cocoa butter, alloys of hydrogenated fats with fat-like substances, emulsifiers or hydrocarbon products are now widely used.

In the industrial production of suppositories, the base of the Nizhny Novgorod Chemical and Pharmaceutical Plant is used, which includes 30% cocoa butter, 49-60% hydrogenated sunflower oil and 10-21% paraffin; lanole base consisting of 60-80% lanol (a mixture of esters of phthalic acid and high molecular weight alcohols), 10-20% cooking fat and 10-20% paraffin.

Of particular interest for the industrial production of suppositories is solid confectionery fat based on palm kernel and on the basis of plasticized straw. These fats have a fine-grained crystalline structure that melts in a narrow temperature range without noticeable phase transformations, which favorably distinguishes them from cocoa butter and a number of other suppository bases.

To increase the melting temperature of alloys, wax, paraffin, ozokerite and spermaceti are used. Lanolin, lecithin, cholesterol are introduced for better emulsification of liquids.

Fatty and fat-like bases, depending on the composition, have different viscosity and plasticity, and the choice of the method of manufacturing suppository forms depends on this.

3 well-known foreign lipophilic bases are particularly interesting: Vitepsol, Estarinum, and Lazupol.

Vitepsol, or Imhausen (Germany) is a mixture of triglycerides of lauric and stearic acids, containing additives of the emulsifier monoglycerin ester of lauric acid. The melting point is 33.5-35.5 °C. The time for complete deformation of the foundations is within 15 minutes.

Vitepsol of various groups H, V, S, E is produced, which differ in the range of physical and chemical properties.

Estarinum is produced in the form of several modifications that differ in physical and chemical characteristics. Chemically, the base is a mixture of mono-, di- and triglycerides of saturated fatty acids.

Lazupol consists of esters of phthalic acid with higher alcohols (for example, cetyl and (or) stearyl).

Several modifications of lazupol are produced, differing in melting point (34-37 °C), solidification and ability to emulsify aqueous solutions.

All described foreign lipophilic bases emulsify aqueous solutions of medicinal substances well, harden quickly, and have a melting point close to body temperature.

Hydrophilic bases. Hydrophilic bases must meet the requirements:

- quickly and completely dissolve in mucous membrane secretions;
- do not irritate mucous membranes;
- mix with hydrophobic medicinal substances or absorb them;
- be chemically and pharmacologically indifferent.

Modern hydrophilic bases are represented mainly *by ethylene glycols*, condensed polymers of ethylene oxide and water. Domestic industry produces polyethylene glycols with different molecular weights - PEG-400, -1500, -2000, -4000, -6000.

Abroad, polyethylene glycol bases are known by the name "carbovax" (CTTTA), "scurol" (France), "postonal", "suppofarm" (Germany).

This group of bases is able to dissolve in the secretions of mucous membranes, completely release medicinal substances without irritating the mucous membrane, has a long shelf life, high physiological indifference, and is relatively affordable.

Gelatin-glycerin and *soap-glycerin bases* are much less often used in the production of suppositories, although they are included in the pharmacopoeias of a number of countries.

It should be noted that polyethylene oxide bases are incompatible with salts of argentum, mercury, bromides, iodides, salicylates, phenol, tannin, and some sulfonamides. In addition, this base dissolves slowly and incompletely in the rectum, dehydrates and irritates the mucous membrane.

Gelatin - glycerin base is incompatible with acids, alkalis and astringents. During storage, it dries quickly and becomes moldy.

These foundations have disadvantages: low structural and mechanical properties, insufficient stability, low resorption capacity.

To eliminate these defects and ensure optimal structural and mechanical characteristics of suppository bases, aluminum stearates, magnesium and other salts of fatty acids are added to them, as well as tweens, emulsifiers T-2, No. 1, bentonite, glucose, starch, Aerosil.

Antioxidants, preservatives, and stabilizers are added to prevent instability of bases.

WAYS OF OBTAINING SUPPOSITORIES IN INDUSTRIAL CONDITIONS.

PRODUCTION TECHNOLOGICAL EQUIPMENT

Suppositories in industrial production are made by two methods — *pouring* the molten mass into molds and *pressing* on special equipment.

method **.** Industrial production of suppositories in this way is most often carried out according to a technological scheme, which consists of the following stages:

1. preparation of the base;
2. preparation of medicinal substances and preparation of concentrate;
3. introduction of medicinal substances into the base;

4. formation (and packaging) of suppositories;

5. packaging of suppositories.

First, reactors, various containers, manifolds, pumps and other equipment are prepared for operation by thorough treatment with hot steam, water with detergents, rinsing and drying. Sanitary treatment of premises and training of working personnel are carried out.

Preparation of the base. First, the base components are weighed. In a stainless steel reactor with a steam jacket and a stirrer, the base components are fused at a temperature of 60-70 °C and stirred for 40 minutes. The base is filtered through a filter press, using a brass mesh or belting, and analyzed for melting point, solidification and time of complete deformation and transferred to the hardware department.

Then, with the help of compressed air, the base is fed into the reactor, in which the suppository mass is prepared. After that, medicinal substances are introduced into the mass.

Introduction of medicinal substances into the base. Medicinal substances are introduced into the base in the form of aqueous solutions (water-soluble), fat solutions (fat-soluble) or suspensions of ground powders in bases (insoluble in water and fats). The resulting solutions or suspensions are called *concentrates.*

Water-soluble components are dissolved in water heated to 45 °C, fat-soluble components are dissolved in part of the melted fat base. The resulting concentrates are filtered through calico, and then mixed with the rest of the base.

Substances insoluble in water and base are introduced in the form of a suspension. Pre-ground medicinal substances are mixed in a reactor with an equal or one-and-a-half amount of base heated to a temperature of 40-50 °C. The resulting concentrate is cooled and ground on colloidal mills or, for heat-labile substances, with the help of three-roll maseters. In addition, rotary pulsation devices, rotary gear pumps and other equipment can be used to obtain high-quality suspensions. The grinding time of the concentrate lasts from 2 to 4 hours to obtain the necessary degree of dispersion of the medicinal substance, which is introduced into the basis by the type of suspension.

The finished concentrate is pumped (through a hose with a kapron screen) into a reactor (with a turbine or anchor stirrer) for mixing with the rest of the base. The

operation of preparing the suppository mass is carried out with constant stirring and a temperature of 45-50 °C. After a positive analysis (homogeneity of the mixing of components, temperature of solidification and melting, time of complete deformation), the mass is submitted to the stage of pouring suppositories.

Suppositories are then formed and packaged.

Automatic lines of the "Sarong 200 S" type are used for *pouring suppositories* with direct dosing of the mass into formed cells made of polyvinyl chloride film with further packing of the products into bundles.

3 two rolls (position *1)* are supplied one vertically placed strip of aluminum foil or polyvinyl chloride film. The two strips first pass separately and are cut vertically in the cutting unit (position *2) to achieve perfect forming.* In addition, thanks to the slits, the subsequent detachment of the packed suppositories from the strip is facilitated. In position *3* , both strips are formed (forged) into cup-shaped halves, which are then (position *4)* joined into a complete form and in position 5 are heat-welded. At the same time, the filling hole remains open on top of each form, through which the filling needle (positions *6, 7)* pours the molten cypositor mass. Thus, the packaging formed from foil simultaneously serves as a casting mold. Filling double-walled container 7 contains almost 30 liters of mass. The necessary temperature of the mass is constantly maintained with the help of water heating with a continuously operating stirrer. Dosing is carried out using a pump. At the next position *8* , the package is hermetically closed and equipped (position *9)* with additional transverse stiffening ribs (cold stamping) between separately welded suppositories. Next (positions *10* and *11)* , strips are cut from the tape for a certain number of suppositories (5, *6, 10).* The cut strip enters the cooling section (position *12),* after passing through which a finished package is formed. The outer surface of the foil (thickness 40 μm) is covered with a stretched polypropylene film (12.5 μm), and the inner one is polished for welding when heated or layered with high-pressure polyethylene weighing 20 g/m ^{2} .

The productivity of the line is 16,000—20,000 pieces per hour.

The automatic line "Farmo Dui FD 22/U" (Italy), which has approximately the same scheme, is also used for pouring suppositories . Productivity 22,000-25,000 pieces per hour.

Sometimes the pouring of suppositories is carried out on machines with separate pouring and packing operations. In such cases, *semi-automatic "Franco-Crespi" devices are used.* Rectal and vaginal suppositories are dispensed here without a packaging operation. The device is equipped with:

- two feeding hoppers with steam heating and blade stirrers (70-600 rpm), into which the suppository mass is fed;
- dispenser receivers;
- dosing pumps;
- three synchronously rotating discs;
- nests of metal forms (forms in the number of 36 pieces are located on the two outermost rotating discs);
- refrigeration unit;
- a heated knife to remove excess mass;
- a device for pushing suppositories into receiving collections and trays.

After the suppositories are formed, they are rejected based on their appearance, and their analysis is carried out. Suppositories are dried at a temperature of 10-15 °C for 2-3 hours with additional air blowing to remove cooling and lubricating components.

Ready suppositories are sent for *packing* and *packaging* using semi-automatic machines.

A semi-automatic machine for packing suppositories operates according to the following scheme. Suppositories are manually inserted into the cells of a rotating disk, from which they are pushed out by a horizontal pusher through the entrance hole formed by cellophane strips. The candles are accepted by the holder, the pressing dies cover and pack the candles in cellophane. With the help of a cutting device, they are divided into 5 pieces and cut off.

Packed candles are delivered to the machines, where 10 pieces are placed in cardboard boxes, where an insert sheet is inserted, the serial number and expiration date are placed on the label.

Store finished products in a dry, light-protected place at a temperature not higher than 20 °C, in tightly closed containers. The label additionally states: the name of the

active substance and its content in a unit of the dosed medicinal product; application method; storage conditions; expiration date.

When preparing suppositories by the pouring method, their mass depends on the size of the mold nest (volume), the specific mass of the medicinal substances used, and the base.

First of all, when medicinal substances are part of suppositories in the amount of up to 5%, or are well soluble in the base, you can ignore this insignificant volume that they will occupy in the forms.

Secondly, when substances are included in suppository bases in large quantities, the volume of the base that will be displaced when pouring into forms cannot be neglected. In these cases, it is necessary to find the exact ratio between the volume occupied by medicinal substances and the volume of the base, otherwise the accuracy of the dosage will be violated. This relationship is expressed by the "substitution coefficient" and the "reverse substitution coefficient".

The replacement factor E $_{is\ the\ same}$ is called the amount of a medicinal substance that replaces one mass part of a fatty base with a specific weight of 0.95, that is, this amount of a medicinal substance occupies the same volume as one mass part of a fatty base.

The inverse substitution coefficient 1/E $_{is}$ the amount of fatty base that replaces one mass part of the medicinal substance. That is, the amount of fatty base is equivalent in volume to 1.0 g of medicinal substance.

The table shows the values of *E* and *1/E* $_{ж}$ for medicinal substances that are most often used in suppository dosage forms.

The disadvantage of the pouring method is that delamination of the mass may occur during dosing and solidification, especially in those cases when the suppository mass includes insoluble ingredients with a high density or liquids that do not mix well with water. To prevent this, it is necessary to increase the viscosity of the base, avoid high temperature when pouring the mass and stir the mass before pouring it into molds.

of non-thermal preparation by pressing compositions of cooled and crushed bases with medicinal substances is of great importance in improving the suppository manufacturing technology .

The coefficient of substitution of fatty and gelatin-glycerol bases for some medicinal substances

Medicinal substance	*Well* _	VE"	£ w-g	!/£; the same Mr
Ampiox	1.14	0.88	0.94	1.06
Ampicillin	1.0	1.0	0.826	1.21
Analgin	1.27	0.79	1.05	0.95
Anesthesin	1.33	0.75	1.1	0.91
Antipyrine	1.25	0.80	1.03	0.97
Apilak	1.48	0.68	1.22	0.82
Barbamil	1.81	0.55	1.55	0.67
Barbital	1.06	0.94	0.875	1.14
Sodium barbital	1.81	0.55	1.50	0.67
Benzylpenicillin sodium salt	1,2	0.83	0.99	1.01
Basic bismuth nitrate	4.8	0.21	3.96	0.25
Glucose	1.23	0.81	1.02	0.98
Aluminum-potassium alums	1.8	0.56	0.49	0.67
Dermatol	2.6	0.38	2.15	0.465
Dicloxacycline	1.1	0.91	0.91	ID
Ethacridine lactate	1.50	0.63	1.31	0.76
Euphilinus	1.25	0.80	1.03	0.87
Ichthyol	1.1	0.91	0.91	1.1
Calcium gluconate	2.01	0.50	1.66	0.60
Calcium lactate	1.53	0.65	1.26	0.70
Camphor	0.98	1.02	0.81	1.23
Ascorbic acid	1.73	0.58	1.43	0.70

Boric acid	1.60	0.625	1.32	0.76
Tartaric acid	1.03	0.97	0.85	1.17
Citric acid	1.27	0.79	1.05	0.95
Cocaine hydrochloride	1.18	0.85	0.975	1.025
Xeroform	4.8	0.21	3.96	0.25
Levomycetin	1.59	0.63	1.31	0.76
Foxglove leaf (powder)	1.81	0.55	1.50	0.67
Lincomycin	1.20	0.83	0.99	1.01
Menthol	1.09	0.92	0.90	1.11
Methacycline	1.14	0.88	0.94	1.06
Methacillin	1.08	0.93	0.89	1.12
Morphine hydrochloride	1.18	0.85	0.97	1.03
Sodium bromide	2.22	0.45	1.83	0.546
Sodium bicarbonate	2.12	0.47	1.73	0.57
Sodium salicylate	2.50	0.40	2.06	0.48
Novobiocin sodium	1.20	0.83	0.99	1.01
Novocaine	1.40	0.71	1,156	0.865
Oxacillin	1.04	0.96	0.86	1.16
Castor oil	1.0	1.0	0.826	1.21
Osarsol	1.45	0.69	1.20	0.83
Papaverine hydrochloride	1.59	0.63	1.31	0.76
Paraffin	1.0	1.0	0.826	1.21
Protargol	1.40	0.71	1,156	0.865
Resorcinol	1.41	0.71	1,165	0.858
Sulfur precipitated	1,141	0.71	1,165	0.858

Streptocide	1.61	0.62	1.33	0.75
Tannin	0.90	1.10	0.74	1.35
Theophylline	1.23	0.81	1.02	0.98
Phenyl salicylate	1.40	0.72	1.16	0.86
Phenobarbital	1.40	0.72	1.16	0.86
Phenol	1.10	0.91	0.91	1.10
Ferum lactate	1.59	0.63	1.31	0.76
Furozalidone	1.81	0.55	1.50	0.67
Quinine hydrochloride	1.20	0.83	0.99	1.01
Quinozol	1.36	0.74	1.12	0.89
Chloral hydrate	1.20	0.83	0.99	1.01
Zinc oxide	4.00	0.25	3.30	0.30
Zinc sulfate	2.0	0.50	1.65	0.61

By the method of pressing on eccentric tablet machines, while cooling the punch, matrix and casing, it is possible to obtain from 40 to 100,000 suppositories per hour. The suppository mass is usually cooled in a refrigerator to 3-5 °C, crushed and sieved. Lactose, sucrose, aerosol, starch are added to the granulate to adjust the technological properties.

The advantage of this method is the ability to prevent the destruction of heat-labile medicinal substances, the absence of sedimentation of the active substance and to avoid its possible incompatibility with the molten suppository base.

This method can be used when using plastic bases. Since the mass is dosed by volume, it is necessary to use the coefficient of substitution of medicinal substances.

In the process of manufacturing pressed suppositories, it is not necessary to apply significant forces for pushing out, because the particles of the fat base play the role of an effective lubricant in the wall layer due to their intensive plastic flow.

The pressing method is particularly suitable for the production of suppositories with cardiac glycosides, some thermolabile hormonal drugs, and biogenic stimulants,

because the preparation process ensures high dosage accuracy and thermal stability of medicinal substances.

STANDARDIZATION OF SUPPOSITORS. NOMENCLATURE

According to the State Pharmacopoeia of Ukraine, suppositories are controlled by the following indicators: description, identification of active substances and antimicrobial preservatives, average weight and uniformity of mass, disintegration, uniformity of content, melting temperature or time of complete deformation, dissolution, accompanying impurities, microbiological purity, quantitative determination of active substances and antimicrobial preservatives. If necessary, the acid and peroxide numbers, as well as the particle size, are additionally controlled.

Suppositories should be uniform. Homogeneity is determined visually, there should be no inclusions on the longitudinal section.

uniformity or average mass is determined by weighing 20 suppositories with an accuracy of 0.01 g. The deviation in mass should not exceed ±5%. If there are no other indications, suppositories with an active substance content of less than 2 mg or less than 2% of the total mass must pass the test for the homogeneity of the active substance content in a unit of a dosed medicinal product.

For suppositories made on lipophilic bases, the melting temperature is determined, which should not exceed 37 °C. The melting temperature is measured by the open capillary method (DFU, item 2.2.15).

If it is difficult to determine the melting temperature, determine the time of complete deformation, which should be no more than 15 minutes.

Determination of the time of complete deformation is carried out according to the methodology of Appendix 1 to the article "Medicines for rectal use" (DFU).

For suppositories that are made on hydrophilic bases, the dissolution time is determined according to the method of the "Dissolution" test for solid dosage forms (DFU, clause 2.9.3). The dissolution time should be no more than 60 minutes.

The test for disintegration of suppositories is carried out according to the method "Disintegration of suppositories and pessaries" (DFU, clause 2.9.2). Fat-based suppositories should disintegrate in 30 minutes, and hydrophilic ones - after 60 minutes.

Nomenclature of suppositories. The following names (examples of spellings) are included in the nomenclature of suppositories and vaginal balls of industrial production:

Cefecon (Suppositoria "Cefeconum"). Composition: salicylamide 0.6g, amidopyrin 0.2g, phenacytin 0.2g, caffeine (or caffeine sodium benzoate) 0.05g.

Bethiol (Suppositoria "Bethiolum"). Composition: belladonna extract 0.15 g, ichthyol 0.2 g.

Anusol (Suppositoria «Anusolum»). Composition: belladonna extract 0.02g (or 0.015g), xeroform 0.1g, zinc sulfate 0.05g, glycerin 0.12g.

Anestezol (Suppositoria "Anaesthesolum"). Composition: anesthesin 0.1g, dermatol 0.04g, menthol 0.004g, zinc oxide 0.02g.

Suppositories with glycerin (SuppositoriacumGlycerino). Composition: glycerin 1.44g (or 2.46g), stearic acid 0.12g (or 0.25g), sodium carbonate crystalline 0.06g (or 0.13g).

Suppositories with digitoxin (SuppositoriacumDigitoxino) contain digitoxin 0.00015g.

Candles antiseptic biological (Suppositoria antiseptica biologica). Composition: dry mixture of bovine plasma and thromboplastin 0.9g, chloramphenicol 0.02g, novocaine 0.12g, belladonna extract 0.015g.

Apilacum suppositories (Suppositoria «Apilacum») contain 0.005g (or 0.01g) of lyophilized apilac.

Neo - Anuzol (Suppositories "Neo-Anusolum"). Composition: zinc oxide 0.2g, basic bismuth nitrate 0.075g, tannin 0.05g, iodine 0.005g, resorcinol 0.005g, methylene blue 0.003g.

Suppositories with ichthyol (SuppositoriacumIchthyolo) contain **0.2** g of ichthyol.

Osarbon (Giobuli «Osarbonum»). Composition: 0.35 g of osarsol, 0.3 g of boric acid , 0.3 g of glucose.

Osarcid (globuli «Osarcidum»). Composition: osarsol 0.3g, glucose 0.2g, boric acid 0.3g, streptocide 0.3 Mr.

Prospects for the development of rectal dosage forms

Rectal suppositories are a promising drug form that is developing in several directions.

Lyophilized suppositories. Due to the porous structure and large internal surface, such suppositories quickly disintegrate in a small amount of secretion of the mucous membrane of the rectum and release the medicinal substances contained in them. They are made from aqueous suspensions or emulsions of auxiliary and medicinal substances; after pouring into molds, they are subject to deep freezing (lyophilization).

Porous suppositories. To increase the contact surface of the mucous membrane of the rectum with the inserted suppositories and to accelerate the release of medicinal components, porous suppositories are proposed, which are made by pouring the molten mass into molds with subsequent vacuuming at a vacuum depth of 80 kPa **(600** mm Hg).

Hollow suppositories are filled with emulsions, suspensions or solutions of medicinal substances, which also contribute to faster release of medicinal substances.

Multilayer suppositories. Two- and multilayer suppositories are patented in a number of countries. The shell of such suppositories is made from a base of less high melting point. It contains medicinal substances of local action (anesthesin, belladonna extract). Substances that have a resorptive effect on the body are injected into the core. A base with a higher melting point is used for the rod.

Suppositories with film coatings. Controlled delivery of medicinal substances during rectal administration can be carried out using suppositories with film coatings that slow down the diffusion of the active component, or by placing suppositories in capsules.

Colored suppositories. The color of suppositories is of great importance, intended not so much for visual identification of different pharmacological groups of substances, but for protecting suppositories from the influence of a certain spectrum of rays that cause oxidation and destruction of the incoming components.

Production of rectal ointments, capsules, aerosols, tampons

Soft drugs for rectal use have recently become widespread in medical practice. They are represented by creams, gels, ointments and are single-dose medicinal products in containers equipped with appropriate applicators.

Significantly, up to 50 g, one-time administration of soft medicine by itself allows you to increase the amount of the applied medicinal substance . In addition, the large amount of base in these medicinal forms allows prescribing medicinal substances that may cause irritation with other methods of administration.

Rectal capsules are one of the promising dosage forms. This is a solid single-dose dosage form, basically similar to soft capsules. They are containers made of a gelatin film in the form of a suppository, filled with a single dose of a medicinal substance in the form of a liniment, ointment, emulsion or solution. The shell of the capsules is prepared from the highest grades of gelatin with the addition of 30-36% glycerin, which ensures the elasticity and relative strength of the capsules, as well as their relatively quick dissolution in the rectum. The advantages of this rectal form include the possibility of choosing available bases, a wider temperature range of storage and use compared to suppositories, full mechanization and automation of the encapsulation process.

Rectal solutions and suspensions (enemas) are liquid medicinal products intended for introduction into the rectum in order to obtain a general or local effect. They can be used for diagnostic purposes . It is known that medicinal substances are absorbed very quickly from aqueous solutions introduced into the rectum in the form of an enema. However, part of the solution spills out. In such cases, medicinal solutions are more convenient to enter with the help of rectal pipettes-rectiols, which consist of an elastic canister with a tip. The canister is made in the form of a corrugated container with a capacity of 2.5-5 ml. The tip is rigidly attached to it and made of polyethylene. The use of oleogels, liniments, and ointments to fill rectiols opens up wide possibilities for expanding the range of proctological dosage forms. Rectal solutions and suspensions are produced in containers with a capacity of 2.5 ml to 2000 ml.

Rectal tampons are a solid single-dose dosage form designed to be inserted into the lower part of the rectum for a certain period of time. They are a plastic rod wrapped in cotton wool with medicinal substances adsorbed on it. A cotton swab is covered with

a thin layer of alginate. Before use, the tampon is immersed in water for some time, as a result of which the alginate shell swells and does not interfere with the diffusion process of the medicinal substance. A tampon is inserted into the rectum for 2 hours. Used, as a rule, for the treatment of hemorrhoids.

Rectal foams have developed intensively in our time. Foams are advantageously different from other medicinal forms used in proctology. Ointments and creams do not penetrate into the folds of mucous membranes and into deeper areas of the intestine. Suppositories do not provide treatment of all areas of the anal canal; they are characterized by a more short-term therapeutic effect in comparison with foams.

Foams are formed at the exit from the aerosol package, if the composition of the concentrate includes a foaming agent (its role is performed by surfactants) and an emulsified or dissolved propellant (as a rule, liquefied gas under pressure). After release through the valve-spray system of the aerosol can, the propellant evaporates and the gas bubbles, increasing in volume, form a foam — a coarse dispersion of propellant vapors in an emulsion or other type of system.

Foams occupy a large volume with a low specific mass. This allows small amounts of emulsion converted **into** foam to treat large surfaces or fill large volumes. The foam is applied locally and painlessly to the affected surface, providing heat and gas exchange and creating a barrier for infection of the wound from the outside.

The presence of surfactant gives it excellent adhesion and the ability to clean the affected surface from necrotic tissues; expanding, foam penetrates into wound pockets and cavities. With the correct choice of auxiliary substances, foams remain stable for a long time, ensuring the prolongation of the effect of medicinal products. A small amount of the drug when turning into foam occupies a large volume, but the concentration of medicinal substances in the intermembrane fluid remains high.

Various dispersed systems can be converted into foam: solutions, emulsions, suspensions, which opens up great opportunities for creating combined preparations.

Foam preparations in aerosol packaging, which are used in proctology, contain antiseptics, anesthetics, corticosteroids, anti-inflammatory substances of a non-steroidal structure. More details about foam preparations in aerosol packaging are described in the chapter "Medicines under pressure".

Materials on the activation of students of higher education during the lecture: questions, situational tasks, etc.:

Question:

1. What are suppositories?
2. Main groups of suppositories.
3. Specify the basis for the manufacture of MLF suppositories.
4. Explain the purpose of excipients. In what cases are they used?
5. Give examples of auxiliary substances.
6. What is the pH value of suppositories?
7. How can the technological properties of suppositories be improved? **General material and bulk-methodological support of the lecture:**

- educational premises - the auditorium of the department;
- equipment - computer, tables;
- equipment – multimedia projector;
- illustrative materials - presentation, slides.

Questions for self-control:

1. What are the quality requirements for suppositories presented by the State Federal Office of Ukraine?
2. Assess the prospects of industrial production of suppositories.
3. What does the process of obtaining different suppositories consist of?
4. Name the drugs produced in the form of suppositories.

References:

1. Study guide for independent work of students of the Faculty of Pharmacy for the licensing exam "Step 2. Pharmacy" / V.Yu. Anisimov, O.I. Belyaeva, H.G. Vidavska, V.O. Helmboldt, A.V. Zamkova, I.V. Lytvynchuk, A.V. Nikitin, B.V. Pristupa, I.B. Petkova, Ya.V. Rozhkovskyi, S.B. Strechen, L.M. Unguryan, N.C. Fizor Odesa: Odesa.nats.med. Univ. 2020. - 240 p.

Mode of access to lecture texts for students of the Faculty of Pharmacy: https://info.odmu.edu.ua/chair/drugs/files/390/ua

Literature used by the lecturer to prepare the lecture.

Main:

1. Industrial technology of medicines: a basic textbook for students. Higher. student pharmacy institutions (pharmacological institutions) / E.V. Gladukh, O.A. Ruban, I.V. Saiko et al. - Kh.: NFaU: Original, 2016. - 632p. : Name - (National textbook series)

2. Workshop on industrial technology of medicinal products specialty "Pharmacy" / Ed. Ruban O.A. - Kh .: NFaU, 2015. - 374 p

3 . INDUSTRIAL technology of medicines : education. manual for students' independent work / O. A. RUBAN , V. D. RYBACHUK , L. M. Khohlova etc. - KH.: NATIONAL UNIVERSITY OF UKRAINE, 2015. - 120 p.

- Excipients in the production of drugs: training. manual for students higher pharmacy education closing / O. A. RUBAN , I. M. Pertsev, S. A. Kutsenko, Yu. S. Maslii; under the editorship I. M. Pertseva. – Kh.: Golden Pages, 2016. – 720 p.
- Technology of drugs for industrial production: tutorial. for university students education closing : in 2 parts / V. I. Chuyeshov, E. V. Gladukh, I. V. Saiko and others. – 2nd ed., revision. and additional - Kh.: National University of Applied Sciences: Original, 2012. - Part 1. - 694 p.
- Technology of drugs for industrial production: tutorial. for university students education closing : in 2 parts / V. I. Chuyeshov, E. V. Gladukh, I. V. Saiko and others. – 2nd ed., revision. and additional - Kh.: National Academy of Sciences: Original, 2013. - Part 2. - 638 p.
- Modern pharmaceutical technologies: education. manual to laboratory classes of full-time, evening and part-time master's students of the specialty 8.110201 "Pharmacy" / under the editorship. O. A. Ruban. - Kh.: Publishing House of the National Academy of Sciences, 2016. - 256 p.
- Encyclopedia of Pharmaceutical Technology: 3-d Ed. / ed. by J. Swarbrick. – New York; London: Informa Healthcare, 2007. – 4128 p.
- European Pharmacopoeia 8.0 [8th edition] / European Directorate for the Quality of Medicines & Healthcare. - Strasbourg, 2013. - 3638 p.
- Handbook of Pharmaceutical Excipients, 6th edition / RC Rowe, PJ Sheskey, ME Quinn. - Pharmaceutical Press and American Pharmacists Association, 2009. - 521 p.

- State Pharmacopoeia of Ukraine / State enterprise " Ukrainian scientific officinal center quality medical means " - 2- e kind . - Kharkiv : State enterprise " Ukrainian scientific officinal center quality medical means ", 2015. - Vol . 1. - 1128 p .
- State Pharmacopoeia of Ukraine / State enterprise " Ukrainian scientific officinal center quality medical means " - 2- e kind . - Kharkiv : State enterprise " Ukrainian scientific officinal center quality medical means ", 2014. - Vol . 2. – 724 s .
- State Pharmacopoeia of Ukraine / State enterprise " Ukrainian scientific officinal center quality medical means " - 2- e kind . - Kharkiv : State enterprise " Ukrainian scientific officinal center quality medical means ", 2015. - Vol . 3. – 732 p .
- About medicinal products: the law of Ukraine dated 04/04/96 No. 123/96 // Bulletin of the Verkhovna Rada of Ukraine. - 1996. - No. 123.
- Zujkina SS The pharmacotechnological studies of the phytospecies composition for the complex therapy of mastopathy / SS Zujkina, LI Vishnevska // Visnyk pharmacy . – 2017. – No. 2 (90). - WITH . 43-47.
- Bogutska , O. _ IS . The main ones directions solution problems pharmaceutical of incompatibilities / O . IS . Bogutska // Contemporary achievement pharmaceutical technologies and biotechnology : collection scientific works _ – issue 2. – Kharkiv . : Type - in NFaU , 2017. - S. 29–31.
- Polovka N . P. _ Rating biopharmaceuticals factors at developers and production new ones medical means / N. _ P. _ Polovko , L. _ And . Vishnevska , O. _ WITH . Shpychak // Modern achievement pharmaceutical technologies and biotechnology : collection scientific works , issue 2. – X .: Ed NFaU , 2017. - S. 155-160.
- Prospects for the creation of new original drugs based on substances of plant origin / O.A. Ruban, S.A. Malinovska, Murad Al-Tawaiti, S.I. Mazurets // Phytotherapy. – 2012. – No. 2. - pp. 63–65.
- The current state of creation, production and quality control of capsules / M.B. Chubka, L.V. Vronska, N.O. Zarivna et al. // Pharmaceutical journal. 2012. No. 2. P. 165168.

- Murachanian, D. Two-Piece Hard Capsules for Pharmaceutical Formulations / D. Murachanian // Journal of GXP Compliance. 2010. Vol. 14. P. 3142.
- Patel H. New pharmaceutical excipients in solid dosage forms – A review / H. Patel, V. Shah, U. Upadhyay // Int. J. of Pharm. & Life Sci. - 2011. - Vol. 2. – P. 1006–1019.
- Recent Trends of Treatment and Medication Peptic Ulcerative Disorder / D. Bhowmik, Chiranjib, KK Tripathi [et al.] // International Journal of PharmTech Research. - 2010. - Vol. 2. – P. 970–980
- The effects of powder compressibility, speed of capsule filling and pre-compression on plug densification / M. Llusa , E. Faulhammer , S. Biserni [et al.] // Int. J. Pharm. – 2014. – Vol. 471. – P. 182–188.

Electronic information resources

- Lecture materials, methodological developments for seminar classes and independent work at the Department of Social Pharmacy: Access mode: http://socpharm.nuph.edu.ua.
- Scientific library of the National Academy of Sciences: Access mode: http://dspace.ukrfa.kharkov.ua; http://lib.nuph.edu.ua
- www.moz.gov.ua is the official website of the Ministry of Health of Ukraine
- nuph.edu.ua is the official website of the National Pharmaceutical University
- library@nuph.edu.ua - website of the library of the National Academy of Sciences of Ukraine
- The website of the Department of Scientific Research of the National Academy of Sciences of the Russian Academy of Sciences. – Access mode: ztl.nuph.edu.ua.
- The website of the Department of Drug Technologies of ONMedU http://info.odmu.edu.ua/chair/drugs/files/195/ua
- The site of distance learning of the National Academy of Sciences: the page of the ZTL department - [Electronic resource]. – Access mode: http://pharmel.kharkiv.edu/moodle/course/index.php?categoryid=154
- fp.com.ua - website of the magazine "Pharmacist Praktik"

- www.provisor.com.ua – the official website of the magazine "Provisor"
- Compendium: drugs. - [Electronic resource]. - Access mode: http://compendium.com.ua/ - as of October 10, 2016.
- State Register of Medicinal Products of Ukraine. - [Electronic resource]. - Access mode: http://www.drlz.com.ua/ - as of January 10, 2017.

Database "Equalizer" LLC "Business Credit" - [Electronic resource]. - Access mode: http://eq.bck.com.ua/ - as of September 20, 2016.

Lecture No. 9

Topic: " Production of TTS plasters" - 2 hours.

Relevance of the topic: Drug technology (industrial technology of drugs) is one of the fundamental technological sciences. It consists of several key aspects that are important for modern medicine and patients: Effectiveness and safety - Modern technologies make it possible to produce drugs with high efficiency and safety for patients. Exact dosage, quality control and the absence of impurities make medicines more effective and safer. Innovations in medicine: New technologies allow the creation of innovative drugs that can be more targeted and effective drug therapy. For example, drugs designed to precisely affect specific cells or genes provide more effective treatments. Minimization of side effects: Technologies make it possible to develop medicinal formulas that minimize side effects and negative effects on the body. This provides a more comfortable and safe treatment for patients. Fast production and delivery process: The use of modern technologies allows to speed up the production process of medicines, which is especially important in the conditions of a rapidly changing medical environment, such as the spread of diseases or epidemics. Individual approach to treatment: Technologies make it possible to develop medicines that take into account the individual characteristics of the patient, which leads to a personalized approach to treatment and increases its effectiveness. Cost-effectiveness and availability Improved manufacturing technologies can reduce production costs, making drugs more accessible to a wide range of patients, providing cost-effectiveness in healthcare.

Thus , the use of modern technologies for the production of medicines is an important factor for improving the effectiveness of treatment, patient safety and the general state of public health.

Goal: get acquainted with the main stages of the industrial production of dosage forms and the discipline "Drug Technology", describe the production of TTS plasters and describe the current state of the pharmaceutical industry.

Basic concepts:

Plasters (Emplastra) are a medicinal form for external use that adheres to the skin, affects the skin, subcutaneous tissues, and in some cases has a general effect on the body. This is one of the oldest medicinal forms.

Corn plaster (Emplastrum ad clavos) — contains *:* salicylic acid 20.0 parts; rosin 27.0 parts; paraffin 26.0 parts; petrolatum 27.0 parts.

Lead plasters contain lead soap. Pig soaps fuse with resins, waxes, medicinal products , do not stain clothes, and are stable during storage.

Leucoplastrum (*Leucoplastrum*). Sticky patch elastic smeared (Emplastrumadhaesikeonkaasticumextensum). The patch has the following *composition:* 25.7 parts of natural rubber; rosin 20.35 parts; zinc oxide 32 parts; anhydrous lanolin 9.9 parts; liquid paraffin 11.3 parts; of neozone D 0.75 parts.

Cerigelum contains: polyvinyl butyral 4.0 parts; 0.2 parts of cytylpyridinium chloride; 96% ethyl alcohol 100.0 parts. Glue is a colorless, opalescent, slightly viscous liquid with an alcohol smell.

Basic concepts:

Plan and organizational structure of the lecture:

No p.p.	**The main stages of the lecture and their content.**	**Goals in levels of abstraction.**	**Type of lecture, lecture equipment.**	**allocation .**
1	**2**	**3**	**4**	**5**

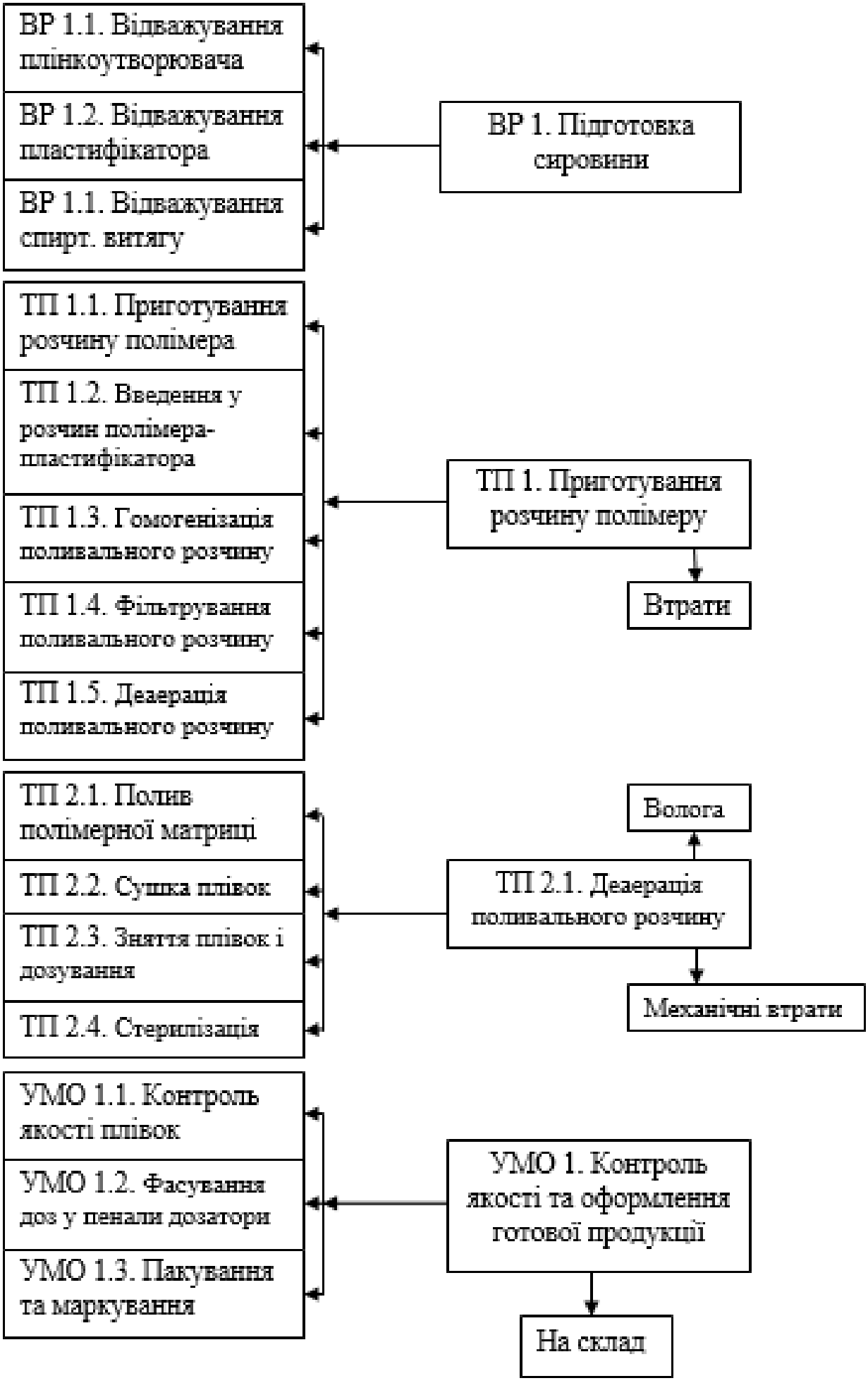
I	***Preparatory stage***			
1.	Determination of educational goals.		The lecture is combined	1%
2.	Providing positive motivation.			2%
	The main stage			
	Presentation of lecture material.			90%
II	Plan:		Slides	
3.	1. Patches 2. Lead plasters 3. Rubber patches 4. Liquid plasters or leather glues	I		
	The final stage	II		
III	Summary of the lecture,			
4.	general conclusions.			2%
5.	Lecturer's answers to possible questions.	III		3%
6.	Tasks for self-training of students.		List of references, questions, assignments.	2%

Structural and logical scheme of the content of the lecture

1. Patches
2. Lead plasters
3. Rubber patches
4. Liquid plasters or leather glues

Content of lecture material (lecture text)

STRUCTURAL AND LOGIC SCHEME OF PHYTOFILM TECHNOLOGY FOR TREATMENT OF THERMAL BURNS


ВР 1.1. Відважування плінкоутворювача
ВР 1.2. Відважування пластифікатора
ВР 1.1. Відважування спирт. витягу
ВР 1. Підготовка сировини
ТП 1.1. Приготування розчину полімера
ТП 1.2. Введення у розчин полімера-пластифікатора
ТП 1.3. Гомогенізація поливального розчину
ТП 1.4. Фільтрування поливального розчину
ТП 1.5. Деаерація поливального розчину
ТП 1. Приготування розчину полімеру
Втрати
ТП 2.1. Полив полімерної матриці
ТП 2.2. Сушка плівок
ТП 2.3. Зняття плівок і дозування
ТП 2.4. Стерилізація
Волога
ТП 2.1. Деаерація поливального розчину
Механічні втрати
УМО 1.1. Контроль якості плівок
УМО 1.2. Фасування доз у пенали дозатори
УМО 1.3. Пакування та маркування
УМО 1. Контроль якості та оформлення готової продукції
На склад

1. Patches

Modern pharmaceutical technology considers the creation of new dosage forms with high therapeutic activity, which ensure the controlled release of drugs and their specific delivery to the site of the pathological process, as one of the basic tasks. This is extremely important because; there are such groups of serious chronic diseases, to overcome which one should take into account not only the effect of the medicinal product itself, but also the method of its delivery to the body. Such a serious disease, characteristic of our time, is atherosclerosis, the social significance of which, unfortunately, is great. One of the reasons for its dominant role in a number of modern pathologies is insufficiently effective pharmacotherapy. Medicines for the treatment and prevention of atherosclerosis are not so many, and the assortment of medicinal forms is limited to tablets or injectable solutions. Statins and fibrates are currently the most common drugs with hypolipidemic effect, but domestic drugs such as diisopropylammonium dichloroacetate (DIPROMIST-ny) are also known, which is low-toxic, and the synthesis is inexpensive and simple. However, when it is taken orally, side effects in the gastrointestinal tract are possible, so it is not widely used in the form of traditional medicinal forms - tablets. Therefore, the improvement of this medicinal product due to the development of original and effective dosage forms is relevant and possible.

Among the various drug delivery systems, transder formal therapeutic systems (TTS), which are alternative forms of oral and parenteral traditional medicinal forms, are the most widespread, have expressed scientific and industrial potential, and have achieved commercial success. at a rate that creates a constant level of drug concentration in the bloodstream, close to the minimum therapeutic level. TTS have many indisputable advantages and obvious advantages over other dosage forms and therefore can be used for drugs, the oral route of administration of which is not very effective, and the injection route is not gentle enough.

By its structure and design, the transdermal therapeutic system is a patch. Therefore, quite often in the literature you can find "intersection" of the concepts of TTS and transdermal patch, which is really the main model of modern TTS.

Despite all the advantages of transdermal patches, which provide the necessary effect by penetrating the active substance through the intact skin, their manufacturers are mainly companies from France, Germany, Japan, and Sweden.

Therefore, the study of the possibility of using a transdermal patch as a dosage form for hypolipidemic drugs, in particular for dipromonium, is an urgent and significant issue from a scientific and practical point of view.

Plasters (*Emplastra*) is a medicinal form for external use that sticks to the skin, affects the skin, subcutaneous tissues, and in some cases has a general effect on the body. This is one of the oldest medicinal forms.

Plasters at room temperature have the appearance of a solid mass. They soften at body temperature, and melt at 65-100 ° C . Under these conditions, they can be alloyed with various medicinal and auxiliary substances and mixed with powdered materials. In addition, plasters can be produced in the form of liquids, in glass bottles, aluminum tubes, aerosol cans.

Depending on the medical Patches are divided into epidermal, endermatic and diadermal.

Epidermal patches used to protect the skin from harmful effects, to close skin defects, bring together the edges of wounds and fix bandages on the surface of the skin.

Endermal patches contain medicinal substances that affect the diseased skin.

Diadermic plasters contain medicinal substances that penetrate through the skin and affect deep-seated tissues, or have a general effect on the body.

Epidermal patches should have good stickiness, adhere tightly to the skin and not irritate it. They may not contain medicinal substances, acting as a dressing material. As a result of the "greenhouse" effect, epidermal patches contribute to the softening of the skin, strengthen the processes of blood circulation and absorption. Endermic and diadermic plasters are softer in consistency, because they should ensure the maximum release of medicinal substances and their penetration to different depths of the tissue or provide a resorptive effect.

Plasters are produced in the form of a plastic mass on a substrate (canvas, chiffon, colencor, paper and others); solid plaster masses (cylinders, bars, tiles, sticks); liquid solutions (leather glues).

The composition of the plaster mass includes medicinal substances and a base. Antibiotics, sulfur, salicylic acid, extracts, tinctures, etc. are used as medicinal substances.

The patch base may contain natural (rosin) and synthetic resins, wax, paraffin, ceresin, petroleum jelly, lanolin, lead salts of higher fatty acids (lead soap), fats, rubber, nitrocellulose, copolymers of vinylpyrrolidone with vinyl acetate, polymethacrylates and acrylates, volatile solvents (ether, gasoline, ethanol). Its composition includes plasticizers (linetol, vegetable oils, dibutyl phthalate, cetyl alcohol, and others), antioxidants, fillers, etc.

Depending on the composition, plasters are classified as lead (lead-resin and lead-wax); resin-waxy; rubber; liquid (leather glues).

The technology of making plasters depends on which group they belong to.

2. *Lead plasters*

Lead plasters contain lead soap. Lead soaps fuse with resins, waxes, medicinal substances, do not contaminate clothes, and are stable during storage.

A simple lead plaster (*Emplastrum Plumbisimplex*). A homogeneous solid mass of grayish or yellowish color, becomes viscous and sticky when heated. The drug should not be greasy to the touch and have a bitter smell.

It is used as a basis for preparing other plasters and externally for purulent-inflammatory skin diseases, boils, carbuncles, etc.

Storage: lead oxide (lead lead) — 10.0 d; sunflower oil - 10.0 d; purified pork fat - 10.0 d; a sufficient amount of purified water.

Chemically, the patch is a mixture of lead salts. The basis of the industrial method of plaster production is the saponification reaction of lead fats with oxide in the presence of water at the boiling temperature of the mass. The main equipment is enameled or stainless steel reactors (the use of copper and tinned copper boilers is excluded), which have a steam jacket and a stirrer.

Preparation of a simple lead patch. The calculated amount of pork fat is placed in the reactor and sunflower oil is melted, adjusting the temperature by the supply of dead steam. The volume of the reactor should exceed the amount of the reaction mass by at least 4-5 times, because the mass foams strongly during cooking. Lead lead is

ground into a fine powder, sifted through a silk sieve and mixed with two parts of freshly boiled purified water. A suspension of lead oxide in water is added to the melted, but not overheated mixture of fats in portions without residue with constant stirring and heating. At the same time, a saponification reaction takes place, as a result of which a fatty lead salt (lead soap) is formed. Chemically, lead plaster is a mixture of lead salts of oleic, palmitic and stearic acids with a significant preference for the latter.

The cooking process must be carried out at a temperature of 100 — 110 °C within 2-3 hours. During the cooking process, hot water is added in small portions to the reaction mass every 5 minutes, making sure that it does not boil completely, as evidenced by the presence of small bubbles. The mass is constantly stirred, because the reaction occurs at the boundary between fat and lead oxide, which have different densities and tend to separate. Adding large amounts of water slows down the process, which contributes to stratification of the system.

The absence of foam when the mass is heated for a long time indicates that the water has boiled off, and the temperature of the mixture may exceed 110°C. Adding successive portions of water leads to spattering of the mass, so you need to be careful.

In the process of cooking, the initial reddish color of the mixture gradually changes to whitish-gray, and towards the end of cooking in whitish

Cooking the patch is considered finished if a small sample, poured into cold water, is a plastic mass that does not smear and does not stick to the fingers when kneaded.

The finished patch is freed from glycerin by repeatedly mixing the mass in warm water with the help of a heated dough mixer. The plaster washed in this way is again transferred to the reactor and heated to 105 - 110 °C until the water is completely removed. A sample of dried lead plaster, taken with a spatula, should be drawn into a thin transparent thread. Poorly dried and insufficiently freed from glycerin plaster becomes hard and brittle during storage, becomes bitter and moldy.

The quality of the patch is affected by the quality of the original fats, lead oxide should not contain suric (Pb_3O_4), which almost does not saponify fats. The water used

should not contain carbonates, sulfates and carbon dioxide, which turn lead oxide into lead sulfates and carbonates, which do not oxidize fats.

Standardization of the finished preparation is carried out according to the reactions of truth and quantitative content of lead oxide. The preparation should not contain peroxide, lead carbonate and lead oxide. Weight loss during drying should not exceed 3%.

A simple lead plaster can be used independently, as well as be part of other plasters and lead (diachial) ointment.

Patches based on a simple lead patch are usually divided into *lead-resin* and *lead-wax.*

Complex lead plaster (*Emplastrum Plumbicompositum*) is a lead-resin patch of this kind *composition:* plaster of lead simple 85.0 parts; rosin 10.0 parts; turpentine oil 5.0 parts

Lead plaster and rosin are fused in a steam-heated reactor. Turpentine is added to the semi-cooled mass with continuous stirring. 3 sticks are squeezed or pumped out of the obtained mass.

It is used as a mild irritant. Epilin plaster 4% (*Emplastrum Epilini*) belongs to lead-wax plasters and has such *storage:* epilin citrate 4.0 parts; simple lead patch 51.0 parts; anhydrous lanolin 20.0 parts; wax 5.0 parts; purified water 20.0 parts.

A homogeneous sticky mass of light yellow or brownish yellow color with a soft consistency. The plaster should not have a bitter smell.

It is used as a depilatory agent for fungal skin diseases.

Preparation of Epilin plaster. Pre-weighed simple lead plaster, wax and anhydrous lanolin are placed in a reactor with a steam jacket and a stirrer. The mixture is fused with constant stirring, filtered while hot through a kapron mesh. Epilin citrate is dissolved in a measured amount of water, introduced into the melt and emulsified by stirring until a homogeneous mass is formed and it cools completely. The finished patch is packaged in dark glass jars.

Standardization of the finished product carried out according to the reactions of the truth and the quantitative content of epilin citrate (3.8 - 4.2%), organoleptic indicators.

Plaster "Ureaplast" (*Emplastrum "Ureaplastum"*) contains urea 20.0 parts; 10.0 parts of water; beeswax 5.0 parts; 20.0 parts of lanolin; lead patch 25.0 parts.

It is used as a keratolytic agent in the treatment of onychomycosis.

RESIN-WAX PATCHES

The bases of resin-wax plasters are alloys of resins and wax. They can also include fats and carbohydrates. The most widely used callus patch.

Callus plaster (*Emplastrum ad clavos*) has its own *composition:* salicylic acid 20.0 parts; rosin 27.0 parts; a pair of Finnish 26.0 parts; petrolatum 27.0 parts.

A homogeneous soft, sticky, but not viscous mass of yellow or dark yellow color. The melting point is not higher than 60 °C. The melted plaster has a characteristic smell of rosin.

It is used as a means to remove calluses (keratolytic agent).

Preparation of a corn patch. A weighed amount of rosin, paraffin and petrolatum is placed in a reactor with a steam jacket and a stirrer and fused. The alloy is filtered while warm through a kapron mesh. Salicylic acid is dissolved in the filtrate with stirring. The resulting homogeneous mass is poured into 3.0 g molds and cooled. Each patch is wrapped in waxed paper and packed in cardboard pencil cases.

Standardization of finished products carried out according to qualitative and quantitative reactions to salicylic acid (19 — 21%), organoleptic indicators, melting point.

3. Rubber patches

Rubber plasters were first proposed in 1888 year and are a mixture of rubber with resins, medicinal and auxiliary substances. They have become widespread due to many advantages compared to other plasters. Rubber patches retain their stickiness for a long time; a significant amount of medicinal substances can be added to them without changing their consistency; they are harmless to the human body; do not interact with medicinal substances and are convenient to use.

Rubber plasters include adhesive plaster, bactericidal adhesive plaster, callus "Salipod", pepper plaster, mustard plaster.

Leucoplastrum (*Leucoplastrum*). Sticky patch elastic smeared (*Emplastrum adhaesivum elasticum extensum*). The patch has this *storage:* natural rubber 25.7 parts;

rosin 20.35 parts; zinc oxide 32 parts; anhydrous lanolin 9.9 parts; liquid paraffin 11.3 parts; of neozone D 0.75 parts

All starting materials must be free of water. Residual moisture in the materials should not exceed 0.5%, because the plaster will be sticky and sticky at first, and then it will lag behind the fabric and crumble. Rosin gives the plaster mass more stickiness and contains resin acids that have an irritating effect on the skin. To neutralize these acids, zinc oxide is introduced into the mass, as a result of which resinates are formed. Zinc oxide has a drying effect, thereby preventing excessive smearing of the patch. Lanolin and petroleum jelly act as plasticizers. To eliminate the "aging" process, antioxidants are introduced into the mass - substances that slow down the oxidation of rubber. These are neozone D (phenyl-P-naphthylamine), paraoxydephenylamine, edgerite (aldolanaphthylamine). Gasoline is used as a solvent.

Cooking technology. Plasters are obtained on the basis of rubber by simple long-term mixing (within 6 hours) of separately prepared:

- rubber glue (a solution of rosin and rubber in gasoline);
- pastes of antioxidants (homogenized mixture of lanolin with an antioxidant);
- zinc base (homogenized mixture of lanolin, wax and zinc oxide).

The prepared plaster mass is applied to the moving ribbon of chiffon with the help of an adhesive (spreading) .

A knife 5 is lowered onto the tucked tape, setting a gap of 0.35 - 0.40 mm. Plaster mass from the bunker is applied to the fabric in front of the knife. As the tape moves, the knife evenly distributes the leukoma across the entire width of the tissue. The speed of the tape is 7.5-8.5 m/min.

When passing the tape over a heated plate (temperature 100 - 105 °C) gasoline evaporates from the applied layer of leukomass, its vapors are sucked through pipe *6.* For more complete evaporation of gasoline, heated air is supplied under pressure to the movement of the belt. Next, the tape passes through the drive shaft *4* over a stream of cold air (4-16 °C), which is supplied through the opening *8* by the fan 7, after which it is wound on the receiving roller. After receiving the tape on the roller *2* the machine is turned off and the rollers are changed, repeating again the process of applying

leukomasa to the fabric. The necessary layer of plaster mass is achieved as a result of 5-6 smears. The layer of plaster mass should be of such thickness that a piece of chiffon with smeared mass measuring 5x5 cm has a mass of 0.64-0.65 g for chiffon article 85.

Tapes from the roll are rewound using unwinding machines onto cardboard spools into rolls of length 1 and 5.2 m. Next, the rolls are cut into coils of different sizes.

The extracted gasoline vapors are passed through the adsorber, where they are absorbed and then desorbed. Regenerated gasoline is put back into production.

Adhesive plaster can be produced in small packages in the form of strips measuring 4x10 cm and 6x10 cm on staple canvas, covered with a protective layer of cellophane, 10 pieces in a bag.

In the finished patch, determine: the uniformity of the smeared layer (per $1m^2$ there should be at least 120 patches g leukomas); peel stickiness — not less than 10 kPa; acid number 32 - 37; amount of zinc oxide 29 - 34%.

Plaster can serve as a basis for applying medicinal substances. Such, in particular, is **adhesive plaster is bactericidal** (Emplastrum adhaesivum bactericidum), consisting of a gauze pad soaked in an antiseptic solution *storage:* furacilin 0.02%; synthomycin 0.08%; diamond green 0.01% in 40% ethyl alcohol), and has a fixing adhesive tape. From above, the patch is covered with a protective layer of starch gauze and cellophane. The patch is produced in different sizes.

Pepper plaster (EmplastrumCapsici). It is a homogeneous sticky mass of yellow-brown color, with a peculiar smell, applied to paper or fabric, size 12x18, 10x18, 8x18 cm, and two pairs of plasters, covered with a protective layer of cellophane, are placed in the package.

It is used as an analgesic for gout, arthritis, sciatica, lumbago and a distraction for colds.

The production technology of pepper plaster consists of the processes of preparing rubber glue, pepper paste and flour base.

In a reactor with a steam jacket and a stirrer, rubber glue is prepared, which is obtained by dissolving rubber, rosin and an antioxidant in gasoline. Pepper paste is prepared separately. To do this, mix a thick extract of capsicum 11% with a part of

melted and cooled to a temperature of 40-50 °Slanolin, add a thick extract of belladonna 0.3% and a 0.3% tincture of arnica. Add the pepper paste to the rubber glue and stir for 30 minutes. A solution of rosin in gasoline is added to the reactor with pepper paste and rubber glue and stirred for 60 minutes.

To prepare the flour base, wheat flour is taken, mixed with heated lanolin, petroleum jelly and a solution of rosin in gasoline. With this base, a fabric tape made of madapolam, mytkal or chintz is primed, and then pepper leucomas is applied on the USPL-1 installation. This equipment provides a one-time application of plaster mass and its drying. The movement of the tape in the drying chamber is based on a spiral trajectory. The dryer is compact, small in size and has three zones in the technological cycle. In the first two zones, heated air is used (35-40 ° C and 65 - 75 °C . s , respectively, the speed of the web is 0.8-1 m/s). In the third zone, the patch cools. The length of the tape is 250-300 m. The total duration of drying the patch mass is 50 minutes. An even more promising chamber-loop drying unit, which allows the use of any lining materials (paper, non-woven materials). The tape with plastic mass *3* moves, with the help of support rollers *4* it passes through drying blocks *1* and is heated by heated air through gas distribution cassettes *2*. The vapor-air mixture enters the adsorber for gasoline regeneration.

Callus plaster "Salipod" (Emplastrum adhaesivum ad clavos « Sali - podum »). Fish and sulfur are part of the adhesive plaster of the hosing unit.

It is produced in the form of rectangular strips of fabric measuring 6x10 and 2x10 cm, protected by cellophane on top.

Hemostatic patch "Feracryl" (Emplastrumhaemostaticum "Feracrylum") is a tape of adhesive plaster with a spacer consisting of layers of gauze impregnated with ferracryl solution. Feracryl is an incomplete ferrous salt of polyacrylic acid, which has the ability to form clots with blood proteins.

Mustard seeds

Mustard seeds (*Sinapismata*) is a variety of rubber plasters, which are produced in the form of rectangular strips of paper measuring 8x12.5 cm, covered with a powder of defatted mustard seeds with a thickness of 0.3-0.55 mm.

The composition of mustards includes mustard powder 98.0 parts; natural rubber to obtain a mass of 100.0 parts; B-70 aviation gasoline 100.0 parts; paper.

It is used as an anti-inflammatory distraction.

The raw material for obtaining mustard powder is Sarepta seed (*Semina Sinapisjunceae*) and black (*Semina sinapis nigrae*) mustard, containing the glycoside sinigrin, which is split under the action of the enzyme myrosin into glucose, potassium hydrosulfate and essential mustard oil (allyl isothiocyanate). Essential oil causes severe irritation and hyperemia of the skin. After collapsing (removing) the shell, the seeds are ground to medium fineness and fatty oil is squeezed out of them with a hydraulic press. The remains of fatty oil from the cake are extracted in Soxhlet-type apparatus. The presence of fatty oil has a negative effect on the quality of mustard seeds — the therapeutic effect slows down and their stability during storage decreases (mustard powder becomes bitter and peels off from the paper).

Preparation of mustards. The technological process consists of five stages:

1. preparation of rubber glue;
2. preparation of mustard mass;
3. spreading the mass on paper, drying, cutting the roll and placing mustard seeds in the feet;
4. packaging;
5. gasoline recovery.

Preparation of rubber glue. To do this, rubber steamed for 24-36 hours and cut into pieces is placed in the glue mixer, gasoline is added and the paddle mixer is turned on for 30-40 minutes. Then the mass is filtered. The resulting glue (a 1.35-2% solution of rubber in gasoline) is a thick, slow-moving mass that easily turns into a jelly-like mass as the gasoline evaporates.

Preparation of mustard mass. Mustard mass - mixture rubber glue and mustard powder in a ratio of 1:1—1.1:1. The content of essential oil in macus should be at least 1.11%. Rubber glue is placed in a mixer, mustard powder sifted from large particles and extraneous impurities is added and mixed until a homogeneous mass is obtained. The finished mustard mass is served with a pump on a table with a tub for spreading.

Production of mustard seeds. The process of spreading, drying and cutting is carried out on a continuous operation unit. Rolled paper passes through the gap between the table top and the tub. Passing under the bath, the top of the paper is covered with a layer of mustard mass 0.3-0.5 mm thick, then it enters the drying chamber (drying time 45 minutes, air temperature 80 °C). The vapor-air mixture formed in the chamber with gasoline is sucked off and fed to the gasoline recovery stage.

The dried tape is cut on a sheet-cutting machine into sheets of 75(76)x90 size cm, which are cooled for 24 hours, then the leaves are cut into separate mustard seeds and discarded.

Packaging. Mustard seeds are packaged in bags of 10 pieces. Every tenth mustard has an inscription on one side about the method of application. Packages are placed in packs of 600 pieces and stored in a dry place. The storage period is 8 months. In the presence of moisture, hydrolysis of sinigrin occurs, and mustards lose their activity.

Standardization of finished products is carried out according to the quantitative content of allyl isothiocyanate, which in mustard seeds (100 cm^2) should be at least 0.0119 g. Mustard, immersed in water for 5-10 c at a temperature of 37 °C and applied tightly to the skin of the hand, should cause severe irritation, burning and redness of the skin no later than after 5 minutes.

Nowadays, they also produce "Mustard bag", which is a heat-sealed bag made of porous paper that does not get wet, on both sides or on one side and paper with a polymer coating on the other. The package is filled with mustard mixture. The mustard bag is produced in size 11x10 cm and divided into four identical bags. Each bag is evenly filled with mustard mixture.

4. Liquid plasters or leather glues

Liquid plasters, or skin adhesives (Emplastra liquida) are viscous liquids that leave an elastic, sticky, strong film on the skin after application of a light-volatile solvent. They are used as epidermal and endermatic plasters. The plaster film in them is formed due to film formation during drying of solutions of rosin, nitrocellulose (in the form of collodion), perorvinyl and formaldehyde resins in organic solvents (ether, ethanol, acetone, less often chloroform, dimethylformamide). To give the film greater

elasticity, vegetable oils, linetol, dibutyl phthalate, triacetin, and cetyl alcohol are added to the composition of the adhesives. Liquid plasters are produced in bottles and aerosol packaging. The latter are widely used as a sterile dressing material for inpatient and outpatient treatment in gynecology, dermatology, and surgery.

Adhesives are conventionally divided into *collodion adhesives*, which include collodion, elastic collodion, callus liquid, Novikov liquid, kolaplast and microplast and *resinous* — cleol, furaplast, BF-6 glue, cerigel.

Collodium (*Collodium*). *Storage* drug: Koloxylin 4.0 parts; 20.0 parts of 96% ethyl alcohol; ether medical 76.0 parts It is a colorless or yellowish, transparent or slightly opalescent syrupy liquid with an ether smell. Contains 4% koloxylin.

Preparation of collodion. The required amount of alcohol is weighed into the reactor. Coloxylin is carefully crushed, because it is an explosive substance (a mixture of mono- and dinitrocellulose of the whole vine), weighed and placed in a reactor, wetting it with alcohol, the rest of the alcohol and a measured amount of ether are added. Leave in a well-closed reactor until the koloxylin is completely dissolved.

Since koloxylin is explosive substance, so it is often transported in the form of safe water slurry. When preparing the plaster, the water is displaced from the jelly with ethanol, and the koloxylin alcogel formed at the same time is dissolved in ether. Collodion is available in bottles of 5 and 15 ml.

It is used for fixing surgical bandages on the skin and covering small wounds.

Quality control of finished products is carried out for cleanliness. To do this, add 20 ml of water to 5 ml of the drug, shake and filter from the formed precipitate. The filtrate should have a neutral reaction. The dry residue should be from 3.8 to 4.2%.

Elastic collodion (*Collodium elasticum*) — collodion to which 3% of castor oil is added as a plasticizer.

Callous liquid (*Liquor adclavos*) contains in its *composition:* 1 part of salicylic acid; 1 part of 96% ethanol; collodion 8 parts; diamond green 0.01 part.

Novikov's liquid (*Liquor Novicovi*) has *storage:* tannin 2 parts; diamond green 0.2 parts; 0.2 parts of 96% ethanol, 0.5 parts of castor oil and 20 parts of collodion.

It is used to treat small skin wounds and cracks.

Kolaplast (*Collaplastum*) — this is a 5% solution of castor oil in collodion.

Microplastic (*Microplastum*) is a 1% solution of levoicetin in colaplasti

Clay adhesives are represented by Cleol, Furaplast, BF-6 glue, Cerigslem.

Cleol (*Cleolum*) consists of: rosin 45.0 parts; ethyl alcohol 95% 37 parts; medical ether 17.0 parts; sunflower oil 1.0 part.

Glue is a transparent sticky thick liquid of yellowish or reddish-brown color with the smell of ether, weakly acidic reaction.

It is used to fix surgical bandages on the surface of the skin.

Preparation *cleola* The required amount of alcohol is weighed into the reactor. The rosin is crushed, weighed and packed in a gauze bag, which is suspended in a reactor with alcohol to dissolve the rosin (gravity method). A measured amount of sunflower oil and ether is added to the resulting solution, dissolved while stirring. The solution is allowed to stand for a day and filtered. Pour into bottles of 50.0 ml.

Standardization of the drug is carried out according to the acid number (60-93) and dry residue (45-54%).

Furaplast (from **perchlorvinyl)** (*Furaplastumcum Perchlorvinyl*). Its ***composition:*** furacilin 0.25 parts; perchlorvinyl resin (film former) 100.0 parts; dimethyl phthalate (plasticizer) 25.0 parts; acetone 400.0 parts; 475.0 parts of chloroform. It is a light yellow liquid of a syrupy consistency with the smell of chloroform. Available in orange glass glasses of 50 Jr.

It is used to treat minor skin injuries with the formation of an elastic film resistant to water.

Glue BF-6 — 20% ethanol solution of synthetic formaldehyde resin from the group of resols. It contains polyvinyl butyral (butvar) as a plasticizer. Available in bottles of 10 and 20 ml.

It is used to treat gardens and cracks.

Cerigelum (*Cerigelum*) contains: polyvinyl butyral 4.0 parts; cytylpyridinium chloride 0.2 parts; 96% ethyl alcohol 100.0 parts glue - colorless opalescent, somewhat viscous liquid with the smell of alcohol.

Available in glass bottles of 400 ml. Store liquid glues in tightly closed bottles in a cool, protected from light place, away from fire.

It is used to form a film on the hands of surgeons and medical personnel before operations and medical manipulations.

we collect blood, produce bacterial preparations and blood substitutes The patch has significant antibacterial activity.

Films and sponges made from animal tissues. In modern medicine, a group of drugs is used that can be tentatively classified as plasters — these are hemostatic and wound-healing preparations from animal tissues in the form of films and sponges.

Film fibrin isogenic (*Membranula fibrinosa isogenic*) is fibrin obtained from the fibrinogen of human blood plasma and impregnated with a glycerol solution.

It has a hemostatic effect, promotes tissue regeneration and wound healing. The film left in the body dissolves.

It is produced in the form of a film **in** sterile glass tubes.

Isogenic fibrin sponge (*Spongia fibrinosa isogena*) — porous fibrin obtained from human blood plasma. In appearance, it is a dry porous mass of white or cream color, size 2x2x1 or 6x2x1 cm.

It is applied locally for hemostasis in case of injuries and operative bleeding. Dissolves in wounds.

Available in sterile glasses.

Sponge **hemostatic** collagen (*Spongia haemostatica collagenica*) is made from a 2% collagen solution with the addition of furacilin and boric acid.

A dry porous mass of yellow color in the form of plates, soft elastic consistency, which absorbs liquid well.

It exhibits a hemostatic and antiseptic effect, stimulates tissue regeneration.

It is produced in the form of 5x5 or 10x10 cm plates packed in polyethylene bags.

"Oblecolum" film (Membranula "Oblecolum") is collagen plates with the addition of 1:100 sea buckthorn oil.

Used externally to treat wounds.

5x5 plates are produced or 10x10 cm in plastic bags.

Gelatin sponge (*Spongia gelatinosa*) is formed from specially processed food gelatin. Dry porous mass of white color.

Has a hemostatic effect.

Available in packs of 0.6 Mr.

An antiseptic sponge with kanamycin (*Spongia antiseptica cum Kanamycino*) — dry porous mass of yellowish color. Contains gelatin with the addition of kanamycin sulfate, furacilin, calcium chloride.

It has a hemostatic and antimicrobial effect.

It is produced in the form of pieces weighing 0.5 — 0.7 g in transparent paper and polyvinyl chloride bags; 10 sponges in a package.

· **Materials on the activation of students of higher education during the lecture: questions, situational tasks, etc.:**

Question:

1. What is TTS?
2. How are TTS classified.
3. Specify the basics for TTS.
4. Explain the purpose of excipients. In what cases are they used?
5. Give examples of auxiliary substances.
6. What is the pH value for TTS?
7. Are alcohols used in the production of TTS?
8. How can technological TTS be improved?
9. What are the quality requirements for TTS presented by the SFU?
10. Assess the prospects of industrial production of TTS.

General material and bulk-methodological support of the lecture:

- educational premises - the auditorium of the department;
- equipment - computer, tables;
- equipment – multimedia projector;
- illustrative materials - presentation, slides.

Questions for self-control:

1. What does the process of obtaining different TTS consist of?
2. Name the drugs produced in the form of TTS.
3. What are plasters?
4. How plasters are classified.

5. Specify the basis for the patch.

6. Explain the purpose of excipients. In what cases are they used?

7. Give examples of auxiliary substances.

8. What is the pH value for plasters?

9. Are alcohols used in the production of plasters?

10. How can technological patches be improved?

11. What are the quality requirements for plasters presented by the State Federal Office of Ukraine?

12. Evaluate the prospects of industrial plaster production.

13. What does the process of obtaining different plasters consist of?

14. Name the drugs produced in the form of patches.

References:

1. Study guide for independent work of students of the Faculty of Pharmacy for the licensing exam "Step 2. Pharmacy" / V.Yu. Anisimov, O.I. Belyaeva, H.G. Vidavska, V.O. Helmboldt, A.V. Zamkova, I.V. Lytvynchuk, A.V. Nikitin, B.V. Pristupa, I.B. Petkova, Ya.V. Rozhkovskyi, S.B. Strechen, L.M. Unguryan, N.C. Fizor Odesa: Odesa.nats.med. Univ. 2020. - 240 p.

Mode of access to lecture texts for students of the Faculty of Pharmacy: https://info.odmu.edu.ua/chair/drugs/files/390/ua

Literature used by the lecturer to prepare the lecture.

Main:

1. Industrial technology of medicines: a basic textbook for students. Higher. student pharmacy institutions (pharmacological institutions) / E.V. Gladukh, O.A. Ruban, I.V. Saiko et al. - Kh.: NFaU: Original, 2016. - 632p. : Name - (National textbook series)

2. Workshop on industrial technology of medicinal products specialty "Pharmacy" / Ed. Ruban O.A. - Kh .: NFaU, 2015. - 374 p

3 . INDUSTRIAL technology of medicines : education. manual for students' independent work / O. A. RUBAN , V. D. RYBACHUK , L. M. Khohlova etc. - KH.: NATIONAL UNIVERSITY OF UKRAINE, 2015. - 120 p.

- Excipients in the production of drugs: training. manual for students higher pharmacy education closing / O. A. RUBAN , I. M. Pertsev, S. A. Kutsenko, Yu. S. Maslii; under the editorship I. M. Pertseva. – Kh.: Golden Pages, 2016. – 720 p.
- Technology of drugs for industrial production: tutorial. for university students education closing : in 2 parts / V. I. Chuyeshov, E. V. Gladukh, I. V. Saiko and others. – 2nd ed., revision. and additional - Kh.: National University of Applied Sciences: Original, 2012. - Part 1. - 694 p.
- Technology of drugs for industrial production: tutorial. for university students education closing : in 2 parts / V. I. Chuyeshov, E. V. Gladukh, I. V. Saiko and others. – 2nd ed., revision. and additional - Kh.: National Academy of Sciences: Original, 2013. - Part 2. - 638 p.
- Modern pharmaceutical technologies: education. manual to laboratory classes of full-time, evening and part-time master's students of the specialty 8.110201 "Pharmacy" / under the editorship. O. A. Ruban. - Kh.: Publishing House of the National Academy of Sciences, 2016. - 256 p.
- Encyclopedia of Pharmaceutical Technology: 3-d Ed. / ed. by J. Swarbrick. – New York; London: Informa Healthcare, 2007. – 4128 p.
- European Pharmacopoeia 8.0 [8th edition] / European Directorate for the Quality of Medicines & Healthcare. - Strasbourg, 2013. - 3638 p.
- Handbook of Pharmaceutical Excipients, 6th edition / RC Rowe, PJ Sheskey, ME Quinn. - Pharmaceutical Press and American Pharmacists Association, 2009. - 521 p.
- State Pharmacopoeia of Ukraine / State enterprise " Ukrainian scientific officinal center quality medical means " - 2- e kind . - Kharkiv : State enterprise " Ukrainian scientific officinal center quality medical means ", 2015. - Vol . 1. - 1128 p .
- State Pharmacopoeia of Ukraine / State enterprise " Ukrainian scientific officinal center quality medical means " - 2- e kind . - Kharkiv : State enterprise " Ukrainian scientific officinal center quality medical means ", 2014. - Vol . 2. – 724 s .

- State Pharmacopoeia of Ukraine / State enterprise " Ukrainian scientific officinal center quality medical means " - 2- e kind . - Kharkiv : State enterprise " Ukrainian scientific officinal center quality medical means ", 2015. - Vol . 3. – 732 p .
- About medicinal products: the law of Ukraine dated 04/04/96 No. 123/96 // Bulletin of the Verkhovna Rada of Ukraine. - 1996. - No. 123.
- Zujkina SS The pharmacotechnological studies of the phytospecies composition for the complex therapy of mastopathy / SS Zujkina, LI Vishnevska // Visnyk pharmacy . – 2017. – No. 2 (90). - WITH . 43-47.
- Bogutska , O. _ IS . The main ones directions solution problems pharmaceutical of incompatibilities / O . IS . Bogutska // Contemporary achievement pharmaceutical technologies and biotechnology : collection scientific works _ – issue 2. – Kharkiv . : Type - in NFaU , 2017. - S. 29–31.
- Polovka N . P. _ Rating biopharmaceuticals factors at developers and production new ones medical means / N. _ P. _ Polovko , L. _ And . Vishnevska , O. _ WITH . Shpychak // Modern achievement pharmaceutical technologies and biotechnology : collection scientific works , issue 2. – X .: Ed NFaU , 2017. - S. 155-160.
- Prospects for the creation of new original drugs based on substances of plant origin / O.A. Ruban, S.A. Malinovska, Murad Al-Tawaiti, S.I. Mazurets // Phytotherapy. – 2012. – No. 2. - pp. 63–65.
- The current state of creation, production and quality control of capsules / M.B. Chubka, L.V. Vronska, N.O. Zarivna et al. // Pharmaceutical journal. 2012. No. 2. P. 165168.
- Murachanian, D. Two-Piece Hard Capsules for Pharmaceutical Formulations / D. Murachanian // Journal of GXP Compliance. 2010. Vol. 14. P. 3142.
- Patel H. New pharmaceutical excipients in solid dosage forms – A review / H. Patel, V. Shah, U. Upadhyay // Int. J. of Pharm. & Life Sci. - 2011. - Vol. 2. – P. 1006–1019.
- Recent Trends of Treatment and Medication Peptic Ulcerative Disorder / D. Bhowmik, Chiranjib, KK Tripathi [et al.] // International Journal of PharmTech Research. - 2010. - Vol. 2. – P. 970–980

- The effects of powder compressibility, speed of capsule filling and pre-compression on plug densification / M. Llusa , E. Faulhammer , S. Biserni [et al.] // Int. J. Pharm. – 2014. – Vol. 471. – P. 182–188.

Electronic information resources

- Lecture materials, methodological developments for seminar classes and independent work at the Department of Social Pharmacy: Access mode: http://socpharm.nuph.edu.ua.
- Scientific library of the National Academy of Sciences: Access mode: http://dspace.ukrfa.kharkov.ua; http://lib.nuph.edu.ua
- www.moz.gov.ua is the official website of the Ministry of Health of Ukraine
- nuph.edu.ua is the official website of the National Pharmaceutical University
- library@nuph.edu.ua - website of the library of the National Academy of Sciences of Ukraine
- The website of the Department of Scientific Research of the National Academy of Sciences of the Russian Academy of Sciences. – Access mode: ztl.nuph.edu.ua.
- The website of the Department of Drug Technologies of ONMedU http://info.odmu.edu.ua/chair/drugs/files/195/ua
- The site of distance learning of the National Academy of Sciences: the page of the ZTL department - [Electronic resource]. – Access mode: http://pharmel.kharkiv.edu/moodle/course/index.php?categoryid=154
- fp.com.ua - website of the magazine "Pharmacist Praktik"
- www.provisor.com.ua – the official website of the magazine "Provisor"
- Compendium: drugs. - [Electronic resource]. - Access mode: http://compendium.com.ua/ - as of October 10, 2016.
- State Register of Medicinal Products of Ukraine. - [Electronic resource]. - Access mode: http://www.drlz.com.ua/ - as of January 10, 2017.

Database "Equalizer" LLC "Business Credit" - [Electronic resource]. - Access mode: http://eq.bck.com.ua/ - as of September 20, 2016.

Lecture No. 10

Topic: " Production of nano- and radiopharmaceuticals " - 2 hours.

Relevance of the topic: Drug technology (industrial technology of drugs) is one of the fundamental technological sciences. It consists of several key aspects that are important for modern medicine and patients: Effectiveness and safety - Modern technologies make it possible to produce drugs with high efficiency and safety for patients. Exact dosage, quality control and the absence of impurities make medicines more effective and safer. Innovations in medicine: New technologies allow the creation of innovative drugs that can be more targeted and effective drug therapy. For example, drugs designed to precisely affect specific cells or genes provide more effective treatments. Minimization of side effects: Technologies make it possible to develop medicinal formulas that minimize side effects and negative effects on the body. This provides a more comfortable and safe treatment for patients. Fast production and delivery process: The use of modern technologies allows to speed up the production process of medicines, which is especially important in the conditions of a rapidly changing medical environment, such as the spread of diseases or epidemics. Individual approach to treatment: Technologies make it possible to develop medicines that take into account the individual characteristics of the patient, which leads to a personalized approach to treatment and increases its effectiveness. Cost-effectiveness and availability Improved manufacturing technologies can reduce production costs, making drugs more accessible to a wide range of patients, providing cost-effectiveness in healthcare.

Thus, the use of modern technologies for the production of medicines is an important factor for improving the effectiveness of treatment, patient safety and the general state of public health.

Goal: To study the general technological scheme of the production of nano- and radiopharmaceuticals , to get acquainted with the proper rules of production. To learn the methods of stabilization of nano- and radiopharmaceutical preparations , to be able to obtain nano- and radiopharmaceutical preparations with various medicinal and

auxiliary substances, to carry out step-by-step control and to be able to standardize the finished product in accordance with the requirements of regulatory and technical documentation, to be able to draw up technological production schemes

Basic concepts:

Radiopharmaceutical preparation (eng. *radioparmaceutica dr u g*) — any pharmaceutical product that contains one or more radionuclides (radioactive isotopes) included in the formulation for diagnostic or therapeutic purposes. Requirements for the storage of radiopharmaceuticals .

A radiopharmaceutical product must have a passport containing the following information: the activity of the drug, the amount of the drug in milliliters or milligrams; specific concentration of the solution; measurement time; the accuracy of the measurements.

Plan and organizational structure of the lecture:

No p.p.	**The main stages of the lecture and their content.**	**Goals in levels of abstraction.**	**Type of lecture, lecture equipment.**	**Time allocation.**
1	**2**	**3**	**4**	**5**
I 1.	***Preparatory stage*** Determination of educational goals.		The lecture is combined	1%
2.	Providing positive motivation.			2%
	The main stage Presentation of lecture material.			90%
II 3.	Plan: The concept of a radiopharmaceutical .		Slides	

	2. The method of diagnosis using a radiopharmaceutical preparation . 3. Measurement of radioactivity and specific activity of a radiopharmaceutical preparation . 4. Storage of radiopharmaceuticals ***The final stage***	I II III	List of references, questions, assignments.	
III 4.	Summary of the lecture, general conclusions.			2%
5.	Lecturer's answers to possible questions.			3%
6.	Tasks for self-training of students.			2%

Structural and logical scheme of the content of the lecture

1. The concept of a radiopharmaceutical .

2. The method of diagnosis using a radiopharmaceutical preparation .

3. Measurement of radioactivity and specific activity of a radiopharmaceutical preparation .

4. Storage of radiopharmaceuticals

Content of lecture material (lecture text)

RADIOPHARMACEUTICAL PREPARATION (eng. *radiopharmaceutica* dr u g) — any pharmaceutical product that contains one or more radionuclides (radioactive isotopes) included in the formulation for diagnostic or therapeutic

purposes. For diagnosis, short-lived RPs are used, the action of which is registered in the body with the help of special devices (scintillators, single-photon emission tomographs and positron (two-photon) emission tomographs), which capture γ - radiation of a labeled radionuclide. Technetium-99 is most often used as a labeled radionuclide. It is a short-lived nuclide with a half-life of about 6 hours. Used for diagnosis of almost all organs. R.p., marked with technetium, make up more than 80% of the R.p. nomenclature. Radioactive isotopes of thallium-201 and -199, iodine-123 and -131, fluorine, etc. are also used for the purpose of diagnosis and treatment.

The method of diagnosis with the help of R. p. called scintigraphy, its uniqueness lies in its accuracy, reliability, the possibility of repeated use, and most importantly, the ability to diagnose diseases at an early stage. To R.p. put forward the following requirements: to be well absorbed from the blood by a certain organ, to contain a radionuclide not associated with the drug (no more than 5% of a radiochemical impurity), to be subject to biological decay and removal from the body within a certain time, to ensure the creation of minimal radiation loads on the patient's body, to be characterized harmlessness, sterility and pyrogenicity, to be inexpensive and available.

Technology R.p. consists of several stages: obtaining the necessary radioisotope; production of isotope carrier reagent; production of the drug tropical to the body, quality control.

Measurement of radioactivity and specific activity of R.p. carried out on animals; purity is determined by the methods of distributive paper chromatography (or electrophoresis) and radiometric analysis. The radionuclide purity of the drug is the ratio of the activity of the main radionuclide to the total activity of the drug, expressed as a percentage, and is not a constant characteristic, but changes over time. Radionuclide impurities are impurities of other radioactive nuclides (in percentage) to the activity of the main nuclide for a certain time (date); determination of radionuclide purity R.p. carried out by the method of nuclear spectroscopy and radiometry; radiochemical purity, investigated by the methods of chromatography and electrophoresis, corresponds to the ratio of the activity of the radionuclide in the main chemical substance included in the preparation to the total activity of RP, expressed as a percentage. Radiochemical impurities are impurities of chemical compounds

different from the main substance that makes up the drug, but contain the same radionuclide. The level of radiochemical impurities is expressed as a percentage of the total activity of the radionuclide in the preparation. Quantitative analysis is carried out by determining the activity of radionuclides in R.p. by β-, γ- and X-ray radiation with respect to the standard sample by comparison.

R.p. must have a passport containing the following information: drug activity in millicuries (or becquerels); the amount of the drug in milliliters or milligrams; specific activity in millicuries (or becquerels) per 1 ml; total substance content in milligrams per 1 ml; concentration of the solution in milligrams per 1 ml; measurement time; the accuracy of the measurements.

R.p. stored in accordance with the current Basic sanitary rules for working with radioactive substances and sources of ionizing radiation, approved by the Ministry of Health of Ukraine, as well as special requirements. Expiry date R.p. determined by the stability of the chemical and radiochemical composition of the drug, the degree of decrease in the activity of the drug over time (according to the law of radioactive decay), the increase in the relative content of long-lived radionuclide impurities that have half-lives longer than the main radionuclide.

Recently, radioactive drugs have been used for the diagnosis and treatment of malignant neoplasms. In addition, radiopharmaceuticals make it possible to diagnose diseases of the cardiovascular system, kidneys, biliary tract, thyroid gland, etc.

The advantage of using this group of drugs is ease of use and relative harmlessness.

A feature of the assessment of the quality of radioactive preparations is the use of chemical and physico-chemical radiometric methods of analysis.

The authenticity of the radionuclide in the preparation is considered confirmed if the instrument spectrum of ionizing radiation, taken with a source, is identical to the spectrum half-dissolved with a sample solution with the same radionuclide and taken under the same conditions.

In the absence of sample sources and solutions with the necessary radionuclide, to establish the authenticity of the radionuclide, specific energy values of individual lines of the spectrum of ionizing radiation and their intensity should be determined.

The activity of radionuclides is measured by beta or gamma radiation, as well as X-ray radiation, depending on the type of radiation emitted by this nuclide.

Determination of radionuclide purity is carried out by the method of nuclear spectroscopy and radiometry with the use, if necessary, of various methods of quantitative chemical separation of impurities.

Chemical separation of impurities significantly increases the efficiency of the analysis.

Radionuclide analysis includes three main stages:

1) detection of radionuclide impurities;

2) identification of impurities;

3) definition of activity.

Radionuclide purity, as a rule, should not be lower than 99.5%.

Radiochemical purity is most often investigated by methods of chromatography and electrophoresis

The expiration date is determined by the following factors:

- Stability of the chemical and radiochemical composition of the drug;

- Decrease in the activity of the drug over time according to the law of radioactive decay;

- An increase in the relative content of long-lived radionuclide impurities that have half-life periods longer than the main radionuclide.

Representatives of this group of drugs:

Solution of sodium phosphate, labeled with phosphorus-32, for injections (Solutio Natrii phosphatis phosphoro-32 notati pro injectionibus) $Na_3P^{32}O_4$

Properties. Colorless transparent liquid. Specific activity 2-10 μm/ml. The relative activity of P^{32} in the form of orthophosphate is not less than 98%.

Identification.

1. A white loose precipitate forms with zirconium nitrate in concentrated nitric acid.

2. The absorption curve (beta radiation) of the preparation should be identical to the absorption curve of beta radiation of the sample solution P^{32}.

3. The activity of the drug decreases with a half-life of 14.2 days. The radiochemical composition is determined chromatographically (on paper).

The specific activity is measured on a counter with a beta-radiation detector by comparing the counting rates from the tested solution and the sample solution P^{32}.

Quantitative determination of phosphorus. Spectrophotometrically (by reaction with vanadate and ammonium molybdate). The optical density of the colored solution is measured at 410 nm.

Storage. In special cabinets for radioactive substances. The shelf life is no more than 2 months.

Use for therapeutic purposes in polycythemia, myeloma disease, chronic leukemia; for the diagnosis of malignant neoplasms.

Solution of sodium - iodohippurate, labeled with iodine -131, for injections

Properties. Transparent colorless or slightly yellowish liquid. The specific activity is not less than 0.1 mcurie / ml. the relative activity of sodium iodohippurate is not less than 98%.

Identification. They are determined spectrophotometrically and by the spectrum of gamma radiation.

The activity of the drug decreases with a half-life of 8 days.

The radiochemical composition is determined chromatographically (on paper).

The specific activity is measured using y- or y-radiation.

Quantitative determination of sodium iodohippurate. Spectrophotometry (in the UV region).

Storage. In special cabinets for radioactive substances at a temperature of +4 to +10 ° C. The shelf life is no more than 20 days.

Application. To study the functional activity of the kidneys.

Decontamination of work premises and equipment In all premises where work is carried out with open radioactive sources, wet cleaning is carried out daily, at least once a month. - Work equipment is fixed behind the work room of each class and stored in specially designated places. Radioactive contamination of external surfaces of equipment, apparatus, tools, laboratory utensils, surfaces of work premises should not exceed the permissible levels of general contamination established by NRBU-97. Daily

wet cleaning must be carried out in all rooms with permanent presence of personnel, intended for work with radiation sources in an open form. Periodically, but at least once a month, general cleaning is done with decontamination of the walls, floor, doors and external surfaces of the equipment. Cleaning is organized with the maximum use of mechanization means. Dry cleaning of industrial premises, with the exception of vacuum cleaning, is prohibited. A permanent supply of decontamination agents and cleaning solutions should be provided in the permanent residence of personnel, where they work with sources in an open form, which are selected taking into account the properties of radionuclides and their compounds with which work is being carried out, as well as the nature of the surfaces to be decontamination. After finishing the work, each worker must clean his workplace and, if necessary, deactivate the equipment, tools, work utensils that were used in the process of working with open sources. In the case of radioactive contamination of the premises or their separate areas, decontamination is started immediately. If the contamination is caused by a powdery dry substance, then it is collected with a slightly damp cloth, having previously turned off the ventilation. A large amount of spilled radioactive liquids is covered with shavings. After the main amount is removed, the remaining pollution is destroyed by treatment with special detergents. Decontamination of contaminated surfaces is carried out with the help of soft brushes, tampons moistened with detergents, or by washing. After decontamination with special detergents, the surface is washed abundantly with water and wiped with a dry, clean cloth. Then the surface cleanliness is controlled with the appropriate radiometric device. Radioactive contamination of the external surfaces of equipment, tools, laboratory dishes, surfaces of working rooms and compartments for storing work clothes should not exceed permissible levels. Used brushes and tampons are collected in plastic bags or other containers and disposed of as radioactive waste. The following solutions can be used as detergents: 1) washing powder - 10 ml, lye - 10 ml, water - up to 1 l. 2) oxalic acid - 5 g, table salt - 50 g, detergent DS-RAS - 10 ml, water - up to 1 l. If it was not possible to effectively carry out decontamination with the indicated means, then for additional treatment of surfaces use a solution of potassium permanganate -40 g, sulfuric acid (specific mass - 1.84) - 5 ml, water - up to 1 l. Potassium permanganate is dissolved in 1 liter of water heated to 600C, then

cooled to room temperature. Add sulfuric acid to the solution and mix. If the processed material is unstable to solutions containing acids, for deactivation use an alkaline solution of caustic soda - 10 g, trilon B - 10 g, water - up to 1 l. Caustic soda is dissolved in water, trilon B is added, and stirred until complete dissolution. The following solutions are prepared for decontamination of valuable equipment and devices: - citric acid - 10 g, water - up to 1 l; - oxalic acid - 20 g, water - up to 1 l; - sodium hexametaphosphate - 10-20 g, water - up to 1 l; - detergent OP-7 - 4 g, hydrochloric acid - 20 ml, sodium hexametaphosphate - 4 g, water - up to 1 l. Acid or sodium hexametaphosphate is dissolved, stirring, in 1 liter of water at room temperature. If decontamination of painted surfaces is necessary, the top layer is removed by mechanical (brushing) or chemical (using special solvents) methods. Clothes (aprons, sleeves, etc.) made of polyvinyl chloride and polyethylene can be deactivated in a solution of sodium hexametaphosphate - 10-20 g, water - up to 1 l. After deactivation, the floor and equipment are thoroughly washed with water and wiped dry with a rag. 84 Such rooms have special requirements for their ventilation, they carry out constant dosimetric monitoring of the level of radiation pollution in the air. 3.5. Measures of individual protection and personal hygiene when working with radioactive substances All personnel who work or visit workplaces with open sources of radiation must be provided with means of personal protection depending on the type and class of work. Because working with radioactive substances, sources of ionizing radiation and staying where they work are potentially dangerous. According to the NRB, three classes of works are distinguished - I, II and III. For Class I work and certain types of Class II work, personnel are provided with overalls, caps, special underwear, stockings, light footwear (rubber boots or shoe covers), gloves, disposable paper towels and handkerchiefs, as well as means of respiratory protection (respirators , gas mask). During work of the II class and certain types of work of the III class, personnel are provided with gowns, caps, gloves, light shoes, and, if necessary, means of respiratory protection. In premises for work with open radioactive sources, it is prohibited: the presence of employees without the necessary personal protective equipment; storage of food products, tobacco products, cosmetics; work with a pipette without a pear. Manipulation with the pipette is carried out with the help of a rubber bulb or automatic

dispensers with replaceable tips are used. All work with radioactive substances is performed in a cuvette covered with a layer of filter paper, which after work is placed in plastic bags for collecting radioactive waste. After the end of work, each employee is obliged to clean his workplace, decontaminate dishes, tools and other equipment to the maximum permissible levels, controlling their cleanliness with radiometric devices. When leaving the premises where work with radioactive substances is carried out, it is necessary to remove overalls, gloves and other means of personal protection, wash your hands thoroughly and check their cleanliness on a radiometric device. With immediate treatment of the skin, regardless of the degree of its contamination and the deactivating substance, up to 90-98% of unfixed radionuclides on it are removed. In the case of minor pollution (exceeding the permissible levels by no more than 2.5 times), radioactive substances are well removed during washing with warm running water with 72% household soap with the help of a hair brush. The brush is used without pressure, so as not to cause skin damage and the penetration of radioactive substances into the body. The water should be flowing with a temperature not higher than 35 ^{o}C, since the use of hot water worsens the cleaning results. In the event that radioactive substances have been fixed as a result of their reaction with skin proteins, the usual treatment with soap and water is not effective. To remove the final activity, detergents are used depending on the chemical properties of radioactive substances: adsorbents (kaolin paste, "Novost" powder, etc.), complexing agents (trilon B, trisodium salt, citric acid, unitiol, oxathiol, soda solution, etc.), weak solutions of acids (more often saline and citric). These agents destroy isotope bonds with skin proteins, absorb radioactive substances and are easily washed off the skin. You can use the "Protection" preparation and cleaning solutions for the deactivation of leather covers

Recipes for detergents used for skin decontamination

No. of the solution	Storage	Massa, g	No. of the solution	Storage	Massa, g
1	Kaolin paste: kaolin (powder) soap	64	5	Potassium permanganate Water	40 1000

	shavings soda Water is hot	15 3 18			
2	Detergent OP10 (OP-7) Polycomplexon Water	 50 10 950	6	Citric acid Water	 3 1000
3	Detergent OP10 (OP-7) Trisodium salt Antibacterial drug Water	 4 30 1 1000	7	Sodium bicarbonate Water	20 1000
4	Trilon B Sodium bisulfate Starch Sodium carbonate Water	5 5 5 35 1000	8	Hydrochloric acid Water	20 1000

When deactivating, it is necessary to take into account chemical laws, for example, contamination with radioactive phosphorus should not be washed off with soap, because in this case insoluble phosphates are formed. In this case, it is better to use synthetic detergents, for example OP-10 or 2% soda solution.

Radioactive iodine is easily removed by treatment with soap and water and subsequent use of oxidizing agents (potassium permanganate) and treatment with sulfite solution. The use of soap and water is effective for 42K and 24Na contamination. In other cases, it is better to use complexing agents: trilon B (with 90Sr and 59Fe contamination); unitiol and oxathiol (with 198Au and 203Hg contamination); kaolin soap (with 226Ra contamination). In the case of small contamination of the skin coverings of the body, it is necessary to thoroughly wash in the shower with household

72% soap or OP10. If more thorough decontamination is necessary, treatment with solution 3 (Table 3.5) is carried out for 2 minutes. Heavily contaminated areas of the skin are first treated with a strong solution of potassium permanganate and a 5% solution of sodium sulfate. Then wash thoroughly under the shower. To wipe treated skin surfaces, it is convenient to use disposable napkins or cotton-gauze tampons, which are then removed as solid radioactive waste.

If radioactive contamination was accompanied by minor skin damage, the wound should be washed several times with warm running water, and then artificially cause bleeding under a stream of water. The skin of the face is deactivated with soap and water, the hair - with water and shampoo, to which a 3% solution of citric acid is added. The eyes are washed under a jet of warm water with the eyelids wide open. To prevent contamination of the tear ducts, the stream of water is directed from the inner corner of the eye to the outer corner. In the case of radioactive substances entering the mouth, it is necessary to rinse it several times with warm water, and to clean the teeth and gums with a toothbrush and paste, after which rinse with a 3% solution of citric acid. If one-time treatment of body parts did not provide the necessary cleanliness, decontamination is repeated. Ineffective retreatments indicate fixation of the isotope by the skin. This is a signal to take such persons under medical supervision.

Radiation control is performed by specially trained employees or representatives of the radiation safety service.

Individual monitoring of staff radiation doses is carried out once a month; control over the level of contamination of working surfaces, equipment, workers' overalls and their skin - every time after working with radioactive substances; the level of pollution of adjacent premises is monitored once a quarter, the control of the content of radioactive substances in the air of working premises - at least twice a month, and in waste water - once a quarter. Data of all types of radiation control are registered in the log.

Personnel who clean the premises and work with radioactive solutions and powders must be equipped (except for those noted) with plastic aprons and sleeves or plastic half-gowns and rubber shoes. When moving from higher-class work premises to lower-class premises, it is necessary to control the levels of radioactive

contamination of personal protective equipment, especially special shoes and hands. Protection against radiation exposure includes:

1. Sealing of radiation sources;

2. Planning the placement of working cities in such a way as to reduce any possibility of radiation exposure of personnel;

3. Rational use of sanitary and technical devices, equipment, means and measures;

4. Use of special protective materials; 5. Use of personal protective equipment;

6. Compliance with the rules of personal hygiene.

Individual protection against radiation exposure includes the following:

- Reduction of the duration of working hours in conditions of exposure;

- Increasing the distance from the radiation source;

- Provision of workers with special gowns, caps, gloves (to protect hands), armbands, glasses (to protect the cornea of the eye), etc.

- Provision of workers with rubber shoes, shoe covers, aprons made of leaded rubber.

- When working with radioactive aerosols and dust, workers must be provided with respirators and gas masks.

- After completing the work, it is necessary to take a shower using household soap and a special shampoo.

- It is forbidden to eat and smoke in places of irradiation;

- All workers, provided they work with sources of radiation, must be provided with full, good nutrition.

In the premises for carrying out work of the 1st class, there must be a sanitary passage to the premises of the 2nd class. In the premises where II-class work is carried out, a sanitary pass to the III-class premises or a shower room with separate lockers for each employee must be equipped.

For works of the 3rd class, a shower of the usual type is provided.

Materials on the activation of students of higher education during the lecture: questions, situational tasks, etc.:

Question:

1. Describe the concept of "nanotechnology". What is the role and place of nanopreparations in medicine and pharmacy?

2. The use of nanotechnology in the production of medicinal products.

3. Define the term "address delivery of drugs." Name the requirements for targeted drug delivery systems.

General material and bulk-methodological support of the lecture:

- educational premises - the auditorium of the department;
- equipment - computer, tables;
- equipment – multimedia projector;
- illustrative materials - presentation, slides.

Questions for self-control:

1. Describe nanomaterials, name the types and classification of nanomaterials.

2. Basic principles and directions of nanotechnology. Nanopreparations. Features of their production. Nanosystems, methods of obtaining nanosystems.

3. Describe the concept of "radiopharmaceutical preparation". Describe the production, application and main diagnostic properties of radiopharmaceuticals.

4. Assortment and composition of radiopharmaceuticals on the pharmaceutical market of Ukraine. Features of their technology and quality control.

References:

1. Study guide for independent work of students of the Faculty of Pharmacy for the licensing exam "Step 2. Pharmacy" / V.Yu. Anisimov, O.I. Belyaeva, H.G. Vidavska, V.O. Helmboldt, A.V. Zamkova, I.V. Lytvynchuk, A.V. Nikitin, B.V. Pristupa, I.B. Petkova, Ya.V. Rozhkovskyi, S.B. Strechen, L.M. Unguryan, N.C. Fizor Odesa: Odesa.nats.med. Univ. 2020. - 240 p.

Mode of access to lecture texts for students of the Faculty of Pharmacy: https://info.odmu.edu.ua/chair/drugs/files/390/ua

Literature used by the lecturer to prepare the lecture.

Main:

1. Industrial technology of medicines: a basic textbook for students. Higher. student pharmacy institutions (pharmacological institutions) / E.V. Gladukh, O.A.

Ruban, I.V. Saiko et al. - Kh.: NFaU: Original, 2016. - 632p. : Name - (National textbook series)

2. Workshop on industrial technology of medicinal products specialty "Pharmacy" / Ed. Ruban O.A. - Kh .: NFaU, 2015. - 374 p

3 . INDUSTRIAL technology of medicines : education. manual for students' independent work / O. A. RUBAN , V. D. RYBACHUK , L. M. Khohlova etc. - KH.: NATIONAL UNIVERSITY OF UKRAINE, 2015. - 120 p.

- Excipients in the production of drugs: training. manual for students higher pharmacy education closing / O. A. RUBAN , I. M. Pertsev, S. A. Kutsenko, Yu. S. Maslii; under the editorship I. M. Pertseva. – Kh.: Golden Pages, 2016. – 720 p.
- Technology of drugs for industrial production: tutorial. for university students education closing : in 2 parts / V. I. Chuyeshov, E. V. Gladukh, I. V. Saiko and others. – 2nd ed., revision. and additional - Kh.: National University of Applied Sciences: Original, 2012. - Part 1. - 694 p.
- Technology of drugs for industrial production: tutorial. for university students education closing : in 2 parts / V. I. Chuyeshov, E. V. Gladukh, I. V. Saiko and others. – 2nd ed., revision. and additional - Kh.: National Academy of Sciences: Original, 2013. - Part 2. - 638 p.
- Modern pharmaceutical technologies: education. manual to laboratory classes of full-time, evening and part-time master's students of the specialty 8.110201 "Pharmacy" / under the editorship. O. A. Ruban. - Kh.: Publishing House of the National Academy of Sciences, 2016. - 256 p.
- Encyclopedia of Pharmaceutical Technology: 3-d Ed. / ed. by J. Swarbrick. – New York; London: Informa Healthcare, 2007. – 4128 p.
- European Pharmacopoeia 8.0 [8th edition] / European Directorate for the Quality of Medicines & Healthcare. - Strasbourg, 2013. - 3638 p.
- Handbook of Pharmaceutical Excipients, 6th edition / RC Rowe, PJ Sheskey, ME Quinn. - Pharmaceutical Press and American Pharmacists Association, 2009. - 521 p.
- State Pharmacopoeia of Ukraine / State enterprise " Ukrainian scientific officinal center quality medical means " - 2- e kind . - Kharkiv : State enterprise "

Ukrainian scientific officinal center quality medical means ", 2015. - Vol . 1. - 1128 p .

- State Pharmacopoeia of Ukraine / State enterprise " Ukrainian scientific officinal center quality medical means " - 2- e kind . - Kharkiv : State enterprise " Ukrainian scientific officinal center quality medical means ", 2014. - Vol . 2. – 724 s .
- State Pharmacopoeia of Ukraine / State enterprise " Ukrainian scientific officinal center quality medical means " - 2- e kind . - Kharkiv : State enterprise " Ukrainian scientific officinal center quality medical means ", 2015. - Vol . 3. – 732 p .
- About medicinal products: the law of Ukraine dated 04/04/96 No. 123/96 // Bulletin of the Verkhovna Rada of Ukraine. - 1996. - No. 123.
- Zujkina SS The pharmacotechnological studies of the phytospecies composition for the complex therapy of mastopathy / SS Zujkina, LI Vishnevska // Visnyk pharmacy . – 2017. – No. 2 (90). - WITH . 43-47.
- Bogutska , O. _ IS . The main ones directions solution problems pharmaceutical of incompatibilities / O . IS . Bogutska // Contemporary achievement pharmaceutical technologies and biotechnology : collection scientific works _ – issue 2. – Kharkiv . : Type - in NFaU , 2017. - S. 29–31.
- Polovka N . P. _ Rating biopharmaceuticals factors at developers and production new ones medical means / N. _ P. _ Polovko , L. _ And . Vishnevska , O. _ WITH . Shpychak // Modern achievement pharmaceutical technologies and biotechnology : collection scientific works , issue 2. – X .: Ed NFaU , 2017. - S. 155-160.
- Prospects for the creation of new original drugs based on substances of plant origin / O.A. Ruban, S.A. Malinovska, Murad Al-Tawaiti, S.I. Mazurets // Phytotherapy. – 2012. – No. 2. - pp. 63–65.
- The current state of creation, production and quality control of capsules / M.B. Chubka, L.V. Vronska, N.O. Zarivna et al. // Pharmaceutical journal. 2012. No. 2. P. 165168.
- Murachanian, D. Two-Piece Hard Capsules for Pharmaceutical Formulations / D. Murachanian // Journal of GXP Compliance. 2010. Vol. 14. P. 3142.

- Patel H. New pharmaceutical excipients in solid dosage forms – A review / H. Patel, V. Shah, U. Upadhyay // Int. J. of Pharm. & Life Sci. - 2011. - Vol. 2. – P. 1006–1019.
- Recent Trends of Treatment and Medication Peptic Ulcerative Disorder / D. Bhowmik, Chiranjib, KK Tripathi [et al.] // International Journal of PharmTech Research. - 2010. - Vol. 2. – P. 970–980
- The effects of powder compressibility, speed of capsule filling and pre-compression on plug densification / M. Llusa , E. Faulhammer , S. Biserni [et al.] // Int. J. Pharm. – 2014. – Vol. 471. – P. 182–188.

Electronic information resources

- Lecture materials, methodological developments for seminar classes and independent work at the Department of Social Pharmacy: Access mode: http://socpharm.nuph.edu.ua.
- Scientific library of the National Academy of Sciences: Access mode: http://dspace.ukrfa.kharkov.ua; http://lib.nuph.edu.ua
- www.moz.gov.ua is the official website of the Ministry of Health of Ukraine
- nuph.edu.ua is the official website of the National Pharmaceutical University
- library@nuph.edu.ua - website of the library of the National Academy of Sciences of Ukraine
- The website of the Department of Scientific Research of the National Academy of Sciences of the Russian Academy of Sciences. – Access mode: ztl.nuph.edu.ua.
- The website of the Department of Drug Technologies of ONMedU http://info.odmu.edu.ua/chair/drugs/files/195/ua
- The site of distance learning of the National Academy of Sciences: the page of the ZTL department - [Electronic resource]. – Access mode: http://pharmel.kharkiv.edu/moodle/course/index.php?categoryid=154
- fp.com.ua - website of the magazine "Pharmacist Praktik"
- www.provisor.com.ua – the official website of the magazine "Provisor"

- Compendium: drugs. - [Electronic resource]. - Access mode: http://compendium.com.ua/ - as of October 10, 2016.
- State Register of Medicinal Products of Ukraine. - [Electronic resource]. - Access mode: http://www.drlz.com.ua/ - as of January 10, 2017.

Database "Equalizer" LLC "Business Credit" - [Electronic resource]. - Access mode: http://eq.bck.com.ua/ - as of September 20, 2016.