MINISTRY OF HEALTH OF UKRAINE

ODESSA NATIONAL MEDICAL UNIVERSITY

Department of Pharmaceutical Chemistry and Drug Technology

APPROVE
Vice-Rector for Scientific and Pedagogical Work

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METHODOLOGICAL DEVELOPMENT FOR LECTURES FROM THE ACADEMIC DISCIPLINE "DRUG TECHNOLOGY" 7TH SEMESTER

Level of higher education : second (master's **)**

Area of knowledge: 22 "Healthcare"

Specialty: 226 "Pharmacy, industrial pharmacy"

Educational and professional program: Pharmacy, industrial pharmacy

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Head of the Department _____ Volodymyr HELMBOLDT
(signature) (First name, last name)

Developers:
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Lecture No. 1

Subject: « **"Medicines for parenteral use. Creation of conditions for sterile production. Preparation of containers and closures (ampoules, vials) " . – 2 hours**

Relevance of the topic: Drug technology (industrial drug technology) is one of the fundamental technological sciences. It consists of several key aspects that are important for modern medicine and patients: Efficacy and safety - Modern technologies allow the production of drugs with high efficiency and safety for patients. Accurate dosing, quality control and the absence of impurities make drugs more effective and safe. Innovations in the medical field: 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 treatment. Minimization of side effects: Technologies allow the development of drug formulas that minimize side effects and negative effects on the body. This provides more comfortable and safe treatment for patients. Fast production and delivery process: The use of modern technologies allows the acceleration of the production process of drugs, which is especially important in a rapidly changing medical environment, such as the spread of diseases or epidemics. Personalized treatment: Technologies allow for the development of medicines that take into account the individual characteristics of the patient, leading to a personalized approach to treatment and increasing its effectiveness. Cost-effectiveness and accessibility Improved manufacturing technologies can reduce production costs, making medicines more accessible to a wider range of patients, ensuring cost-effectiveness in healthcare.

Thus, the use of modern pharmaceutical manufacturing technologies is an important factor in improving the effectiveness of treatment, patient safety, and the overall state of public health.

Purpose: The discipline provides, on the basis of general knowledge and principles, regularities of the technology of factory production, to form in students knowledge about: theoretical foundations, acquisition of professional skills and abilities in the preparation of dosage forms, phased 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 facilities and personnel. To get acquainted with the main stages of industrial production of dosage forms and the discipline "Technology of Medicines", to characterize the basic principles of stabilization. To get acquainted with the main factors that affect the stability of injection solutions. Describe stabilizers used in the production of injectable solutions

Basic concepts:

Parenteral drugs (PDD) — c Sterile preparations intended for administration by injection , infusion or implantation into the human or animal body .

Incisional doctors for dogs — c e sterile solutions , emulsions or suspensions .

Intravenous infusion drugs ***for dogs —*** c e sterile aqueous solutions or emulsions in which the dispersion medium is water ;

I implants — Sterile solid medicinal products having dimensions and shape suitable for parenteral implantation .

Lecture plan and organizational structure:

No. 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*	I		
	Defining learning goals.			1%
1.	Providing positive motivation.		Combined lecture	
2.	*Main stage*	II		
	Presentation of lecture material.			2%
	Plan:			
	1. The concept of stability of medicinal products. The basic	III		
II	principle of stabilization.			
3.	2. Factors affecting the stability of injectable solutions.		Slides	90%
	3. Theories of redox processes of A.N. Bach and I.O. Engler.			
	4. The theory of branched chains by N. N. Semenov.			
	5. Chemical stabilization methods.			
	6. Stabilizers used in the production of injection solutions.			
	7. The influence of surfactants on			

	the kinetics of chemical reactions. 8. Physical stabilization methods. 9. Gas protection of injection solutions. 10. The influence of glass quality on the stability of substances. 11. Characteristics of a 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 injection. 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 IUDs to stabilize injectable solutions. 14. The influence of pH and the presence of heavy metals on the rate of oxidation reactions. 15. Methods for removing oxygen		Bibliography, questions, assignments.	

III 4. 5.	from solvents used in the manufacture of injection solutions. 16. Use of preservatives. 17. Technological methods for stabilizing ampoule solutions *Final stage* Lecture summary, general conclusions. The lecturer's answers to possible questions. Tasks for student self-study.			2% 3% 2%

Structural and logical diagram of the lecture content

1. The concept of medical means for parenteral application .
2. Characteristics of injectable drugs.
3. Intravenous infusion medications.
4. Concentrates for injectable or intravenous infusion medicinal products.
5. Powders for injectable or intravenous infusion medicinal products.
6. Implants.
7. Conditions for sterile products.
8. Process production sterile preparations for parenteral use.
9. Requirements for primary packaging for sterile products.
10. Preparation of containers and closures.

    10.1 Preparation glass ampoules.
    10.2 Methods for washing ampoules.
    10.3 Drying and sterilization of ampoules.

11. Polymeric materials for packaging parenteral medicines

Content of the lecture material (lecture text)

Medical means for parenteral application .

General characteristics. Classification. Requirements.

Medicinal products for parenteral use — These are sterile preparations intended for administration by injection, infusion or implantation into the human or animal body. These include aqueous and non-aqueous solutions, emulsions, suspensions, powders and tablets for the preparation of solutions and implantation, lyophilized preparations that are administered parenterally (subcutaneously, intramuscularly, intravenously, intra-arterially, retrobulbarly or subconjunctivally, into various cavities, etc.).

Parenteral drugs (PDs) — A relatively young dosage form. The first subcutaneous injections of drugs were performed in early 1851 by military doctor P. Lazarev. Today, among all the medicinal products produced by the domestic pharmaceutical industry, parenteral drugs account for about 30%. The parenteral route of drug administration has many advantages over other methods:

- ✦ ambulance action and full biological accessibility medical substances;
- ✦ precision and convenience dosage;
- ✦ possibility introduction medical substances to the patient, What is located in unconscious, or when medication cannot be administered by mouth;
- ✦ absence actions secrets GIT and enzymes liver, What has place when taking medications internally;
- ✦ the possibility of creating large stocks of sterile solutions, which facilitates and accelerates their release from pharmacies.
- ✦ Near from advantages parenteral way introduction has and some disadvantages:

- ✧ at introduction drugs through damaged skin in blood easily can pathogenic microorganisms get in;

✧ together with parenteral means in organism can be introduced air, which can cause vascular embolism or cardiac arrest;

✧ even a small amount of foreign impurities can negatively affect the patient's body;

✧ psycho-emotional aspect associated with the painfulness of the parenteral route of administration;

✧ introduction sterile drugs must be carried out by qualified specialists.

The administration of PLZ is carried out by ***injection.*** (injection of a small volume), ***infusions*** (single infusion of more than 100 ml drip or jet) or *implantations* by with help special devices with violation

integrity of the skin or mucous membranes. Such application is quite painful, so less painful methods of needle-free injection of injection solutions in the form of the thinnest (about 0.1-0.12 mm diameter) of a high-pressure jet that is sprayed from the opening of a special injector at a speed of 300 m/s and penetrates through the skin to a depth of 3 cm.

According to the State Federal University of Ukraine, drugs for parenteral use are classified into the following groups.

Injectable drugs — These are sterile solutions, emulsions or suspensions. Solutions for injection should be clear and practically free from particles. Emulsions for injection should not show any signs of separation. Suspensions for injection may contain a precipitate which should disperse rapidly on shaking to form a suspension. The resulting suspension should be sufficiently stable to ensure the required dose upon administration.

Intravenous infusion medications — These are sterile aqueous solutions or emulsions in which the dispersion medium is water; they should be pyrogen-free and usually isotonic with blood. They are intended for use in large doses, so they should not contain any antimicrobial preservatives.

Concentrates for injectable or intravenous infusion medicinal products are sterile solutions intended for injection or infusion after dilution. Before use, the concentrates are diluted to the specified volume with an appropriate sterile liquid.

After dilution, the resulting solution must meet the requirements for injectable or infusion medicinal products.

Powders for injectable or intravenous infusion medicinal products — These are solid sterile substances placed in a sterile container. When shaken with the specified volume of an appropriate sterile liquid, they must rapidly form either a clear, particle-free solution or a homogeneous suspension. After dissolution or suspension, they must meet the requirements for injectable or infusional medicinal products.

Gels for injections are sterile gels with a defined viscosity that ensures modified release of LR after injection.

Implants — Sterile solid medicinal products, of a size and shape suitable for parenteral implantation. The active substances must be released over a long period of time. They must be packaged in individual sterile containers.

The requirements of the article of the State Federal University of Finance and Economics do not apply (***!***) to drugs made from human blood, immunological and radiopharmaceutical drugs, and implantable prostheses.

Parenteral use of drugs involves disruption of the skin barrier. cover, What related with possible infection pathogenic microorganisms and the introduction of mechanical inclusions. Therefore, sterile production of drugs compared to other areas of the pharmaceutical industry, it has specific features dictated by the requirements for parenteral dosage forms. The main ones are: absence of mechanical impurities, sterility, stability, pyrogenicity, and for some - isotonicity, osmolarity or osmolality, isoionicity, isohydricity, a certain viscosity value, which is indicated in the corresponding ND.

ESTABLISHMENT OF THE CONDITIONS FOR THE COMPETITION OF STEEL PRODUCTION

To create optimal conditions that ensure the production of high-quality medicines, over the past decades, requirements for the production of sterile products have been developed, set out in the books "Good Manufacturing Practice for Medicines" (1999 and 2001), the Guidelines ST-N MOZU 42-4.0:2015 "Medicines.

Good Manufacturing Practice", GMP (Good Manufacture practice) WHO and GMP CC.

GMP principles require paying attention not so much to the control of the finished product as to ensuring its quality through proper organization and perfect production technology.

To ensure all quality indicators of finished sterile products, special requirements must be met for documentation, technological process, cleanliness of production premises, operation of technological equipment, ventilation and air cleanliness, preparation systems for basic raw materials and auxiliary materials to minimize the risk of contamination by microorganisms, particles and pyrogenic substances. Certain requirements are also imposed on personnel and industrial sanitation. Compliance with these rules depends, first of all, on the proper qualification, education, level of practical experience and industrial discipline of all personnel.

Requirements for production premises. The production of PLZ is carried out in special areas designated only for these purposes. The equipment of these premises must ensure a minimum possibility of contamination of the finished product of production, i.e. a minimum of dust accumulation areas, supply of air of controlled purity, maintenance of increased pressure. A certain temperature and humidity are maintained in the premises. Such premises are called " *chuctumu* ". A clean room may contain one or more clean zones, which can be created in local volumes: laminar flow cabinets, modules, isolators, blocks, etc.

An important characteristic of a clean room is its ***class*** , which is characterized by a classification number that determines the maximum permissible accounting concentration aerosol particles certain size in 1 m^3 of air. To obtain air with the required characteristics, validated methods must be used, included in the production documentation and allowed in established order authorized

government agency. In the production of sterile medicinal products, four classes of cleanliness are used, which are designated by the letters A, B, C, D. Premises of a higher class of cleanliness must be located inside premises of a lower

class, and the entrance to them is only through air locks.

In clean areas, all exposed surfaces should be smooth, impervious and undamaged to minimize the formation and accumulation of dust and microorganisms, and to ensure the possibility of repeated use of cleaning and disinfectants. Materials used in the treatment of production premises should be dust-free, non-flammable, easy to clean and resistant to disinfectants. After the completion of technological work, the premises should be treated with disinfectants and UV radiation.

Premises (including production, warehouse, sanitary and household) should be combined into separate functional and technological blocks, and if necessary - with autonomous systems engineering production facilities should be used strictly for their intended purpose and be sufficiently spacious to minimize the risk of mixing different medicinal products, cross-contamination or skipping one of the stages of the technological process. They should be equipped with the necessary amount of equipment. Each clean room should have a signaling system that warns of a violation or cessation of the sterile air supply process. Clean rooms should have a laminar air flow. The staff preparation rooms should be designed as airlocks and used in such a way as to ensure the distribution of the different stages of changing and thus minimize the risk of contamination of the process clothing by microorganisms and mechanical particles. The last part of the room for changing clothes should have the same cleanliness class as the working area to which it leads.

Access of personnel and/or equipment and materials to clean production rooms or areas should only occur through airlocks, in which the incoming air should be cleaned using filters of appropriate efficiency.

Providing production premises with clean air. Air in production premises — potential source of contamination of medicines, so its cleaning is one of the key tasks of preparation for production. The level of cleanliness of the air in the room determines its cleanliness class .

Air supplied to rooms of cleanliness class D is supplied with air that has undergone at least one stage of purification. Air supplied to rooms of cleanliness class C may be two-staged, and to rooms of cleanliness classes A and B. — only three-

stage. To create ultra-clean rooms or separate zones, a special module is placed inside them or laminar, in which is served autonomously laminar flow sterile air. Recently, efficient air filters HEPA (High-efficiency particulate air), VEPA, have become widespread. ULPA and other types.

To ensure sterility, more air is blown into clean rooms than is extracted. Excess sterile air leaks through gaps in enclosures, doors, and prevents unfiltered air from outside from entering the room.

Exhaust air purification should also be carried out through coarse or fine filters to protect the environment from possible harmful or dangerous emissions from production premises. Air supply system lactam antibiotics must be completely isolated from the air systems of other drug production.

If necessary, the building must have a system for supplying compressed air, nitrogen, etc., as well as a scheme for their distribution to all production facilities where necessary.

Requirements for personnel and technological clothing. Equipping the production with laminar flow systems and supplying clean and sterile air to the premises does not yet solve the problem of clean air, since the personnel working in the premises are also an active source of pollution. Therefore, the minimum number of employees provided for by the relevant instructions should be present in clean production premises during work .

Personnel entering the production area must be dressed in special clothing that corresponds to the production operation being performed. The personnel's technological clothing must correspond to the cleanliness class of the area in which they work, i.e., it must protect the product of production as much as possible from particles released by a person. As a rule, technological clothing consists of a suit (one-piece or two-piece) with tight-fitting cuffs to the wrists, a high collar and appropriate footwear or shoe covers. Clothing and footwear should not release lint or other particles. Hair (beard, mustache) must be covered, and rubber or plastic gloves must be worn on hands.

Workers in clean areas are subject to high demands regarding their personal

hygiene and cleanliness. In It is forbidden to wear a wristband in clean rooms. clock, jewelry ware, use cosmetic Workers are required to inform their immediate supervisor of any illness or other circumstances that may increase the risk of contamination of sterile medicinal products.

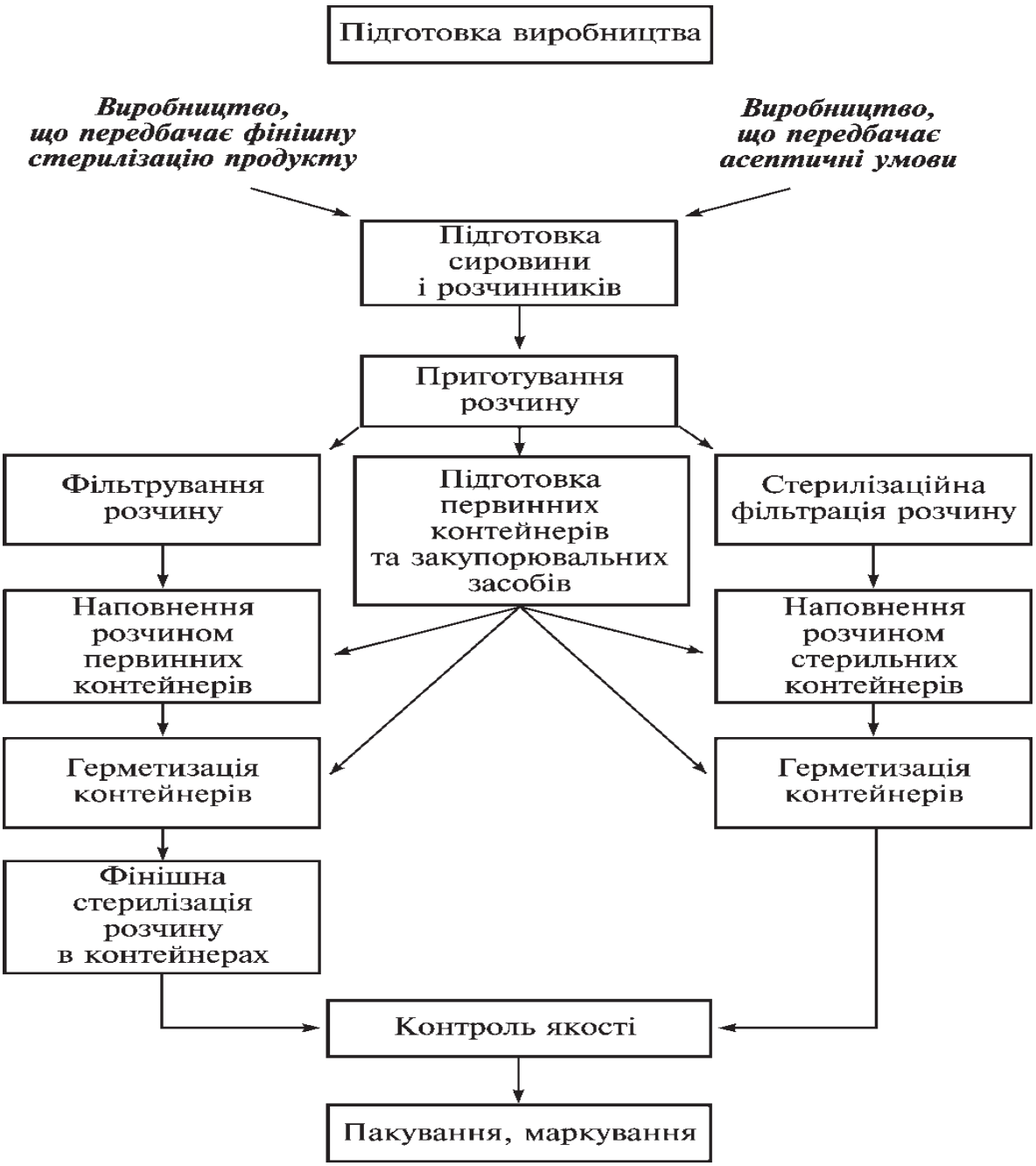
All personnel (including those involved in cleaning and maintenance) working in clean areas should receive regular professional training related to good sterile manufacturing practices , hygiene and basic microbiology.

Requirements for the technological process. Production of sterile products has to be carried out by methods, clearly laid out in technological regulations and production instructions, taking into account the principles and rules of GMP as a necessary condition for obtaining high-quality finished products in accordance with registration and licensing documentation.

The production of sterile products, depending on ***the method of achieving sterility,*** is divided into the following categories *:*

- production, What provides finish line sterilization product;
- production carried out under aseptic conditions at one or all stages of preparation of the drug.

On rice. 14.1 depicted sequence technological operations, What foresees different conditions production sterile products.



Scheme technological process production sterile preparations for parenteral use.

When ***producing products that are sterilized in their primary packaging,*** preparation of starting materials and primary packaging, as well as the production of many types of medicinal products, must be carried out in clean areas with a cleanliness class of at least D to ensure a sufficiently low level of risk particle contamination and microorganisms, necessary for filtration and sterilization. If microbial contamination poses a particular risk to the product (for example, when it

is a nutrient medium for the growth of microorganisms, or when a considerable period of time elapses before sterilization, or when the technological process is carried out in open vessels), preparation should be carried out in an area with cleanliness class C. The packaging of the product into primary packaging before final sterilization should be carried out in an area with cleanliness class not lower than C. The various operations of component preparation, product preparation and container filling should be carried out in separate areas within the clean room.

In ***the production of products obtained under aseptic conditions,*** The prepared primary packaging must be in a clean area with an environment not lower than cleanliness class D. Technological operations for preparation, sterilization filtration and packaging of products in aseptic conditions conditions have to be carried out on working place with class purity A and in an environment corresponding to class B.

Requirements for technological equipment.

To create conditions that prevent opportunities microbial insemination PLZ, important value has equipment, that implements technological processes. It determines a series requirements for the design of technological equipment, the choice of shapes, materials and coating of its parts.

Production equipment must not adversely affect the quality of the product. Parts or surfaces of the equipment that come into contact with the product are made of materials that do not react with it, do not have absorbent properties and do not release substances in such quantities that this could affect the quality of the product. It should also have recording devices to monitor the process parameters.

Recently, there has been a trend towards the creation of local clean zones through the use of the latest technologies and equipment of the CIP (Clean In Place) class and the transition to barrier isolation technologies, which allow minimizing or eliminating the presence of personnel in production facilities. This makes it possible to create special cleanliness in a limited volume, directly in the material processing area, as a result of which sanitary and hygienic conditions are maintained throughout the production facility. Limiting the volume of cleaning zones not only improves the quality of the processed air, but is also the most expedient from an economic point of view.

One way to solve these problems is to use of modern ***automatic lines*** ampouleing of parenteral drugs. Such flow-automated lines have obvious advantages over equipment designed to perform only one operation. The use of automated lines allows for almost complete elimination of human physical labor through the use of devices, machines and machines combined with automatic transportation of work items, i.e. automation of the entire production process.

REQUIREMENTS TO PRIMARY PACKAGING FOR STERILE PRODUCTS

The task of every pharmaceutical company is to production of high-quality pharmaceuticals in optimal conditions and their reliable delivery to the consumer. At the same time, along with strict requirements for the production of sterile products, the same high requirements must be imposed on both primary packaging and packaging materials, that come into contact with the drug.

Factory-made PLZ are produced in glass containers (ampoules, carpules-cartridges, vials, bottles, syringes), in transparent packaging made of polymer materials (vials, syringe-ampoules, syringes, soft containers). Information on the range of glass and polymer containers, as well as closures for parenteral drugs, is provided in Chapter 2.

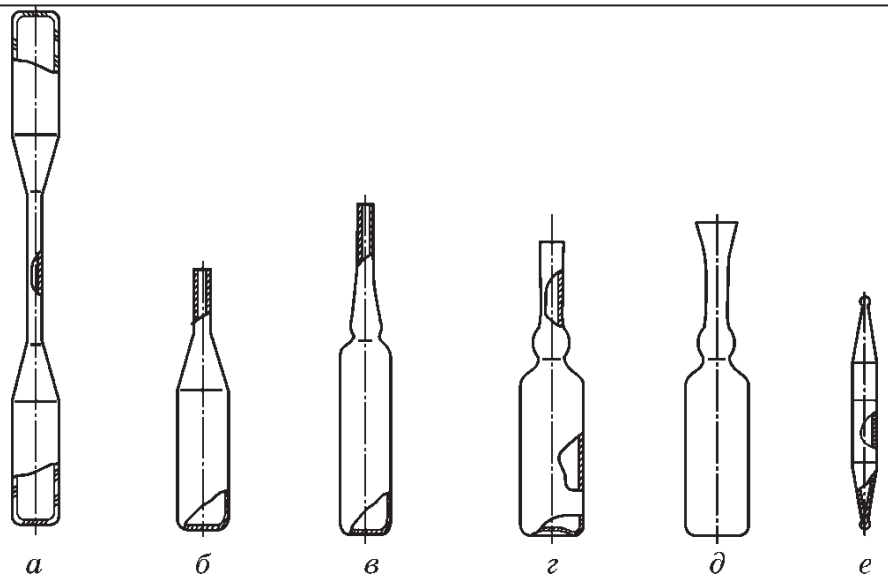
Containers for PLZ divide on two groups:

— ***single-dose*** , containing a certain amount of the drug intended for a single injection;

— ***multidose*** , that provide the possibility of multiple selection from a vessel a certain amount of the drug contained in it, without violating sterility.

The most common single-dose container is the ampoule. Ampoules — These are glass containers of various capacities (1; 2; 3; 5; 10; 20 and 50 ml) and shape. The ampoule consists of an expanded part - a body (bulk), where medicinal substances (in solution or another state) are placed, and 1-2 capillaries ("stems"), which are used for filling and emptying ampoules. Capillaries can be smooth or with a break. The break on the capillary prevents the solution from entering its upper part during sealing and improves the conditions for opening the ampoules before injection.

Ampoules are usually made of colorless glass, sometimes - from yellow and very rarely from colored. Usually ampoules are made with a flat bottom, although for technological reasons it must be concave inward. This provides the opportunity to settle in this “groove” the glass fragments that are formed when opening. Also, the bottom must ensure the stability of an empty ampoule with a cut stem on a horizontal plane. Ampoules must correspond to the shape and geometric dimensions specified in the set of technical documentation approved in accordance with the established procedure, and are produced in six standard sizes with different markings



Form and types glass ampoules:

and — type WITH; *b* — type BB; *in* — type IPV; *g* — type IP-V; *d* — type IP-C; *e* — type G (for glycerin)

Pharmaceutical companies can use ready-made ampoules manufactured by glass factories or produce them themselves at glassblowing sites.

The main material for making ampoules is glass. ***Glass*** —is a solid solution obtained as a result of cooling a molten mixture of silicates, metal oxides and some salts. It consists of various oxides: SiO_2, Na_2O, CaO, MgO, B_2O_3, Al_2O_3 and other compounds. Among the types of inorganic glass (borosilicate, borate and others), a large role belongs to silicate glass fused on the basis of silica. By introducing certain oxides into its composition, glass with predetermined physicochemical properties is obtained. The simplest composition is that of glass obtained by melting quartz sand

(95-98 % silica) to form a glassy mass, from which so-called quartz ware is made, which has high thermal and chemical resistance.

However to make and to solder ampoule with quartz glass practically impossible due to its high melting point (1550-1800 °C). Therefore, to reduce the melting point, metal oxides are added to the glass composition, the introduction of which also reduces its chemical resistance. To increase chemical resistance, boron and aluminum oxides are introduced into the glass composition. Adding magnesium oxide to the glass composition greatly increases its thermal resistance. Adjusting the content of boron, aluminum and magnesium oxides increases the impact strength and reduces the brittleness of the glass. By changing the composition of the components and their concentration, it is possible to obtain glass with specified properties.

The following requirements are imposed on ampoule glass: ***colorlessness*** and ***transparency*** — for control on absence mechanical inclusions and possible detection of signs of solution deterioration; ***fusibility*** — for high-quality sealing of ampoules; ***water resistance ; mechanical strength*** — to withstand loads during ampoule handling during production, transportation, and storage (this requirement must be combined with the necessary fragility of the glass for easy opening of the ampoule capillary); ***thermal stability*** — the ability of glass not to break during sudden temperature fluctuations, in particular during sterilization; ***chemical (hydrolytic) stability*** , which guarantees the constancy of the composition of all components of the preparation.

Glass, as a complex alloy, upon prolonged contact with water or aqueous solutions (especially when heated), releases individual components from its surface, i.e., it undergoes leaching or dissolution of the upper layer of glass.

Leaching — This is the transition from a glass structure consisting mainly of alkali and alkaline earth metal oxides to an aqueous solution due to its high mobility compared to the high charge of tetravalent silicon. In deeper leaching processes, alkali metal ions easily move from the inner layers of the glass to the place of the ions that have reacted. As a result, the surface layer of the glass completely goes into solution, undergoes hydrolysis and leads to a change in the pH of the solution. In this case, the following phenomena become possible:

— falling out free basics alkaloids from theirs salts;

— sedimentation substances from colloidal dissolved in results changes pH;

— sedimentation hydroxides or oxides metals with theirs salts;

— hydrolysis of esters, glycosides and alkaloids with a complex ester structure (atropine, scopolamine, etc.);

— optical isomerization of active substances with the formation of physiologically inactive isomers, for example, hornbeam alkaloids;

— oxidation of substances sensitive to the action of oxygen in a neutral or weakly alkaline environment, for example, morphine, adrenaline, etc.

The chemical resistance of the inner surface of ampoules can be increased by changing its surface structure. The most commonly used method is to treat the surface of ampoules with silicones. However, siliconized and plastic ampoules have not yet found wide application in our country.

There are other ways to eliminate the leaching process: using non-aqueous solvents; separate ampoules of the drug substance and solvent; dehydration of drugs; replacing glass with other materials.

Classes and grades of glass. Depending on the qualitative and quantitative composition, as well as the obtained properties, several classes and grades of glass used in the production of PLZ are currently distinguished by hydrolytic resistance.

Domestic brands (grades) of ampoule glass include NS - neutral and AB - boron-free glass. Ampoule glass of the NS-3 brand is the most chemically resistant of neutral glasses due to the large amount of boron. oxide (6%). It glass used for production ampoules and vials for solutions of substances subject to hydrolysis, oxidation, etc. (for example, solutions of alkaloid salts). Neutral glass of the HC-1 brand contains a larger amount of boron oxide and a smaller amount of sodium oxide compared to the HC-2 and HC-2A brands and is used for ampouleing LRs that are less sensitive to alkalis (solutions of sodium chloride, magnesium sulfate, calcium chloride, etc.).

Neutral glass of grades NS-2 and NS-2A is currently used mainly for the manufacture of vials and bottles for blood and infusion drugs. Boron-free ampoule

glass of grade AB-1 is alkaline and is used for the manufacture of ampoules and bottles, in which substances stable in oil solutions are placed, since practically no leaching occurs. Glass of grade SNS-1 is used for light-sensitive substances — light-shielding neutral glass. Since 1996, a new grade of medical glass for the manufacture of ampoules has been introduced in Ukraine - USP-1 (TU U 480945—2002), which corresponds to the first class. Production glass ampoules, fly and bottles for infusion The solutions are produced at glass factories using various molding methods (with preliminary glass wire production, jet-blowing, press-blowing, etc.) using high-performance machines.

PREPARATION CONTAINERS AND BUYING EQUIPMENT

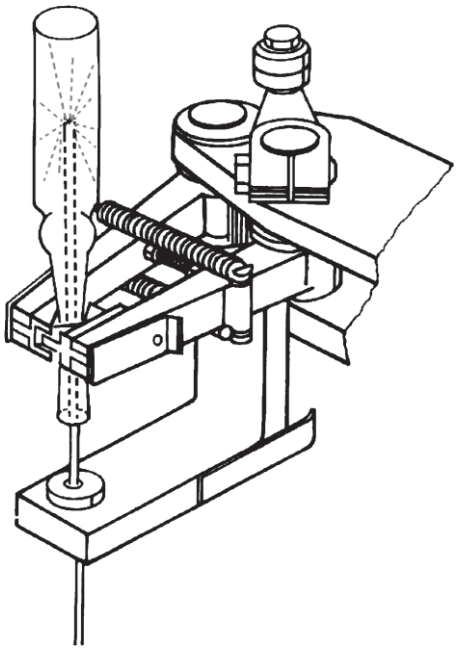
Preparation glass ampoules

Preparation of glass ampoules for filling includes the following operations: their washing, drying and/or sterilization. If paired ampoules are used in the technological process, then these operations are preceded by opening of the capillaries, for which special devices or separate machines are used.

Methods of washing ampoules. This is one of the most important stages of ampoule production, which consists of external and internal washing of ampoules.

For external washing of ampoules, the method of showering with hot water jets is used. Internal washing of ampoules can be carried out by the following methods: *vacuum* (varieties: turbovacuum, vortex and steam condensation), *vibration, ultrasonic and vibroultrasonic, thermal and spray* .

In recent years, ***the technology of syringe*** (***jet***) ***washing*** of ampoules has become widely used, although it also does not provide high quality of their cleaning. The essence of syringe washing is that a hollow syringe needle is inserted into the ampoule, oriented with the capillary down, through which water is supplied under pressure. The turbulent jet of water from the needle washes the inner surface of the ampoule. The schematic diagram of syringe washing of ampoules is removed through the gap between the needle and the capillary opening.



Obviously, What washing intensity many in Why depends from the speed of circulation of the liquid inside the ampoule, i.e., the speed of its entry and displacement. However, a syringe needle inserted into the capillary opening reduces its free cross-section, which is necessary for the evacuation of water. In addition, a large number of needles complicates the design of machines, and also increases the requirements for the shape and size of ampoules. The productivity of this method is low, but to increase efficiency it is combined with ultrasonic treatment. The combination of syringe washing of ampoules with the use of ultrasound is widely used in automatic ampoule preparation and filling lines of various foreign manufacturers.

To check the quality of washing, when loading the washing machine, control ampoules with specially applied colored stains inside are placed in several places in each ampoule cassette. After washing, these ampoules must be clean.

Drying and sterilization of ampoules. After washing, the ampoules are quickly transferred to drying or sterilization (with the exception of those washing methods that include these processes), depending on the ampoule conditions, to prevent secondary contamination.

Drying can be carried out in special ***drying cabinets.*** at a temperature of 120—130 °C 15—20 If sterilization is necessary, both operations are combined and the ampoules are kept in a dry air sterilizer at 180 °C for 60 min. The sterilizer is installed

between two rooms so that the loading of washed ampoules is carried out in the washing compartment, and the unloading of dried or sterilized ampoules is carried out in the — in the department for filling ampoules with solution (in a room of a higher cleanliness class).

This method of drying and sterilization has a number of disadvantages. First, the air in the sterilizer contains a large number of particles in the form of dust and scale, which are released by the heating elements. Second, the temperature in different zones of the chamber is not the same. Third, non-sterile air enters the sterilizer with each load.

It is more effective to use new types *of sterilizers with a laminar flow* of heated sterile air for sterilization of ampoules. In them, air with a slight excess pressure is supplied by a fan. in heater, heats up to temperatures sterilization 180— 300 °C, is filtered and enters the sterilization chamber through the distribution device in the form of a laminar flow across its entire cross-section, which creates a uniform temperature field across the entire cross-section of the chamber. Filtration through sterilization filters and a small air pressure guarantee the absence of mechanical contaminants and microflora in the sterilization zone .

For drying and sterilization, large pharmaceutical enterprises use *tunnel dryers* , in which cassettes with ampoules move along a conveyor while being heated by infrared rays in the drying section to 170 °C, and in the sterilization section to 300 °C.

The final rinsing of the vials is carried out with water for injection filtered through a membrane filter with pores no larger than 5.0 microns.

After washing, the vials are sent for sterilization. For this purpose, tunnel-type drying and sterilization installations are used, where the vials pass through three zones: heating to the sterilization temperature (315±35 °C), holding at a given temperature for a certain time (5—30 min) and cooling with sterile air filtered through a fine filter.

For sealing glass vials and bottles, rubber stoppers are used, which are obtained by vulcanization (cross-linking) of macromolecular elastomers with the introduction of special additives. Elastomers are obtained from natural or synthetic

raw materials as a result of the polymerization or polycondensation process. The composition of rubber mixtures may include catalysts (metal salts and oxides), dyes, stabilizers, plasticizers, fillers, which, when migrating into solutions, can cause a change in the quality of drugs and have a side effect on the body. Therefore, great importance is attached to the preparation of stoppers.

Rubber or elastomeric shaped stoppers are fixed to the glass container using aluminum and plastic caps with tamper-evident opening, which are rolled or screwed on. Some companies produce caps - Flip-Off" (consisting of a metal base with a plastic cover that protects the needle insertion site) and combined caps - Combi Seals" (aluminum + plastic + elastomer).

Washing of stoppers and caps includes several consecutive processing and rinsing operations. The ND regulates the following processing sequence: washing of stoppers from rubber crumbs, washing in a detergent solution, boiling in a solution of sodium hydroxide, soda ash or trisodium phosphate, hydrochloric acid. After each operation, the stoppers are rinsed with running tap water, and then purified water. The last rinse is carried out with water for injection, filtered through a filter with a pore size of no more than 5.0 microns. Before sterilization, the stoppers are siliconized. The stoppers and caps are sterilized with saturated in pairs in sterilizers from further drying sterile by air.

For the preparation of sealing agents, industrial machines with a rotating drum and boiling boilers, steam sterilizers of domestic and foreign production are used, but preference is given to automatic lines and multifunctional devices that combine all operations. washing and sterilization (for example, production firms “Pharmaklin” (Switzerland), “BOSCH” (Germany), “Truking Science & Technology Co., Ltd” (China), etc.).

Sterile vials, stoppers and caps are unloaded into sterile containers with airtight lids and stored in a clean area with an environment of at least Class D for no more than 24 hours.

Polymeric materials for packaging parenteral medicines

The existing defects of glass vessels are associated with the phenomenon of

leaching and dissolution of glass, the impact on the stability and quality of injection and infusion solutions; the complexity of transportation and storage due to the fragility of the packaging material; its relatively large tonnage, etc. They indicate the need to find and use more advanced materials for packaging PLZ.

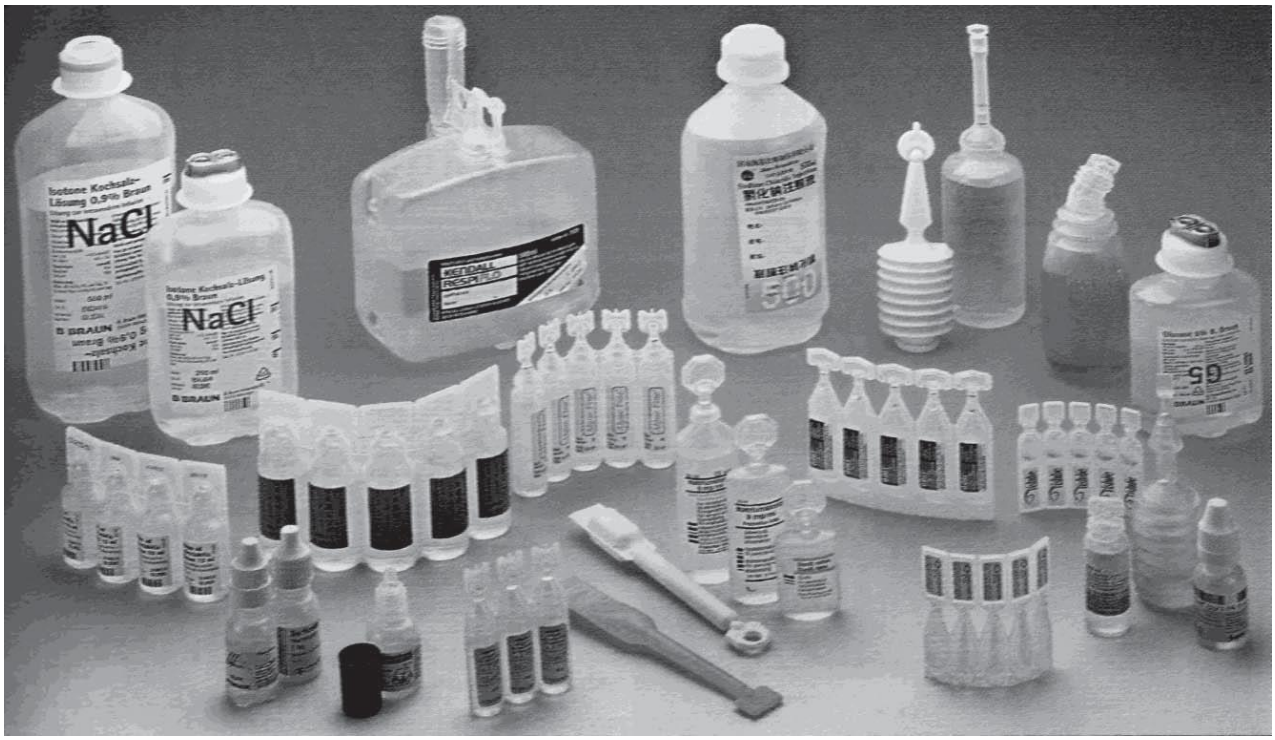
In recent decades, scientists have become increasingly interested in creating various kinds of plastic packaging for storing sterile dosage forms. Interest

plastics and polymeric materials in general is explained by the fact that they have such a combination of valuable properties that no other material has. Yes,

Compared to glass, high-polymer materials exhibit less brittleness or none at all.

Devoid of it with satisfactory mechanical strength, stiffness and surface hardness.

Many plastics are inert, neutral and at the same time resistant to alkalis, acids, many oxidants and reducing agents. They are quite easily processed into products of complex configurations, and the elasticity of some polymers allows you to create with them fundamentally new constructions containers and packaging (rice. 14.4). These circumstances served as an impetus to further extensive study of the possibilities of using plastics in harmaceutical production. From polymeric materials for the production of primary packaging The most promising and basic requirements for PLDs are polyethylenes, polypropylene and polyvinyl chloride



Puc. Types polymeric packaging

Among the requirements for polymer packaging, the following should be highlighted: containers must meet sterilization conditions, and their design and sterilization method must ensure the possibility of sterilization of all elements of the container that come into contact with the drug. Closures are part of the container. After sealing, polymer containers must ensure sterility and maintain integrity during storage and transportation. For more reliable storage, the container is packed in a protective shell. Such packaging must be transparent enough to ensure visual inspection of the contents at any time. Polymer containers may have an attachment for an infusion set, the design of which would ensure a reliable connection.

A characteristic feature of these types of packaging — no need for their prior preparation (washing and drying) before filling, which significantly reduces costs compared to the production of PLZ in glass containers. LR solutions are placed in polymer packaging and sealed in one automatic complex of equipment, reducing the risk of any type of contamination.

In connection with the widespread use of polymer packaging in the production of PLCs, fundamentally new technologies for their production have been developed,

including ***technology BFS*** (*Blow-Fill-Seal*) « *blowing — filling — sealing* » principle —bottle "rask", features whose will be described below.

Materials for activating higher education students during lectures: questions, situational tasks, etc.:

Question:

1. What are the advantages of the parenteral route of drug administration over other methods?
2. What are the ways in which PLZ is administered?
3. Give a characteristic of solutions, emulsions, and suspensions.
4. What are the requirements for ampoule glass?
5. Describe the requirements for personnel and technological clothing.
6. Where is the drying and sterilization of ampoules carried out?
7. What corks are used to seal glass vials and bottles?
8. What are the features of polymer materials for packaging parenteral medicines?

General material and methodological support for the lecture:

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

Questions for self-control:

1. What name can be used to combine: sterile solutions, emulsions or suspensions?
2. What are the features of the introduction of PLZ?
3. What types of PLCs are produced in the factory?
4. What is the essence of syringe washing of ampoules?
5. At what temperature is the drying and sterilization of ampoules carried out?

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Access mode 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 of higher. educational. pharmaceutical institutions (pharmac. faculties) / E.V. Gladukh, O.A. Ruban, I.V. Saiko and others. - Kh.: NPhU: Original, 2016. - 632p. : Named after. - (Series "National textbook")

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Lecture No. 2

Topic: "Requirements for starting substances and solvents (production of water for injection in industrial conditions). Preparation of parenteral solutions (isotonization, stabilization. – 2 hour .

Relevance of the topic: Drug technology (industrial drug technology) is one of the fundamental technological sciences. It consists of several key aspects that are important for modern medicine and patients: Efficacy and safety - Modern technologies allow the production of drugs with high efficiency and safety for patients. Accurate dosing, quality control and the absence of impurities make drugs more effective and safe. Innovations in the medical field: 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 treatment. Minimization of side effects: Technologies allow the development of drug formulas that minimize side effects and negative effects on the body. This provides more comfortable and safe treatment for patients. Fast production and delivery process: The use of modern technologies allows the acceleration of the production process of drugs, which is especially important in a rapidly changing medical environment, such as the spread of diseases or epidemics. Personalized medicine: Technology enables the development of 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 accessibility Improved manufacturing technologies can reduce production costs, making medicines more accessible to a wider range of patients, ensuring cost-effectiveness in the healthcare sector. Thus, the use of modern technologies for the manufacture of medicines is an important factor in improving the effectiveness of treatment, patient safety and the overall state of public health.

Purpose: : The discipline provides, on the basis of general knowledge and principles, regularities of factory production technology, to form in students knowledge about: theoretical foundations, acquisition of professional skills and abilities in the preparation of dosage forms, phased 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 facilities and personnel. To get acquainted with the preparation of parenteral solutions, information about pyrogenicity, and toning

solutions, methods of stabilizing solutions, emulsions and suspensions. The principle of ampouleing solutions in an inert gas environment.

Basic concepts:

1. ***Water for injection*** is the most common solvent for parenteral drugs.

2. ***Pyrogenicity*** is possessed by living microorganisms, their waste products (endotoxins), and the bodies of dead bacteria, which may be contained in solutions after sterilization.

3. ***Depyrogenation*** **-** procedures for removing, destroying, or inactivating pyrogens.

4. ***Chemical methods*** are based on the interaction of pyrogens mainly with chemicals.

5. ***Physical methods*** are based on measuring electrical conductivity and polarographic maxima.

6. ***Reverse osmosis*** - a method for removing endotoxins .

7. ***Physical stabilization methods*** - elimination of factors that cause or accelerate negative processes in parenteral solutions.

Lecture plan and organizational structure:

No. No. pp.	**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* Defining learning goals. Providing positive motivation. *Main stage* Presentation of lecture material. Plan:		 Combined lecture	 1% 2%

III 4. 5. 6.	**1.** equirements for starting materials and solvents **.** 2. ntroduction to high-performance case-type apparatuses, thermocompression distillers of various designs, and multistage reverse osmosis units. 3. n the News about pyrogenicity. 4. Preparation of parenteral solutions. 5. Physical, chemical and other stabilization methods. *Final stage* Lecture summary, general conclusions. The lecturer's answers to possible questions. Tasks for student self-study.	I II III	Slides Bibliography, questions, assignments.	90% 2% 3% 2%

Structural and logical diagram of the lecture content

1. Main requirements for starting materials and solvents.

1.1. Obtaining water for injections in industrial conditions.

1.2 Preparation of parenteral solutions.

1.3 Obtaining water for injections in industrial conditions

2. Characteristics and types of high-performance case-type apparatuses, thermocompression distillers of various designs and multi-stage reverse osmosis units.

3. News about pyrogenicity

3.1 Methods for detecting pyrogens.

3.2 Chemical methods, physical methods, bioassay methods.

4. Varieties of the LAL method.

5. Depyrogenation.

6. Basic methods of preparing parenteral solutions.

6.1. Isotonization solutions

6.2 Stabilization of solutions

6.3 Chemical stabilization methods.

6.4Physical stabilization methods

7. Stabilization of solutions of salts of weak bases and strong acids

8. Stabilization of emulsions and suspensions.

9. The influence of surfactants on the kinetics of chemical reactions.

10. Stabilization of solutions of easily oxidizable substances.

11. Theory of redox processes.

12. The principle of ampouleing solutions in an inert gas environment.

Content of the lecture material (lecture text)

REQUIREMENTS FOR THE WEEKEND SUBSTANCES AND SOLVENTS

All starting and auxiliary substances must have a permit for medical use and meet the requirements of the ND. PLZ must be made from substances of the highest purity. For some substances used for the preparation of parenteral solutions, the ND sets increased requirements to purity from unacceptable chemical and others impurity — this is the grade "for injections". These include: magnesium sulfate, calcium chloride, sodium caffeine benzoate, euphylline, hexamethylenetetramine, sodium

citrate and hydrocitrate, sodium bicarbonate and other substances. For glucose and gelatin substances, high requirements for microbiological purity have been introduced, since they are good nutrient media for microorganisms. Some APIs should not contain pyrogenic substances.

As solvents for medicinal substances in the preparation of parenteral solutions, water for injection, isotonic solutions of some LRs and non-aqueous solvents of natural, synthetic and semi-synthetic origin that meet the requirements of the ND are used. Strict requirements are imposed on solvents: high dissolving capacity, necessary chemical purity, pharmacological indifference, chemical compatibility with the API, i.e. absence of chemical interaction, stability during storage, availability and low price.

Water for injection is the most common solvent for parenteral drugs. It is the most convenient of the physiological from a solvent point of view, since in quantitative terms it is the main component of all body secretions and at the same time the main agent that transports nutrients and metabolic products in the body.

It is known that a number of drugs due to poor solubility in water either cannot be used in medical practice, or to a large extent lose their therapeutic effect. These include steroid compounds, antiseptics, furanochromones, alkaloids, glycosides and other substances. To improve their solubility, non-aqueous solvents are used: alcohols, ethers, oils, etc. Non-aqueous solvents, along with other requirements, must be low-toxic, transparent, and have a low viscosity.

Obtaining water for injections in industrial conditions

According to regulatory requirements, water for injection (*Aqua pro injectionibus*) must meet all the requirements for purified water, and must also be sterile and pyrogen-free. Water for injection must be free from mechanical visible inclusions, which are determined in accordance with the regulatory documents.

The shelf life of water for injection is regulated as 24 hours from the moment of receipt, provided that it is stored in aseptic conditions. With longer storage, water can absorb carbon dioxide and oxygen from the air and further interact with medicinal substances, packaging material, causing migration of metal ions, or be a

medium for the development of microorganisms. Therefore, the most preferable is the use of freshly prepared water. Its most reliable storage is guaranteed by special systems ("circulation loops") made of inert material, in which the water is at a high temperature (80-95 °C) and in continuous motion (1 - 3 m/s).

IN pharmacopoeias some countries water for injections share:

- for water for injection - “ in bulk ”, which is used as a solvent in the production of PLZ;
- Sterile water for injection, packaged in suitable sealed containers and sterilized by heat treatment, which is used for dissolving or diluting substances, concentrates or parenteral drugs application before introduction.

Water for injection obtained by distillation is not always suitable for the production of immunobiological, bacterial and some injectable drugs. Therefore, it is often necessary to further purify the water and obtain highly purified water for injection (*Aqua valde purificata*), i.e. especially pure, sterile, pyrogen-free, free from impurities of organic and inorganic substances (specific electrical conductivity - no more than 1.1 μS/cm at a temperature of 20 °C, total organic carbon content - no more than 0.5 mg/l, nitrates — no more 0.00002 % (0.2 million $^{-1}$), heavy metals — no more 0.00001 % (0.1 million $^{-1}$), bacterial endotoxins — Less 0.25 IU/ml, total number of viable aerobic microorganisms — not more 10 in 100 ml of water). They are obtained by combined membrane separation methods (for example, double osmosis with deionization and ultrafiltration) in specially designed equipment. To ensure the proper quality of such water, validated procedures and regular monitoring of electrical conductivity and microbial purity during the production process should be used.

In industrial conditions, obtaining water for injection and purified water (used for the preparation of production and primary packaging) are carried out using *high-performance case apparatuses, thermocompression distillers of various designs and multi-stage reverse osmosis units.*

Representatives of column chamber apparatuses are multistage distillers, which come in various designs. The most commonly used are ***three-six-stage***

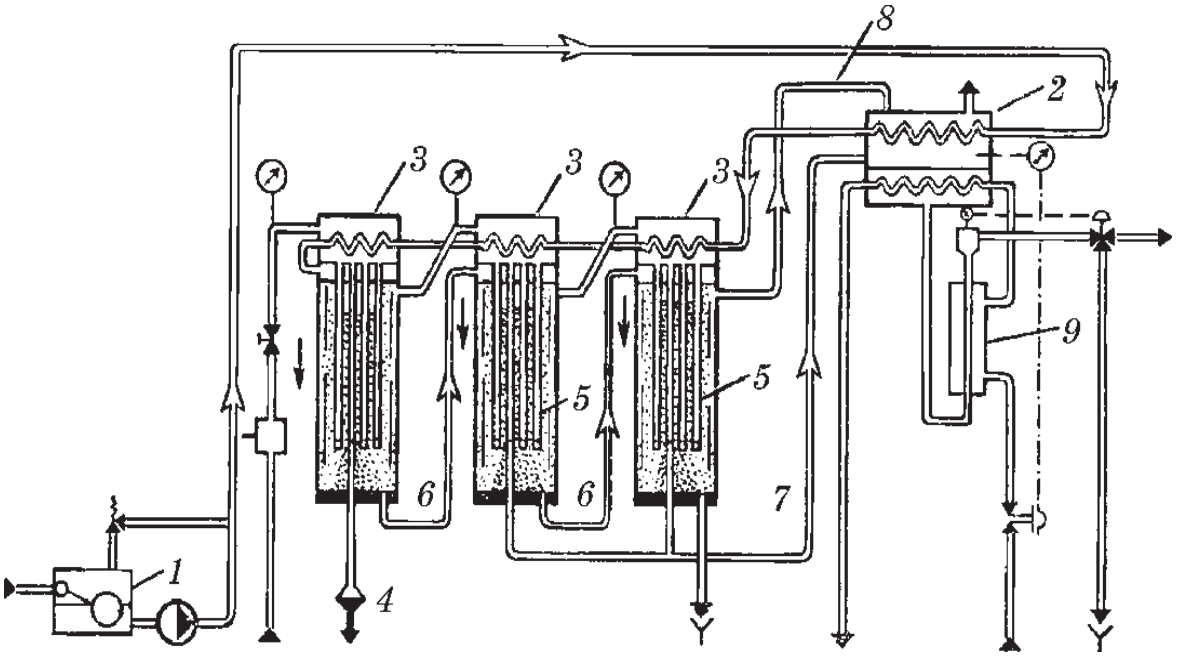
column apparatuses with bodies (evaporators) arranged vertically or horizontally. A feature of column apparatuses is that only the first evaporator is heated by steam, the secondary steam with the first hulls comes in second as a heater, where condenses and purified water is formed. From the second housing, the secondary steam enters the third — as a heater, where it also condenses. Thus, purified water is obtained from the second and third housings (in a three-stage distiller). The productivity of such a plant is up to 10 t/h of distillate. The quality of the obtained distillate is satisfactory, since the bodies have a sufficient height of the vapor space and the removal of the droplet phase from the vapor using separators is provided.

For software apyrogenicity received water necessary create conditions that prevent pyrogenic substances from entering the distillate. These substances are non-volatile and do not distil with water vapor. Contamination of the distillate with them occurs by the overturning of water droplets or their removal by a steam jet into the refrigerator. Therefore, the issue of improving the quality of the distillate is constructively solved by using distillation apparatuses of appropriate designs, in which the possibility of the overturning of the droplet-liquid phase through the condenser into the collector is excluded. This is achieved by installing special traps and reflectors, and by placing steam lines high relative to the evaporation surface. It is also advisable to regulate the heating of the evaporators, ensuring uniform boiling and optimal evaporation rate, because excessive heating leads to rapid boiling and overturning of the droplet phase. Carrying out preliminary water treatment by desalination also reduces foaming and, consequently, the release of water droplets into the vapor phase.

On some chemical and pharmaceutical enterprises water for injections are received by with help ***distiller "Mascarini"*** (Italy), productivity whose close 1500 l/h. He equipped device control water purification , bactericidal lamps, air filters, a device for removing pyrogenic substances, as well as a double water distillation unit with a capacity of 3,000 l/h.

The Vaponix distiller (USA) includes a combination of methods: a sharp change in the speed of the steam flow, its filtration through a special filter with a hole diameter of 40 microns, and the separation of drops in a centrifugal field.

The three-body water distiller "Finnaqua-300-S-4" (Finland) operates by using demineralized water and provides its four-fold distillation.



Principle works water distiller "Finn Aqua":

1 — pressure regulator; *2* — condenser-refrigerator; *3* — chamber heat exchanger previous heating; *4* — vapor barrier device; *5* — zone evaporation; *6* , *7* , *8* — pipes; *9* — heat exchanger

Water enters the condenser through the pressure regulator, passes through the heat exchangers of the preheating chambers, and after heating enters the evaporation zone, which consists of a system of tubes heated internally by heating steam. The heated water is supplied to the outer surface tubes, What heated, in in the form of films, flows down on them and is heated to boiling. In the evaporator, due to the surface of the boiling films, an intense flow of steam is formed, which moves from bottom to top at a speed of 20 - 60 m/s. The centrifugal force that arises in this case ensures that the drops flow into the lower part of the housing, pressing them against the walls.

Most perfect currently **thermocompression distillers** , the design of which was developed by the Italian company "Voparase". Their advantage over other types of distillers is that to obtain 1 liter of water for injection, it is necessary to spend 1.1

liters of cold tap water. In other devices, this ratio is 1:9 -1:15. The principle of operation of the device is that the steam formed in it, before entering the condenser, passes through a compressor and is compressed. When cooled and condensed, it releases heat, the magnitude of which corresponds to the latent heat of vaporization, which is spent on heating the cooling water in the upper part of the tubular condenser. The device is supplied with water from the bottom up, the distillate outlet is top down. Distiller productivity — up to 2.5 t/h. The quality of the obtained pyrogen-free water is high, since the droplet phase evaporates on the walls of the evaporator tubes. Heating and boiling in the tubes occurs evenly, without interruptions, in a thin layer. The height of the vapor space also contributes to the retention of drops from the steam.

Disadvantages — complexity of construction and operation .

The most common method of obtaining water for injection until recent years was distillation. This method requires a significant amount of energy, which is a major drawback. Among other disadvantages, it is worth noting the bulkiness of the equipment and the large area occupied by it; the possible presence of water pyrogenic substances; difficulty of maintenance and so on. When developing new designs of modern distillers, the listed disadvantages are taken into account. Membrane separation methods are devoid of these disadvantages. New membrane separation methods are increasingly being introduced into production, since they occur without phase transformations and require significantly lower energy costs for their implementation. They are recognized as economically advantageous and promising. Membranes methods cleaning are being grounded on properties partitions (membranes), which have selective permeability, due to which separation is possible without chemical and phase transformations. Thanks to the development of membrane technology, it has become possible to obtain sterile, pyrogen-free water using ultrafiltration installations. Such purification systems have a sterilization installation, ultrafiltration membranes and devices for water ozonation, and UV emitters of submerged and non-submerged types can also be used. The combination of UV radiation and ozonation methods leads to photolysis of ozone with the formation of hydroxyl radicals, which react with organic substances, including

pyrogens, forming carbon dioxide, water and a small amount of other compounds. In addition, UV radiation prevents the replication of bacterial DNA, and ozonation, due to its high oxidation potential, contributes to the destruction of spore forms of microorganisms. Some enterprises use modern water purification plants, which consist of several mechanical disc filters, ceramic filters with automatic flushing, carbon filters, two water softening units, reverse osmosis system with automatic membrane flushing, recycling concentrate and purified water, systems water filtration (1 microns). They also include an electroionizer, circulation pumps, an ultraviolet disinfection system, and means of automatic regulation and control of technological parameters. Such installations are highly productive and meet GMP requirements.

Water for injection obtained by any of the above methods must meet the requirements of the ND and be pyrogen-free.

News about pyrogenicity

With parenteral, especially intravascular administration of drugs, a rapid increase in body temperature to 40 is sometimes observed. °C. This phenomenon is accompanied by increased pulse, chills, profuse sweating, nausea and headache. In especially severe cases, these phenomena lead to death. They are associated with the presence of pyrogens in the solution.

Pyrogenicity is possessed by living microorganisms, their waste products (endotoxins), and the bodies of dead bacteria, which may be contained in solutions after sterilization. Pyrogenic substances are usually divided into *exogenous* (mainly bacterial) and *endogenous* (cellular and tissue). The source of endogenous pyrogens can be leukocytes and blood proteins, which under certain conditions form and allocate biologically active substances from pyrogenic properties (leucopyrogens).

From a chemical point of view, pyrogens are complex substances with a molecular weight of 10,000–20,000 and a particle size of 50 to 1 μm, which consist mainly of lipopolysaccharides adsorbed on a protein carrier. Pyrogens are soluble in water, insoluble in alcohol and acetone, and resistant to the action of elevated temperature. Heating in steam sterilizers at 120 °C for 20 min leads to the death of

microorganisms, but does not destroy pyrogens. The sensitivity of pyrogens to high temperature is different, and the change in pH of aqueous solution practically not affects on their thermolability. Dry heat treatment at 250 °C for 30 min leads to almost complete decomposition of endotoxins, but the thermal depyrogenation process is used only for objects that can withstand such harsh treatment (glass ampoules, vials, etc.).

When heated to a temperature of 180 °C, the concentration of endotoxins in water does not decrease, therefore, it is practically impossible to free water or parenteral solutions from them by thermal sterilization. Therefore, it is necessary to strive for the concentration of pyrogenic compounds to be minimal even before processing the objects. Since pyrogenic substances are sensitive to the action of oxidants, for example, hydrogen peroxide or potassium permanganate, this property is used in the sanitary preparation of production.

Pyrogen test — one of the tests that characterizes quality and safety PLZ. Ago necessary not only have guaranteed methods detection and removal of pyrogenic substances, but provide measures to prevent contamination of the PLZ with them during their manufacture.

Methods for detecting pyrogens. For practical purposes, along with methods for removing pyrogenic components, methods for their detection are of great importance, which are divided into chemical, physical, and biological (bioassay methods).

Chemical methods are based on the performance of certain color reactions.

Physical methods are based on measuring electrical conductivity and polarographic maxima. Due to a number of shortcomings of the first two methods , ***bioassay methods*** introduced into the pharmacopoeias of various countries of the world are most often used. To date, the main and officially accepted in all countries method of testing medicines for the presence of *pyrogenic impurities* is This is a method based on three measurements of the body temperature of a rabbit after intravenous administration of the test drug. An increase in temperature of 0.5 °C or more, according to the requirements of the pharmacopoeia, is considered to be

evidence of the presence of pyrogens .

In addition to the above-mentioned pyrogenic substances, many pharmacopoeias identify *bacterial endotoxins* , the source of which is gram-negative microorganisms. Endotoxins — the most common cause of pyrogenic toxic reactions. Their activity is much higher than that of most other pyrogenic substances. Bacterial endotoxins are very small and pass through the densest filters with pore sizes from 0.005 to 0.001 microns.

By chemical structure, endotoxins are: lipopolysaccharides. Despite the fact that pyrogens of a different chemical nature exist, it is usually the absence of bacterial endotoxins in a medicinal product that is taken into account. when recognizing the solution as pyrogen-free. It is generally accepted that if the depyrogenation process leads to the destruction of endotoxins, then it guarantees the absence of other pyrogens. Recently, the method of testing drugs for pyrogenicity *in vitro* using a lysate of amebocytes of the horsetail *Limulus polyphemus* (LAL test) has become widely used. The addition of a solution with endotoxins to a solution of the lysate containing an endotoxin-binding protein leads to the appearance of turbidity, precipitation or gelation. mixtures. The reaction rate depends on the concentration of endotoxins, pH and temperature. The concentration of endotoxins can be determined by the amount of dye released in the lysis reaction of the chromogenic peptide in the lysate solution (LAL reagent) after its activation by endotoxins.

There are several types of LAL methods: ***gelation methods, turbodimetric kinetic method, kinetic method using a chromogenic peptide*** **, and** ***endpoint method using a chromogenic peptide*** . Gelation methods are divided into methods A and B. Using method A, the limiting concentration of endotoxins (in IU per 1 ml) is determined, using method B - semi-quantitative content of bacterial endothelium and average geometric concentration values, which has be less than the limiting concentration.

These methods have several advantages over biological testing for pyrogens: they are 5-10 times more sensitive, the result is obtained faster, and endotoxins can

be quantified. In addition, the listed methods can be used to control drugs that cannot be tested on rabbits. One of the disadvantages of these methods is their specificity for endotoxins of gram-negative bacteria, i.e. the risk of not detecting the presence of pyrogens of other origin in medicinal products. Replacing the rabbit pyrogen test with the LAL test actually determines the use of an alternative method, therefore, validation is required.

Methods for removing pyrogenic substances.

Depyrogenation is the procedure for removing, destroying or inactivating pyrogens. Various objects can be subjected to depyrogenation (solvents, PLS, substances, excipients, primary packaging, technological vessels and equipment, etc.). With such a variety of objects, there are a large number of different options for carrying out depyrogenation treatment. Usually, methods for removing pyrogens are divided into two large groups. The first includes methods that which lead to endotoxin removal from the surface products, equipment or from solutions. The second group combines methods that lead to the destruction or inactivation of endotoxins. Depyrogenation methods are also divided by the nature of the processes occurring into *chemical, enzymatic and physical* . Due to the possible interaction of components, chemical and enzymatic methods are not very suitable for the industrial production of parenteral drugs. However, with the help of chemical agents, depyrogenation of external and internal surfaces of equipment, production premises, pipelines, etc. is carried out.

Chemical methods are based on the interaction of pyrogens mainly with chemicals. For the inactivation of endotoxins, treatment with acid or alkali can be used. Hydrolysis in an acidic or alkaline environment leads to partial destruction of the lipopolysaccharide molecule and a decrease in its biological activity. Heating or boiling accelerates hydrolysis, and the destruction of the endotoxin molecule is deeper.

The easiest way to remove pyrogens from the surface of equipment, containers, and closures — This is multiple rinsing with clean water (the last time with water for injection). This method is used for materials that cannot withstand

harsher treatments, such as plastic products, rubber stoppers, etc. The effectiveness of the method depends on the purity of the water, the number of rinsing cycles, the adhesive properties of the materials being treated, etc. The use of disinfectant solutions (hydrogen peroxide, degmin, neochlor, chlorantoin, AHD 2000, deconex 50, lysoformin, sterilium, desefekt and other substances) does not guarantee the complete elimination of pyrogenic substances.

Physical methods of pyrogen removal are used for depyrogenization of primary packaging, pipelines, internal surfaces of equipment, obtaining pyrogen-free medicinal substances, water for injection, parenteral solutions. These methods are based on the use of physical factors (temperature, radiation, ultrafiltration, sorption, etc.), which lead to the removal, inactivation or destruction of pyrogens.

One of the most reliable methods of depyrogenation is This is *a thermal treatment* of an object, although complete removal of pyrogens can only be achieved under strict conditions. This method is relevant for the treatment of thermostable substances (sodium chloride and other substances), glass containers (ampoules, vials) at temperatures above 180 °C in drying and sterilization tunnels or dry heat cabinets.

The ultrafiltration method is widely used to remove endotoxins from solutions . Their effective removal can be achieved using filters with within separation by molecular by mass 10000 - 100000 Daltons. Such a wide range is determined by the specific properties of endotoxin molecules. Usually in solutions they form micelles with molecular by mass 10,000—20,000. If in If positively charged ions are present in the solution, very large aggregates with a molecular weight of over 100,000 are formed around them. Dalton. Therefore, the efficiency of ultrafiltration largely depends on the properties of the solution, and the method of separation of endotoxins must be selected individually.

Conventional sterilization filtration through filters with a pore size of 0.22 microns is completely ineffective. These filters retain microorganisms, but endotoxins — only small fragments of the outer wall of the bacteria. On the surface only one gram-negative bacteria can to be up to 3.5 million endotoxin molecules.

Another method of depyrogenation of parenteral solutions is based on the phenomenon *of adsorption of pyrogens* by activated carbon, kaolin, asbestos, cellulose, etc. The amount of pyrogenic substances is reduced after treatment with activated carbon or using activated carbon-based filters, while the efficiency of purification depends on the nature of the pyrogenic substances. Granulated coal is less effective. Coal used for purification of solutions must be very thoroughly purified, good washed with water, no contain pyrogens and dried at temperature 250 °C for 2 h. However, treatment of solutions with activated carbon does not always lead to complete depyrogenation. In addition, this method cannot be used to purify solutions of LRs that are easily adsorbed by carbon (for example, salts of alkaloids) or easily oxidized (ascorbic acid). A number of authors recommend using ion-exchange resins (for example, for amino acids) for purification from pyrogens, believing that they are more effective than activated carbon.

Because endotoxin molecules are negatively charged, they can be removed from solution by due to adsorption on positively charged filters, for example on asbestos filters. The use of deep asbestos filters can be particularly effective. The disadvantages of the method include the possibility of binding of molecules of the active substance and the restriction of the use of asbestos in pharmaceutical production.

Methods for removing endotoxins include the use of *endotoxin-binding protein* , isolated from a lysate of Limulus amebocytes in pure form. It is an excellent sorbent that specifically binds to endotoxins. Filters and resins have been created based on the isolated protein, which are used to remove endotoxins from parenteral solutions.

A very important way to remove endotoxins — *reverse osmosis.* The pore sizes of the reverse osmosis membrane are so small that they are only able to pass water molecules, while retaining "larger" ions. However, this method cannot be considered as one that absolutely guarantees the absence of pyrogens.

Classic methods for removing endotoxins from water include *multi-stage distillation* , in which water goes through several stages of phase transition. If all process parameters are met, the resulting water is pyrogen-free.

On some enterprises Ukraine use original a filter for obtaining pyrogen-free water, the action of which is based on *the retention of microorganisms and pyrogens by dielectric materials in an electric field* , the lines of force of which are directed perpendicular to the movement of the flow of the liquid being sterilized.

Physical methods for removing pyrogens from solutions include *their destruction using ultrasound* with a frequency of 2 MHz and an intensity of 2 W/cm ^{2} for 10 minutes. This achieves complete destruction of pyrogenic substances.

can be used to inactivate endotoxins . Under the influence of gamma radiation, there is a decrease in activity and partial or complete destruction of the endotoxin molecule. However, the method has significant limitations in application, since it leads to significant physical and chemical changes in the treated objects. Non-aqueous solvents for the preparation of parenteral dosage forms, in addition to water for injection, non-aqueous solvents are also used. The use of these solvents allows you to obtain solutions from insoluble or poorly soluble substances in water, eliminate the hydrolysis of BAS, and prolong the therapeutic effect of LR. Non-aqueous solvents have different dissolving power, anti-hydrolysis, stabilizing and bactericidal properties. However many with They cannot be used to prepare sterile solutions due to their pharmacological activity, toxicity, and sometimes hemolytic action. In this regard, the following requirements are imposed on non-aqueous solvents: they should not have acute and chronic toxicity, cause local irritation; should have high solubility of the API; be chemically and biologically compatible; be stable during sterilization; have a negligible viscosity. Except that, temperature boiling has be no more 100 °C, freezing temperature - no higher than +5 °C.

By chemical nature , non-aqueous solvents are divided into several groups: *fatty vegetable oils, mono- and polyhydric alcohols, ethers and esters, amides, sulfones and sulfoxides* , etc.

For the preparation of parenteral solutions, non-aqueous solvents are used, both individual and mixed: water-glycerol, water-propylene, alcohol-water-glycerol, etc. Mixtures of fatty oils with benzyl benzoate, ethyl oleate are very widely used. Mixed solvents have a greater dissolving power than each solvent separately. This phenomenon is called ***co-dissolution*** , and solvents — cosolvents.

Vegetable oils — Non-aqueous solvents used for the preparation of injectables are the most common solvents after water. Parenteral preparations based on fatty oils are used for intramuscular injections and, quite rarely, for subcutaneous injections.

Vegetable oils — These are esters of unsaturated fatty acids, a mixture of phosphatides, free fatty acids and other substances. Fatty oil contains lipases, which, in the presence of the slightest amount of water, cause saponification of the oil with the formation of free fatty acids, therefore the oils must be completely dehydrated. The products formed can interact with many medicinal and auxiliary substances, changing their properties, In addition, oxidized oils irritate nerve endings and can cause pain.

These are transparent, slightly colored oily liquids, low viscosity, odorless or with a weak odor, insoluble in water, slightly soluble in alcohol, slightly soluble in ether, chloroform, petroleum ether. Oils for the preparation of sterile solutions should be obtained by cold pressing from fresh seeds. When analyzing fatty oils, their color, taste, odor, solubility and numerical indicators (acid, ether, peroxide, hydroxyl, iodine numbers, saponification number, specific viscosity, etc.) are determined. Fatty oils should not contain water, protein, mineral and other foreign impurities.

The disadvantages of oil solutions include their relatively high viscosity, painful injections, poor absorption and the possibility of granulation at the injection site. To reduce viscosity, ethyl or ethyl glycol ether is sometimes added. The solubility of some substances in oils is increased by adding co-solvents or solubilizers. (benzyl alcohol, benzyl benzoate), which simultaneously increase and stability of oil solutions. The most widely used oils are peach, almond, olive, sunflower, soybean and others, which must be refined and deodorized. All oils intended for the preparation of injection solutions must be subjected to preliminary sterilization at a temperature of 120 °C for 2 hours.

Non-aqueous solvents are also used for the preparation of parenteral drugs containing hormones, fat-soluble vitamins, antibiotics, camphor, barbiturates, and other substances.

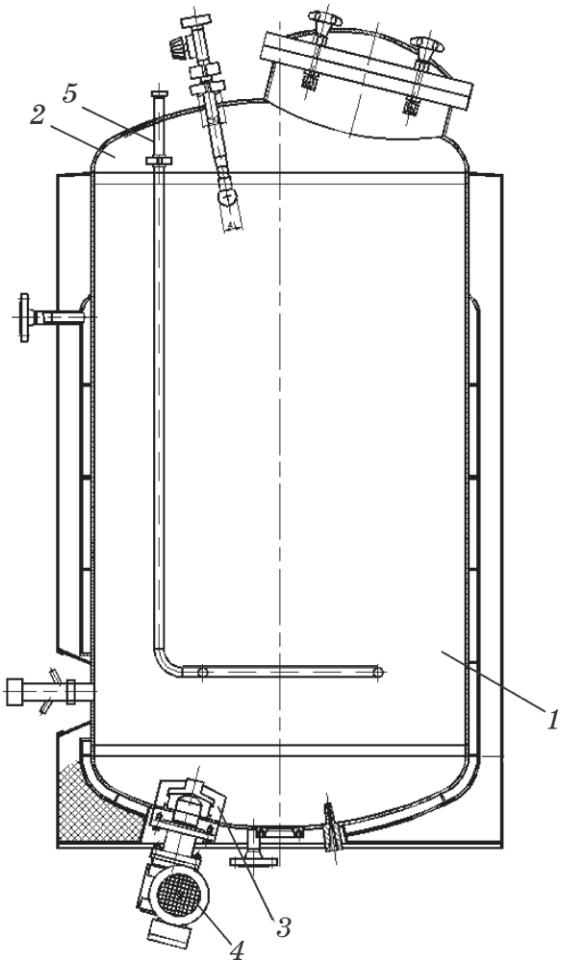
PREPARATION PARENTERAL SOLUTIONS

Preparation of the solution includes the following operations: dissolution of substances, isotonization, stabilization, introduction of preservatives, filtration. Depending on Some of the operations may be excluded from the properties of the API, such as isotonization, stabilization, and introduction of preservatives.

The preparation of solutions for parenteral use is carried out in special production facilities of cleanliness classes C or A/B with observance of all the rules of asepsis. The preparation of aqueous or non-viscous solutions for injections is carried out by the mass-volume method, using hermetically sealed reactors made of inert materials, equipped with a shell and a stirring device. In cases where the density of the solvent is significantly different from the density of water, the mass method is used, in which both the drug substance and the solvent are taken by mass. The dissolution of slowly soluble or poorly soluble drugs is carried out by heating and stirring.

The surfaces of reactors and collectors in contact with the product are made of materials that do not react with it, do not have absorption properties and do not release substances in such quantities that this could affect the quality of the product. Currently, the dissolution of substances is mainly carried out in stainless steel reactors with a lower turbine mixer to eliminate the possibility of lubricants getting into the solution.

Modern reactors used for the preparation of PLZ are manufactured by some domestic manufacturers, but mainly by foreign companies, which have proven themselves well on the pharmaceutical equipment market (— BOSCH" (Germany), — Alloy Produkts Group Waukes Wiskonsin" (USA), "Lab & Pharma" Czech Republic, —KATES" Poland, etc.). Such reactors are vertical cylindrical apparatuses with or without a shell, an elliptical lid and a bottom with a total capacity of 100 to 1000 l, made of stainless or special steel (Fig. 14.6). They are equipped with an ultrasonic liquid level sensor, a solution temperature sensor, a bubbler (sometimes removable) and allow the solution to be saturated with an inert gas.



Puc. 14.6. Construction modern reactor:

1 — corps; *2* — cover; *3* — turbine mixer; *4* — electromagnetic drive; *5* — bubbler

Reactors are mostly equipped with an automated control system that provides functions for presetting the necessary technological parameters, a device for totalizing the water or solution, countdown, and totalizing the difference between the set values .

The design of such a device minimizes the risk of microbial contamination, meets GMP requirements, and has undeniable advantages.

1. In completely bottom reactor built-in turbine mixer, which provide-

provides better dissolution of active substances due to the intensity of mixing. The frequency of rotation of the mixer is set by a frequency converter, which is very important when dissolving poorly soluble substances. This design of the mixer with

an electromagnetic drive guarantees the absence of stagnant zones and accumulation of the product, ease of maintenance and the absence of a direct connection of the mixer with its drive, which is sometimes a critical parameter, since it can contaminate the solution with lubricants .

2. The reactor design has an original shell, divided by special ribs in such a way that steam (refrigerant) fills it in a spiral, resulting in uniform heating (cooling) of the solution with more economical use of the heat or coolant.

3. Another advantage of such reactors is CIP-SIP cleaning system ("cleaning in place") in the form of two devices for washing the apparatus (spray), which allow for high-quality preparation of the apparatus for operation and economical use of highly purified water. Some provide additional polishing and brightening of the inner surface of the reactor.

4. Some reactors are equipped with special elevators that facilitate the loading of bulk materials.

5. Reactors can operate at both excess and reduced pressure.

6. The presence of a bubbler in the design ensures the possibility of gas protection of the solution from the action of oxygen.

Isotonization solutions

Among the PLZ, a special group is made up of *isotonic solutions* , which are understood as solutions with an osmotic pressure equal to the osmotic pressure of body fluids (blood plasma, lymph, cerebrospinal fluid, etc.). Osmotic pressure of solutions — a consequence of the thermal motion of the molecules of a dissolved substance, which strives to occupy the largest possible volume. In the body, it is maintained at a constant level by the action of self-regulators. The osmotic pressure of blood plasma is normally maintained at 725.2 kPa, or 7.4 atm. Solutions with less osmotic pressure are called *hypotonic,* with bigger — *hypertensive.*

When a large amount of solutions is administered in the form of intravascular infusions, the osmotic pressure of the body fluids is disturbed. This is explained by the fact that cell membranes, having the property of semi-permeable, allow water to pass through and prevent the penetration of many substances dissolved in them. In

this regard, if the cell is surrounded from the outside by a solution with a different osmotic pressure than the pressure inside the cell, then water moves into the cell or out of the cell until the concentration is equalized, i.e. the phenomenon of osmosis is observed.

When a hypertonic solution is introduced into the blood ($P_{\text{solution)}} > > In_{\text{the middle cells}}$) water leaves the cell. It becomes dehydrated, and the phenomenon of plasmolysis occurs, in which erythrocytes shrink. When a hypotonic solution is introduced ($P_{\text{in solution}} < P_{\text{in the medium) cells}}$) fluid enters the cell until the concentration equalizes. The cell swells, the cell membrane may burst, and the cell may die. This phenomenon is called lysis, and for erythrocytes - hemolysis. In addition, intramuscular and subcutaneous administration of non-isotonized solutions causes pain, which is the stronger the more sharp the osmotic difference. Therefore, when intravascularly using some parenteral solutions, their isotonization is necessary.

Isotonic concentrations of LR in solutions can be calculated by the following methods:

- method, built by by law Van't Hoff;
- cryoscopic method, built by by law Raoul;
- method equivalents medical substances by sodium chloride.

The graphical calculation method is also used for the border isotonic concentrations, which allows, using the developed nomograms, to quickly, but with some approximation, determine the amount of sodium chloride necessary for isotonization solution medical substances.

To prevent such dangerous complications of parenteral administration of drugs as hypo- and hyperosmolar states, impaired blood clotting, thrombus formation, and so on, recently, *osmolality* and *osmolarity indices have been determined in parenteral solutions* .

According to the definition of the European Pharmacopoeia, ***osmolality*** □ ***m*** — This is an indicator that allows you to estimate the total contribution of various dissolved substances. in the osmotic pressure of a solution. Osmolality is expressed in osmoles per kilogram of solvent — *osmol/kg* (in practice, as a rule, milliosmoles

per kilogram — *mosmol/kg is used*). *Osmol* is the ratio of the molecular mass of a substance divided by the number of units or ions that are formed when it dissolves. An approximate calculation of the osmolality of an aqueous solution is carried out by the formula

□ •*m*• □ = $_{m}$ □,

where □ is the total number of ions formed from one molecule of the solute as a result of dissociation. If the solute does not dissociate into ions, □ = 1; *m* is the molality of the solution, i.e. the number of moles of solute per 1 kg of solvent; □ is the molal osmotic coefficient, which takes into account the interaction between ions of opposite sign in the solution and depends on *m* .

Order with concept "osmolality" in practices used the concept ***of osmolarity*** □ as an indicator that also allows us to estimate the total contribution of various dissolved substances to the osmotic pressure of a solution (usually expressed in *mosmol/l*).

As we can see, both indicators are similar in content and are distinguished by each in a different way of expressing the concentration of solutions per unit mass (molar) or per unit volume (molar). The ratio quantities osmolarity and osmolality can to submit as mass-volume concentration solvent in solution, which follows with Definition of these concepts:

$$\frac{\square}{\square} = X,$$

where *X* — amount of solvent in 1 liter of solution, kg; □ — osmolarity of the solution, osmol/l of solution; □ — osmolality of the solution, osmol/kg of solvent.

For dilute solutions close to ideal, the values of osmolality and osmolarity can be calculated theoretically. However, as the concentration of the solution increases, the interaction between its particles increases, and the actual osmolality (osmolarity) decreases compared to the ideal. Therefore, the theoretical calculation of the osmolality (osmolarity) of highly concentrated solutions solutions, as well as solutions of substances with a high molecular weight (for example, protein

hydrolysates) is impossible. In such cases, these indicators are determined experimentally using osmometers, the principle of operation of which is based on measuring the decrease in the freezing point of the solution or the vapor pressure above it. The results are considered reliable if the obtained value does not exceed the osmolality values of two standard solutions used to calibrate the osmometer. Sodium chloride solutions are used as standard solutions. The determination method is given in the State Federal University (clause 2.2.35).

Decrease temperatures freezing on 1.86 °C and decrease pressure couples on 40 Pa (0.3 mm mercury (C.) at a temperature of 25 °C corresponds to 1 osmol per 1 kg of water. The relationship between osmolality and freezing point depression □ *T* is expressed by the ratio:

$$\square\ m = \frac{\square T}{1.86} \square 1000 \text{ mosmol/kg.}$$

Determining the osmolarity of solutions is important when using parenteral nutrition (correction of gross disturbances of water-electrolyte and acid-base balance, struggle from life-threatening conditions - shock, cerebral edema, etc.), when infusion is necessary within 24 hours The limiting factor in parenteral nutrition is the amount of fluid administered, which affects the circulatory system and water and electrolyte balance. balance. WITH another side, with review on defined boundaries "endurance" of veins, solutions of arbitrary concentration cannot be used. Osmolarity is about 1100 mosmol/l (20 % sugar solution) in an adult is the upper limit for administration through a peripheral vein .

The osmolarity of blood plasma is about 300 mosmol/l, which corresponds to a pressure of almost 780 kPa at 38 °C. This value — starting point for the stability of infusion solutions. For parenteral solutions used in practice, the osmolarity value can range from 200 to 700 mosmol/l. The value of osmolality (osmolarity) should be indicated on the labels of infusion solutions.

Stabilization of solutions

During the manufacture and storage of some medicinal products, changes in their properties are often observed, which occur with different speeds and degrees of detection. This is due to a decrease in the content of APIs or a decrease in their pharmacological activity, changes in the properties of dosage forms, etc. Such changes affect the shelf life (storage) of the products, which can range from several hours (antibiotic solutions) or days (enzyme solutions) to several years. Special attention is currently being paid to the task of increasing the stability of medicinal products.

The processes occurring in preparations can be conditionally classified into physical, chemical and biological. The conditionality lies in their interrelation: chemical transformations can cause changes in physical properties, while physical changes cause undesirable chemical processes. Biological processes are accompanied by both chemical, as well as physical transformations.

Physical processes that occur mainly during storage include the enlargement of particles of the dispersed phase, delamination, change in consistency, evaporation, sublimation, etc.

Chemical processes often occur during the manufacture of a drug, especially during thermal sterilization, and are accompanied by various chemical reactions. — hydrolysis, saponification, redox processes, photochemical and enzymatic transformations, less frequently observed polymerization and isomerization, etc.

Biological processes caused by the vital activity of microorganisms often lead to unwanted chemical transformations active substances, sometimes to changes external appearance medical forms.

The stability of pharmaceutical preparations depends on many factors: the initial quality of solvents, medicinal and auxiliary substances, the method of preparation, i.e. the technology of the drug, the type of dosage form, especially its aggregate state, the presence of oxygen and heavy metal ions in water and solutions, the pH of the solution, the temperature and time of sterilization, the primary packaging that comes into contact (the class and brand of glass of ampoules and vials), storage conditions (temperature, light), etc. The basic principle of drug stabilization involves the maximum elimination of factors that contribute to the change in medicinal substances.

Currently used methods for stabilizing drugs — chemical and physical — are often used in combination, complementing each other.

Chemical methods are based on the addition of chemicals — stabilizers, antioxidants and preservatives.

Physical methods are based on protecting medicinal substances from adverse environmental influences, using medicinal and auxiliary substances of high degree cleaning, use modern technological equipment and results of scientific research in the technology of dosage forms — use of non-aqueous solvents, dehydration of drugs, ampouleing in a stream of inert gases, etc.

Chemical stabilization methods. Stabilization of homogeneous disperse systems built on muffled process decomposition of medical substances by binding or neutralizing those chemical compounds that activate the destruction of the medicinal substance. Such compounds are contained in the solution in insignificant quantities or pass into the solution from the packaging material (glass, polymers) during its

technological processing and storage.

Optimal concentration hydrogen ions in parenteral solutions is a significant stabilization factor. It is achieved by adding stabilizers provided for in the ND, as well as using a complex of technological techniques in cooking process parenteral solutions. Stabilizers can slow down or accelerate undesirable chemical reactions, create certain pH values of solutions, increase the solubility of LR or keep the latter in a suspended state. Among the requirements imposed on stabilizers, we can note: therapeutic indifference, good solubility in the solvent, effectiveness in the concentrations used, chemical purity, availability. The choice of stabilizer, first of all, depends on the nature of the medicinal substances.

Despite the diversity and extreme complexity of the processes occurring in solutions, medicinal substances that require stabilization can be conditionally divided into groups:

- solutions salts, formed weak basics and strong acids;
- solutions salts, formed strong basics and weak acids;
- solutions easily oxidizable substances.

Stabilization of solutions of salts of weak bases and strong acids. This group includes solutions of salts of nitrogenous alkaloids and synthetic nitrogenous bases (Alc), which occupy a prominent place in the assortment of injection solutions. Depending on the strength of the base, the solutions have a neutral or weakly acidic reaction. The latter is explained by the hydrolysis of the salt, which is accompanied by formation weakly dissociated foundations and strongly dissociated

acids, i.e., the presence of hydroxonium ions OH_3^+ . This phenomenon is enhanced by thermal sterilization.

An increase in the excess of OH_3^+ ions (i.e., free acid) reduces the degree of water dissociation and inhibits hydrolysis, causing the equilibrium to shift to the left:

$$Alc{\bullet}HCl + H2O \rightleftarrows Alc\square + OH_3^+ + Cl^- \quad HCl + H_2O \; Alc\; OH_3^+ + Cl^-$$

A decrease in the concentration of OH_3^+ ions in the solution due to the alkalinity of the glass shifts the equilibrium to the right. Heating the solution during sterilization

increases the degree of water dissociation, and an increase in the pH of the solution due to the leaching of the glass causes increased hydrolysis of the salt, which leads to the accumulation of a sparingly soluble nitrogenous base in the solution.

In solutions of salts of very weak bases, poorly soluble in water, a slight increase in pH leads to the formation of a precipitate. This is observed in solutions of strychnine nitrate, papaverine hydrochloride, dibazole and other substances. With significant increases in the pH of the solution (strong alkaline glass), the release of strong free bases, for example, novocaine, is sometimes observed.

If the bases of the alkaloids are strong or well soluble in water, then when the pH increases, no precipitate is formed (bases are ephedrine, codeine, pilocarpine). Sometimes the free base does not precipitate because it is able to react with alkali to form soluble products (morphine, apomorphine, adrenaline). In addition, in a weakly alkaline environment, these solutions undergo oxidation with a change in color (the morphine solution turns yellow, the apomorphine solution turns green, and the adrenaline solution turns pink).

If an alkaloid or synthetic nitrogenous base has ester or lactone groups (atropine, scopolamine, novocaine, dicaine), then when weakly alkaline or neutral solutions are heated, the ester or lactone is saponified, which is accompanied by a change in pharmacological action.

The above changes necessitate stabilization of solutions of many nitrogen-containing alkaloids and bases. Most of them are stabilized by adding a 0.1 mol/l solution of hydrochloric acid, which neutralizes the alkali released by the glass and shifts the pH of the solution to the acidic side. This creates conditions that prevent hydrolysis, saponification of esters, and oxidation of phenolic and aldehyde groups. The amount of acid required to stabilize the solution depends on the properties of the medicinal substance. Most often, 10 ml of a 0.1 M solution of hydrochloric acid is added to 1 l of the stabilization solution, which corresponds to the formation of a 0.001 mol/l solution of acid (pH = 3...4). This amount of 0.1 M hydrochloric acid solution is recommended for atropine sulfate, strychnine nitrate, apomorphine hydrochloride, cocaine hydrochloride, dibazole, dicaine and other substances.

Stabilization of solutions of salts of weak acids and strong bases. In aqueous solutions, salts of weak acids and strong bases are easily hydrolyzed, creating a weakly alkaline reaction of the medium. This leads to the formation of sparingly soluble compounds and turbidity of the solution or precipitation, which is unacceptable for injection solutions. Hydrolytic processes are enhanced in an acidic environment, which is created by dissolving carbon dioxide in water. To suppress the hydrolysis reaction, a 0.1 M solution of sodium hydroxide or sodium bicarbonate is added.

Preparation of sodium nitrite solution is carried out by adding 2 ml of 0.1 M sodium hydroxide solution per 1 l (pH = = 7.5...8.2). Sodium thiosulfate solution has an environment close to neutral, and with a slight decrease in pH it decomposes with the release of sulfur:

$$Na2S2O3 + 2H2O + H2S2O3 + 2NaOH\ H_2S_2O_3 + H_2O + S\square + SO_2$$

Stable solutions are obtained by adding 20.0 g sodium bicarbonate per 1 l (pH = 7.8...8.4). When preparing sodium caffeine benzoate solutions, 4 ml of 0.1 M sodium hydroxide solution should be added per 1 liter (pH = 6.8...8.6).

Euphyllin as a complex salt of a very weak acid (theophylline) and a weak base (ethylenediamine) is easily decomposed in an acidic environment; adding a strong alkali to a solution of euphyllin also leads to decomposition of the salt. To obtain a stable solution, euphyllin of the “for injection” grade with an increased content of ethylenediamine (18-22 instead of 14-18%) is used. Water for injection must be freed from carbon dioxide by boiling.

If necessary, the optimal pH value of the solution is maintained using buffer solutions; however, their use is limited because many of them react with medicinal substances in the solution. ***Buffers*** and ***buffer solutions*** are solutions that are able to maintain an almost constant pH value when acid or alkali is added to them in small quantities.

The influence of surfactants on the kinetics of chemical reactions. Changing the pH of the medium — is not the only way to protect medicinal substances from hydrolysis. Recently, works have appeared on studying the influence of surfactants on

the kinetics of chemical reactions. It has been shown that nonionic and anionic surfactants inhibit, and cationic surfactants accelerate, the hydrolysis process of a whole group of medicinal substances. It has been established that in the presence of surfactants, a decrease or increase in the reaction rate is due to the formation of micelloassociates of surfactant molecules. Surfactant micelles have large colloidal dimensions and a greater volumetric capacity. Relatively small molecules of the medicinal substance can penetrate into the cavities of the micelles under the action of intermolecular attraction forces. Molecules with hydrophobic properties penetrate deep into the micelle. The hydrophilic molecule occupies a position between individual molecules of the micelle. The hydrophilic molecule of the medicinal substance attaches to the outer, most hydrophilic part of the micelle. The complex compounds that are formed are more stable than the medicinal substances. In this regard, surfactants are used to suppress the hydrolysis of medicinal substances, such as anesthetics, antibiotics, etc. In each specific case, the use of stabilizers requires careful study when introducing them into the composition of the injection solution.

Other ways are also used to maintain pH in the solution. without noticeable fluctuations. Because ampoule glass causes a change in the pH of solutions, to increase the chemical resistance of ampoules, silicone coatings are used on the inner surface of the ampoules or glass is replaced with polymers. However, siliconized and plastic ampoules have not yet found widespread use in our country.

Stabilization of solutions of easily oxidizable substances. The presence of oxygen in the dissolved state and in the gas space above the solution in the container is one of the main reasons for the oxidation of APIs in solutions. Many APIs are subject to oxidation: derivatives of aromatic amines and phenothiazines, alkaloids and nitrogenous compounds with phenolic oxygroups and amino groups, a number of vitamins, as well as other compounds with a mobile hydrogen atom. In the oxidation process, inactive and sometimes toxic products are formed. The rate of oxidative processes depends on the oxygen concentration, temperature, pH of the medium, the presence of catalysts, the state of aggregation, the concentration of substances in the solution, etc.

A very important factor affecting the oxidation rate, as well as the hydrolysis process, is the concentration of hydrogen ions, which can vary under the influence of

different brands of ampoule glass. It has been established that the neutrality of the glass is mainly determined by the amount of boric anhydride, the percentage of which in ampoule glass of the brand HC-3 is significantly lower than in German, American, Czech. And since the changes in the pH of the solution in ampoules of glass NS-3, USP-1 are minimal compared to other grades of glass NS-1, NS-2, AB-1, it is advisable to use ampoules of the 1st hydroclass of glass to obtain stable solutions with easily oxidizable substances.

Theory of redox processes. The mechanism of the redox process is revealed in the peroxide theory of O. N. Bach, I. AT. Engler and the branched chain theory of M. M. Semenova. According to the theory of chain reactions, oxidation develops due to the interaction of molecules of the starting substance with free radicals, which are formed under the influence of initiating factors. The free radical begins a chain of oxidative transformations. It reacts with oxygen, forming a peroxide radical, which, in turn, interacting with other molecules of easily oxidizable substances, forms an intermediate product hydroperoxide and a new free radical. Hydroperoxide decomposes with the formation of free radicals, which continue the oxidation of new molecules of the medicinal substance. The process takes on the character of chain reactions.

During oxidation, a branching chain reaction may occur, resulting in the formation of a complex mixture of oxidation products.

Mechanism of action of antioxidants. Stabilizers that protect LR from the undesirable effects of oxygen, the so-called antioxidants (AO), are of great importance . ***According*** to the mechanism of protection of sensitive APIs, three groups of antioxidants are distinguished **.**

1. *Actually AOs* , which inhibit oxidation by reacting with free radicals, interrupting the chain reaction. They are mainly used for stabilization oil solutions. To them belong butyloxytoluene (BOT), butyloxyanisole (BOA), □-tocopherol, propyl gallate, ascorbyl palmitate , etc.

2. *Reducing agents* that have a higher oxidation capacity and, by binding oxygen, prevent undesirable processes in solutions. These include salts of sulfuric acid, organic compounds sulfur, alcohol and phenols and others, What have low redox

potential.

1. *Negative catalysts* , or *anticatalysts* — substances, which form complex compounds with heavy metal ions, provoking redox reactions processes. For stabilization are used yes complexes:

EDTA — ethylenediaminetetraacetic acid, trilon B, thetacin-calcium, calcium-disodium salt of ethylenediaminetetraacetic acid, hydroquinone, mannitol, glycerin, 8-hydroxyquinoline, etc. Complexones are indirect antioxidants. By origin, oxidation inhibitors are divided into *natural* and *synthetic* . Natural antioxidants are isolated from various parts of plants. According to their chemical structure, most of the natural antioxidants used in practice belong to *derivatives of polyphenols* . According to their solubility, antioxidants are classified into *water-soluble* and *oil-soluble* .

Requirements for AOs used in the production of pharmaceuticals :

- harmlessness in the doses used, absence of irritating effects, allergic reactions to both the AOs themselves and the products of their metabolism and other ingredients formed during interaction with them;
- efficiency at low concentrations;
- good solubility in products, which are subject to protection from oxidation.

Other methods of chemical protection. The rate of the oxidation reaction depends to a large extent on pH value of the solution, since hydroxyl ions can exhibit a catalytic effect. Therefore, to slow down the oxidation processes to many dissolved easily oxidized substances for To create the optimal pH value, buffer mixtures or a solution of hydrochloric acid are added.

The oxidation (self-oxidation) capacity of LR decreases with *decreasing oxygen concentration* in the solvent and above the solution. Therefore, solvents used for the production of parenteral solutions should be freed from oxygen by boiling or saturation with carbon dioxide or nitrogen .

Another method of stabilizing easily oxidizable substances can be the use of such *high-molecular substances* as polyglucin, propylene glycol, low-molecular-weight polyethylene oxide, and other compounds. In the environment of these substances,

oxidation slows down, which is explained by the penetration of a low-molecular-weight drug substance into the molecule of a high-molecular-weight compound and, therefore, a decrease in their reactivity.

Oxidation can be reduced by eliminating *the effects of light and temperature* . The rate of destructive processes in drugs increases under the influence of ultraviolet radiation. The energy of the radiation activates the molecules or atoms of the substance, which, in turn, in turn, causes the development of chemical reactions, which can occur in gases, solids and solutions. When a substance absorbs light radiation of a certain wavelength, accelerated decomposition of drugs can occur. Sometimes the preparation of some drugs (for example, a solution of phenothiazine) is advisable to carry out in red light or to use ampoules made of light-proof glass for storage.

The rate of decomposition also depends on *the state of aggregation of the substance* . It is known that the decomposition of substances in dry form occurs much slower compared to the rate of decomposition of substances in solutions. More concentrated solutions oxidize more slowly than diluted ones.

A common technological method for obtaining stable aqueous solutions for injections is the conversion of an insoluble active substance into physiologically acceptable soluble salts or complex compounds.

Synergism of inhibitors is of great importance , when the action of several substances exceeds the sum of the effects of each individually. Synergism can occur when an inhibitor that interrupts the oxidation chain and an inhibitor that destroys hydroperoxides are jointly administered. The stabilizer may be multifunctional, which can inhibit oxidation both due to the formation of a peroxide radical and its decomposition.

The use of *antimicrobial preservatives* also helps to increase the stability of many parenteral drugs.

Use of preservatives.

One of the reasons for the decline in the quality of drugs is their microbial contamination in the process of production or use, which can lead to a decrease in the therapeutic effect of drugs or the development of various diseases in the patient. In this

regard, parenteral drugs can be used only for the absence of microorganisms in them, i.e. sterile. Preservatives are added to solutions when Sterility cannot be guaranteed. Antimicrobial agents used for drug preservation must ensure patient safety and adequate drug quality. Accordingly, The following requirements are made for preservatives:

- wide antimicrobial spectrum actions if low concentrations;
- high solubility; compatibility from most medical and auxiliary substances, we are packing materials;
- stability in a wide range of pH and environmental temperature throughout the shelf life of the drug;
- lack of influence on the organoleptic properties of the drug ;
- lack of ability to form microorganisms in a stable form. Preservatives should not reduce the pharmacological effectiveness of active substances or have a toxic, allergic or irritating effect on the human body.

To this day not found yet none chemical compounds, which completely would meet these requirements. Each of the preservatives has certain limitations when used, so they are used in cases where it is impossible to prevent drug contamination by other means.

The mechanisms of influence of preservatives on microorganisms are diverse and are determined their chemical structure. Basic result if this — disruption of the vital functions of the cell, in particular inactivation of the protein part of cellular enzymes. Depending on the degree of inactivation, either the cell dies or its vital functions slow down. The speed and depth of the transformations that occur during this process depend on both physical (temperature, concentration, phase state, pH of the medium, etc.) and chemical factors. For the preservation of liquid medicinal products, the following can be used: benzalkonium chloride, chlorobutol, phenylethyl alcohol, chlorhexidine diacetate or bigluconate, thiomersal, sorbic acid, boric acid, rongalite, nipagin, nipazole and other compounds. A promising approach to solving the problem of antimicrobial protection of drugs is the use of a combination of preservatives. This will allow expanding the spectrum antimicrobial action, apply them in at lower concentrations to

prevent the emergence of possible mutant microorganisms. Most often, the use of preservatives is combined with other sterilization methods (gas or sterilization filtration) for the preparation of solutions under aseptic conditions that do not require heat sterilization.

Medicinal products for intracavitary, intracardiac, intraocular or other injections with access to the cerebrospinal fluid, as well as for single doses exceeding 15 ml, ***should not contain preservatives*** (***!***).

Thus, the choice of preservative is determined by the composition of the drug, the pH of the environment, and the mode of its use. Only a comprehensive approach and strict adherence to GMP requirements for the production of sterile products will help solve the problem of antimicrobial protection of drugs.

Complex stabilization. Solutions of a number of substances cannot acquire the necessary stability using any one form of stabilization. In this case, it is necessary to use a combination of stabilization factors *of combined effect* .

Stabilization of emulsions and suspensions. Among parenteral drugs, LFs are used, which are heterogeneous systems (emulsions, suspensions) containing two or more phases. The stability of such systems is associated with two types of resistance:

- *sedimentation* , which is characterized by the speed of settling or rising of the dispersed phase;
- *aggregate* , which is manifested in the constancy of the size of the particles of the dispersed phase and the nature of the distribution of these particles in the dispersion medium .

Sedimentation stability expresses the stability of the dispersed phase with respect to gravity and depends on the intensity of the thermal motion of particles, the influence of the gravitational field on them, and the viscosity of the dispersion medium. Sedimentationally unstable systems can be aggregatively stable, i.e., when solid particles settle, they do not aggregate due to clumping, or, conversely, aggregatively unstable, if the particles stick together, forming large flakes, which accelerates sedimentation. If aggregative stability is lost, the suspended particles stick together, forming large aggregates, which leads to coagulation of the particles of the solid

dispersed phase. In the case of a liquid dispersed phase (emulsion, foam) its droplets or bubbles merge, and the process is called coalescence. During coagulation or coalescence, the sedimentation stability of the system is violated, as a result of which phase separation occurs. Aggregation stability depends on the properties of the surface or surface layer at the interface of the dispersed phase and the dispersion medium, in other words, it depends on the surface energy or forces that occur in the surface layers. Aggregation stability is influenced by the electrostatic barrier caused by repulsion forces and the absorption-solvation barrier that surrounds the particle and prevents it from approaching other particles.

To increase the stability of heterogeneous dispersion systems, stabilizers are used that can adsorb on the surface of hydrophobic particles or increase the viscosity of the dispersion medium. According to the principle of action, a distinction is made between *a stabilizer-emulsifier* and *a stabilizer- thickener* .

Stabilizers of LF heterogeneous disperse systems include methylcellulose derivatives, pectins, alginates, bentonite clays, aerosil, tweens, foams and a number of other substances. Often, to reduce the amount of these substances and increase their activity, various combinations of stabilizers are used. natural, synthetic and semi-synthetic origin.

Physical stabilization methods are also aimed at maximally eliminating factors that cause or accelerate negative processes in parenteral solutions. Technological methods for increasing the stability of solutions in ampoules include:

- ✦ study and maximum elimination factors, which contribute change LR;
- ✦ justified choice LF, excipients , technology, that ensure the stability of the drug;
- ✦ using substances high degree purity or carrying out additional (special) purification of starting substances or solvents;
- ✦ coating the inner surface of the primary packaging with chemically resistant films, varnishes, etc. or the use of chemically inactive packaging materials;
- ✦ use of optimal technological methods and heat treatment (sterilization) modes;

- ✦ manufacturing of medicinal products in the form of sterile dehydrated powders, from which PLS are prepared before use (separate ampouleing);
- ✦ pre-binding or removal oxygen with solvents;
- ✦ using technology from application gas protection;
- ✦ application modern technological equipment.

To *remove oxygen from water,* electrolytic, chemical and physical methods can be used. Some physical methods deserve attention: removal of oxygen by boiling; bubbling with inert gases; spraying water in a vacuum; distillation of water in a carbon dioxide or nitrogen environment. In some cases, it is possible to use organic resins to bind dissolved oxygen. However, in the conditions of industrial production of parenteral solutions, preliminary binding of oxygen in the solvent is irrational, because at subsequent technological stages of production of solutions in ampoules its saturation occurs again. Therefore, it is more expedient to remove it immediately before filling the ampoules.

gas protection, or ***the principle of ampouleing solutions in an inert gas environment,*** has become widespread . The gas space and the solution contain a sufficient amount of oxygen, which contributes to the oxidation of LR solutions. To obtain stable solutions, it is necessary to replace the air with an inert gas in the ampoule as much as possible and remove oxygen from the solution, because the solubility of a gas in a liquid varies widely depending on the gas, solvent, pressure and temperature. At this solution or solvent saturates inert gas and All technological operations (filtration, blowing the ampoule immediately before filling, filling the package) are carried out in a gas environment until the container is hermetically sealed. Carbon dioxide, nitrogen, and very rarely argon are used as an inert environment.

Thus, the stability of solutions of unstable substances depends on many factors, and their stabilization can be carried out by various technological methods, subject to a number of conditions. But one of the main conditions for the production of high-quality sterile products is creation and provision of a system for guaranteeing the quality of drugs by implementing, first of all, the principles and rules of the NVP, which imposes requirements not only for the conduct of the technological process, but also for the system for preparing medicinal and auxiliary substances, the air

environment, equipment, personnel, technological clothing, etc. in order to minimize the risk of contamination of drugs with microorganisms, particles and pyrogenic substances and thus increase the stability of drugs for parenteral use.

Materials for activating higher education students during lectures: questions, situational tasks, etc.:

Question:

1. What are the main requirements for starting materials and solvents?
2. What are the main methods of obtaining water for injections in industrial conditions?
3. What operations does the preparation of parenteral solutions include?
4. By what mechanisms is water obtained? for injections in industrial conditions?
5. Give the main characteristics and types of high-performance case-type apparatuses, thermocompression distillers of various designs, and multi-stage reverse osmosis units.
6. What is pyrogenicity?
7. What are the methods for detecting pyrogens?
8. What are the methods of stabilizing solutions?
9. The principle of ampouleing solutions in an inert gas environment?

General material and methodological support for the lecture

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

Questions for self-control:

1. How to get water for injections in industrial conditions ?
2. What are thermocompression distillers used for ?
3. What is the principle of ampouleing solutions?

List of sources used:

1. A textbook for independent work of students of the Faculty of Pharmacy for the licensing exam "Step 2. Pharmacy" / V.Yu. Anisimov, O.I. Belyaeva, G.G. Vidavska, V.O. Helmboldt, A.V. Zamkova, I.V. Lytvynchuk, A.V. Nikitin, B.V. Prystupa, I.B. Petkova, Ya.V. Rozhkovsky, S.B. Strechen, L.M. Unguryan, N.S. Fizor Odessa: Odessa National Medical University. 2020. - 240 p.

Access mode 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 of higher. educational. pharmaceutical institutions (pharmac. faculties) / E.V. Gladukh, O.A. Ruban, I.V. Saiko and others. - Kh.: NPhU: Original, 2016. - 632p. : Named after. - (Series "National textbook")

2. Workshop on industrial technology of medicines, specialty "Pharmacy" / Edited by Ruban O.A. - Kh .: National University of Physics and Technology, 2015. - 374 p.

3. INDUSTRIAL technology of medicines : a teaching aid for independent work of students / O. A. Ruban , V. D. Rybachuk , L. M. Khokhlova etc. – KH.: NATIONAL UNIVERSITY OF PHYSICS AND TECHNOLOGY, 2015. – 120 p.

- Excipients in the production of medicines: a manual for students of higher pharmaceutical schools / O. A. Ruban , I. M. Pertsev, S. A. Kutsenko, Yu. S. Masliy; edited by I. M. Pertsev. – Kh.: Zoloti storyny, 2016. – 720 p.
- Technology of industrial drug production: a textbook for students of higher education institutions: in 2 parts / V. I. Chuyeshov, E. V. Gladukh, I. V. Sayko and others – 2nd ed., revised and supplemented – Kh.: National University of Physics and Technology: Original, 2012. – Part 1. – 694 p.

- Technology of industrial drug production: a textbook for students of higher education: in 2 parts / V. I. Chuyeshov, E. V. Gladukh, I. V. Sayko and others – 2nd ed., revised and supplemented – Kh.: NPhA: Original, 2013. – Part 2. – 638 p.
- Modern pharmaceutical technologies: teaching aids for laboratory classes of undergraduates of full-time, evening and correspondence forms of study in the specialty 8.110201 "Pharmacy" / edited by O. A. Ruban. – Kh.: Publishing house of the National University of Physics and Technology, 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 Ukraine / State enterprise « Ukrainian scientific officinal center qualities medical " means " - 2nd ed . – Kharkiv : State enterprise « Ukrainian scientific officinal center qualities medical means ", 2015. – T. 1. – 1128 p .
- State Pharmacopoeia Ukraine / State enterprise « Ukrainian scientific officinal center qualities medical " means " - 2nd ed . – Kharkiv : State enterprise « Ukrainian scientific officinal center qualities medical means ", 2014. – T. 2. – 724 p .
- State Pharmacopoeia Ukraine / State enterprise « Ukrainian scientific officinal center qualities medical " means " - 2nd ed . – Kharkiv : State enterprise « Ukrainian scientific officinal center qualities medical means ", 2015. – T. 3. – 732 p .
- On medicinal products: Law of Ukraine of 4.04.96 No. 123/96 // Bulletin of the Verkhovna Rada of Ukraine. – 1996. – .№ 123.

Lecture No. 3

Topic: Filtration, sterilization of parenteral solutions. Quality control of

these products. – 2 hours.

Relevance of the topic: Drug technology (industrial drug technology) is one of the fundamental technological sciences. It consists of several key aspects that are important for modern medicine and patients: Efficacy and safety - Modern technologies allow the production of drugs with high efficiency and safety for patients. Accurate dosing, quality control and the absence of impurities make drugs more effective and safe. Innovations in the medical field: 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 treatment. Minimization of side effects: Technologies allow the development of drug formulas that minimize side effects and negative effects on the body. This provides more comfortable and safe treatment for patients. Fast production and delivery process: The use of modern technologies allows the acceleration of the production process of drugs, which is especially important in a rapidly changing medical environment, such as the spread of diseases or epidemics. Personalized treatment: Technologies allow for the development of medicines that take into account the individual characteristics of the patient, leading to a personalized approach to treatment and increasing its effectiveness. Cost-effectiveness and accessibility Improved manufacturing technologies can reduce production costs, making medicines more accessible to a wider range of patients, ensuring cost-effectiveness in healthcare.

Thus, the use of modern pharmaceutical manufacturing technologies is an important factor in improving the effectiveness of treatment, patient safety, and the overall state of public health.

Purpose: The discipline provides, on the basis of general knowledge and principles, regularities of the technology of factory production, to form in students knowledge about: theoretical foundations, acquisition of professional skills and abilities in the preparation of dosage forms, phased 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 facilities and personnel. To get acquainted with the main stages of

industrial production of dosage forms and the discipline "Technology of Medicines", to characterize the basic principles of stabilization. To get acquainted with the main factors that affect the stability of injection solutions. Describe stabilizers used in the production of injectable solutions

Basic concepts:

Filtration is the purification of parenteral solutions from mechanical inclusions.

Syringe method - is carried out using installations with special dispensers (piston, membrane, etc.).

Sealing containers — the most responsible operation in the technological process, because poor quality blockage vials or Prolonged sealing of ampoules will lead to product shortages, and all the work spent on previous operations will be nullified.

By capillary pulling , when part of the capillary is unsoldered by pulling and the ampoule is sealed during the unsoldering process;

About ***melting of capillary tips ,*** when the tip of the capillary is heated in a continuously rotating ampoule, and the glass, softening, melts the capillary opening itself.

Sealing control (capping or sealing) is carried out all 100 % of containers for which four methods are widely used to determine their tightness.

Flexible (soft) containers - polymer bags with a capacity of 100 to 1000 ml, heat-sealed around the perimeter.

Lecture plan and organizational structure:

No. 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* Defining learning goals.	I	Combined lecture	1%

2.	Providing positive motivation.			
	Main stage	II	Slides	2%
II	Presentation of lecture material.			
3.	Plan:			
	1. Sources of mechanical contamination of parenteral solutions.	III	Bibliography, questions, assignments.	90%
	2. Types of filtration: coarse, fine, microfiltration, etc.			1%
	3. Depth filtering.			
	4. Membrane filtration			
	5. Sterilization filtration.			2%
	6.Filling containers solution.			
	7. Equipment for sealing containers.			
	8. Automatic lines ampoule.			
	9. Operation of washing machines.			90%
	10. Flexible (soft) containers.			
	11. Sterilization methods.			
	12. Use of preservatives.			
	13. Production of drugs under aseptic conditions.			
	14. Emulsions and suspensions for injections.			
III	*Final stage*			2%
4.	Lecture summary, general conclusions.			
	The lecturer's answers to possible questions.			3%
5.	Tasks for student self-study.			2%

Structural and logical diagram of the lecture content

1. Sources of mechanical contamination of parenteral solutions.
2. Types of filtration: coarse, fine, microfiltration, etc.
2.1 Depth filtering.
2.2 Membrane filtration
2.3 Sterilization filtration.
3. Filling containers solution.
4. **Equipment for sealing containers.**
5. Automatic lines ampoule.
6. Operation of washing machines.
7. Flexible (soft) containers.
8. Sterilization methods.
8.1Mechanical methods sterilization.
8.2 Chemical sterilization methods
8.3 Gas sterilization.
8.4 Use of preservatives.
8.5 Thermal sterilization.
8.6 Sterilization in pairs under pressure (autoclaving).
8.7 Dry heat sterilization (air sterilization),
8.8 Ultrasonic sterilization
8.9 Sterilization with high and ultra-high frequency currents.
8.10 Sterilization by ultraviolet radiation.
8.11Sterilization infrared and laser radiation. Electronic sterilization .
9.Production of drugs under aseptic conditions.

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Sources of mechanical contamination of parenteral solutions.

Contamination of sterile drugs can occur at all stages of production. Contamination of parenteral drugs is divided into three types: ***chemical*** (soluble), ***microbial*** and ***mechanical*** . Inadmissible chemical impurities are removed by converting them into an insoluble state with subsequent adsorption on sorbents (activated carbon, kaolin, etc.). The last two types of contamination are closely related: their sources of origin are the same; they are detected simultaneously by most modern devices; the methods of combating them are similar.

Sources of possible contamination have a wide range. The main ones are: air in the production room, starting materials and solvents, technological equipment, communications, primary packaging materials (ampoules, vials, stoppers), filter partitions, service personnel. From these sources, particles of metal, glass, rubber, plastic, coal, asbestos fibers, cellulose, etc. can enter the parenteral solution. Microorganisms and pyrogens can be adsorbed on all solid particles.

The severity of adverse effects of foreign particles depends on their size, nature and number. Mechanical inclusions contained in parenteral solutions can lead to the formation of blood clots, granulomas, allergic reactions and other pathological phenomena. From the above it follows, What introduction in regulatory documents various countries with requirements that limit the number of mechanical particles is an important condition that ensures high quality of the parenteral solution.

Pharmacopoeias of most countries of the world define ***mechanical inclusions*** in injectable and intravenous infusion solutions as foreign mobile insoluble particles, with the exception of gas bubbles, accidentally present in solutions and divide them into *visible* and *invisible* particles to the naked eye.

Purification of parenteral solutions from mechanical inclusions is most often achieved by their filtration. Depending on the size of the solid particles to be removed, the following types of filtration are distinguished:

- *rough* — for removal solid particles in size over 50 microns;
- *thin* — to remove solid particles and some microorganisms size from 50 to 5 microns removal

- *microfiltration* (sterilization filtration) - for microorganisms and others particles in size from 5—10 to 0.02 microns;
- *ultrafiltration* — for removing pyrogens and microparticles with a size of 0.1-0.001 microns;
- *hyperfiltration* (reverse osmosis) — for separating substances at the molecular level with a molecular weight of less than 500 and sizes from 0.0001 to 0.001 microns.

In the production of parenteral solutions, the most common uses are coarse and fine filtration as the main or preliminary one, preceding microfiltration and ultrafiltration.

The most important part of any filter — a filter partition that must retain solid particles, have low hydraulic resistance and chemical stability. It must not change the properties of the filtrate, be available and cheap. The requirements for filters for injection and infusion solutions are much higher than those already listed: filter materials must retain very small particles and microorganisms; have high mechanical strength to prevent the release of fibers and mechanical inclusions; resist water hammer and do not change the functional characteristics; do not change the physicochemical composition and properties of the filtrate; do not interact with drugs, excipients and solvents; filter design and materials should maximally protect the solution from contact with air; withstand thermal sterilization. The choice of filter partitions is also determined by the physicochemical properties of the filtered solution (viscosity, pH of the medium, etc.). etc.), concentration and dispersion of the solid phase, requirements for filtrate quality, production scale, etc.

Filter partitions used for this purpose can retain particles both on the surface and deep within the filter material. Depending on the mechanism of particle retention , filters are classified as *depth* and *surface* , or membrane filters.

Depth filtration. In depth filtration, particles are retained on the surface and mostly in the thickness of the capillary-porous filter. Catching particles is happening by score *mechanical retention in the place of intersection of the fibers of the filter partition; as a result of adsorption on the filter material or on the section of the capillary that has a bend or irregular shape; due to electrokinetic interaction* . The efficiency of

the filter depends on the diameter, thickness of the fiber and the density of the structure of the filter partition. This method of filtration expedient apply for low-concentration solutions (with a volume fraction of solid phase less than 1%, because the pores gradually become clogged and the resistance of the partition increases).

Depth filters are made of fibrous and granular material, woven, compressed, sintered or otherwise bonded materials that form a porous structure.

Examples of fibrous materials of natural origin include cotton and linen fabrics, cellulose fiber. Among artificial fibers, the following can be distinguished: acetate, acrylic, fluorocarbon, nylon, capron, lavsan, etc. Of the granular materials, the most common are diatomite, perlite, activated carbon and other substances. Diatomite is obtained from the silica shells of algae — diatomaceous earth. Perlite — It is a glassy mountain rock of volcanic origin, used mainly for the manufacture of cartridge filters. Granular materials have found their application for filtering difficult-to-filter liquids (biological fluids, gelatin solution for injections, etc.).

Depth filters by composition and structure material can compare with a volumetric labyrinth sieve, which consists of extremely small cells with extremely thin and infinitely branched tubules. They form a hollow structure that occupies approximately 70-85 % of the total volume of the filter, which provides a high ability to trap microparticles. The filter partition consists of several layers with variable porosity: the average pore size decreases from the periphery to the inner layers. This structure of the filter material allows you to capture microparticles throughout the depth of the partition: large particles are trapped in the outer layers, and small ones - in a deeper area of the filter.

Depth filters effectively remove most particles and colloidal contaminants (98-99.9 %), ensuring high flow rate and consistently high service life during long-term processes. Advantages of depth filters — their high dirt holding capacity at high filtration rates and relatively low pressures, while protecting and extending the service life of membrane filters installed downstream of them.

Membrane filtration. Surface filtration occurs with the formation of sediment on the surface of the partition. The sediment forms an additional filtering layer and gradually increases the overall hydraulic resistance to fluid movement. The role of the

partition in this case is *to mechanically retain particles* . This group includes membrane (barrier) filters. A distinction is made between ***isotropic*** , or symmetric membranes (having pores of the same size on the surface, in depth and on the reverse side) and ***anisotropic*** , or asymmetric (usually having pores that increase in size from the surface to the reverse side of the membrane).

In membrane or sieve filtration, all particles larger than the filter pore size are retained on the surface. Membrane filters are made of polymeric materials in the form of a polymer film-matrix, penetrated through with pores throughout the thickness of the material. They should not contain fibers and bound particles. Membrane filters are made of cellulose, cellulose acetate and nitrate, polyamide, poly(ester)sulfone and polytetrafluoroethylene and other materials. A wide range of membrane filters allows for the production of clarified and sterile liquids and gases - from neutral aqueous solutions, non-aqueous solvents to aggressive liquids.

For sieve filtration, mesh-type membranes are used, which are called nuclear, or capillary-porous. Such membranes are made of durable polymer materials (polycarbonate, lavsan and other substances), which are subjected to bombardment in a nuclear reactor. The thickness of such filtering partitions is 5-10 microns. Currently in the pharmaceutical industry by abroad Mesh-type membranes from Pall and Gelman and other manufacturers are used.

The sieve effect of membrane filters explains their rapid clogging in relation to deep ones. Therefore, for filtering parenteral solutions, the most promising combination of both types of filter partitions or the use of a cascade filtration system, when the filtered solution sequentially passes through several membrane filters with pore sizes that decrease in progression. Moreover, membrane partitions should be used in the final stage of purification mainly for the removal of small particles and microorganisms.

Deep and membrane partitions are structurally designed into filter elements in the form of cartridges, capsules, modules, round or rectangular plates (cassettes).

Sterilization filtration

Sterilization filtration is used to remove microorganisms, as well as microparticles 5–10 microns in size and smaller, from solutions and gases in the industrial production

of parenteral solutions.

Sterilization ***filtration*** is understood as the liberation of solutions of thermolabile substances from microorganisms, their spores, and waste products (pyrogens and endotoxins) using deep and membrane filtration partitions.

Due to their mechanically strong, uniform and stable structure of holes, membrane partitions are most often used as sterilization filters. Microporous membranes are used to purify solutions containing no more than 0.1% solid particles. The thickness of such membranes is 50-120 microns, the pore diameter is 0.002-1 microns. To remove pyrogenic substances and microparticles with a size of 0.1-0.001 microns, ultrafiltration through microporous partitions is used.

The main function of microporous partitions used in these cases consists of the adsorption of microorganisms on the large surface area formed by the filter pores. The adsorption capacity of filters may depend on from kind microorganisms, their concentrations in solution and conditions filtration. It is generally accepted that the size of the holes is no more than 0.20-0.22 μm conditionally ensures the sterility of the solution. Sterilization filtration is necessarily preceded by preliminary purification of the solution using depth or membrane filters with a relatively large pore diameter (about 0.45 Prefilters retain mechanical microparticles and some "large" microorganisms.

According to the design of the filter element, there are shower and cartridge filters. filter (rice. 14.7), which establish in filter holders. Many companies also use filtration systems in the form of cassettes, modules, capsule, which are releasing popular in saints companies and companies:

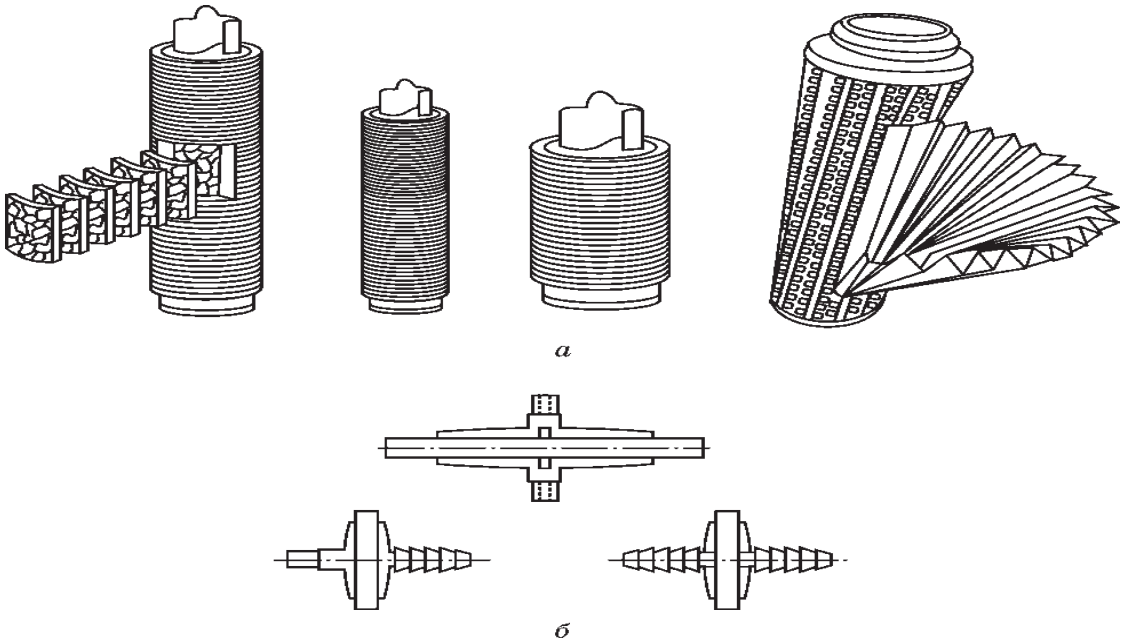


Fig.14.7. Constructions microporous filtering partitions:

and — ammunition elements wound and corrugated structures various diameter and lengths; *b* — disk filters

Millipore" (USA), –Sartorius" (Germany), –Nuclepore" and –Dominick Hunter" (England) and others.

Filter elements used for sterilization filtration are distinguished *by material, method of obtaining the porous partition and its geometric shape, structural features of the porous membrane layer* , etc.

According to the method of production, membranes are classified into *nuclear* (from macromonomer films), *film* (from polymer solutions and melts), *powder* and *fiber* .

Depending on the material used , membrane filters are divided into the following types:

1) membrane filters with natural polymers;

2) membrane filters from synthetic polymers;

3) fibrous membrane filters;

4) deep-type membrane membranes with globular-cellular or globular-fibrillar pores (currently the most common);

5) composite ceramic membranes (a while ago) their developed big quantity);

6) metal membrane filters.

WITH the newest achievements trace to note filters series "Vairosolv" companies

–Millipore", which are unique nanoselective membranes, made in the form of modules (for filtration in tangential flow) and capsules (for filtration in normal flow). They allow reducing the concentration of viruses with a size of 15 nm by 4-6 orders of magnitude, and larger retroviruses by 8 orders of magnitude.

According to GMP requirements, when using filtration systems in technological processes, filter testing is required, during which the reliability of the filtration equipment and membranes is confirmed. When using systems for sterilization filtration, integrity testing should be carried out before and after the filtration process. Testing is based on physical phenomena associated with the membrane filtration process and is divided into: *diffusion test* and *bubble point test* (for hydrophilic filters); *pressure test* (for hydrophilic and hydrophobic filters), *water intrusion test* (for hydrophobic filters), *combined test* (diffusion and bubble point tests), which are given in the State Federal Institute of Chemical Technology.

For simplification checks membrane filters on integrity developed and used automatic, validated and calibrated testers of membrane filter systems, which provide an objective result, which is displayed on the display and in the form of a printed protocol. Devices for testing the integrity of filters are manufactured by well-known firms and companies: — Sartocheck" by Sartorius Stedim Biotech" (Germany), — Microcheck" by CUNO 3M" (France, USA), model IT-4 by Millipore" (USA), tester — Membra-Check IT-01" by Donaldson Ultrafilter" and others.

The purity of the parenteral solution during filtration can be controlled using special optoelectronic particle counters of flow or periodic type. To control *invisible particles* of mechanical inclusions, devices are used, the action of which is based on the principle of light blocking and which allow automatic measurement of the number and size of particles. To determine *visible particles,* visual assessment equipment is used,

which consists of black and white matte screens and a lamp shade. To establish the nature of the particles and their characteristics, the microscopy method is used, which can indicate a possible source of contamination. Other validated methods for determining mechanical particles in solutions for parenteral use, specified in the relevant ND, are also allowed.

After obtaining satisfactory results of the purity of the solution according to all indicators, it is transferred to the stage of filling the primary packaging.

FILLING I SEALING PRIMARY PACKAGING

The stage consists of the following operations: filling primary containers with solution, sealing ampoules or sealing other containers, and checking their quality.

Filling containers solution

The filling operation is carried out in rooms and areas of cleanliness classes A/B or not lower than C, in compliance with all aseptic rules. The actual filling volume of the containers must be greater than the nominal one to ensure the required dose (i.e. the volume withdrawn) when filling the syringe. The State Federal Drug Control Service establishes the norms for filling containers.

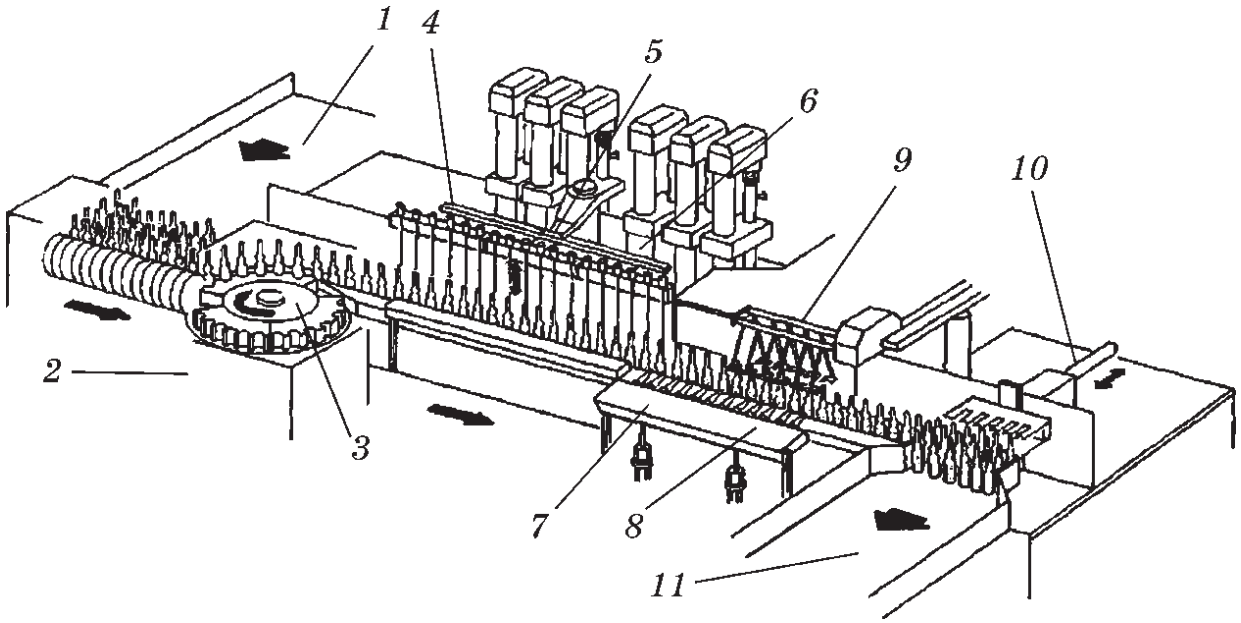
Until recently, the ampoule filling process used two methods of filling ampoules: syringe and vacuum. Since 2011, the vacuum method has not been recommended in the production of parenteral products.

The syringe method of filling ampoules has become widespread and is carried out using installations with special dispensers (piston, membrane, etc.). The method has a more complex hardware design than the vacuum method and more stringent requirements for the size and shape of the ampoule capillaries, but due to a number of advantages it is the best for use in ampoule technology. These advantages are especially evident when performing filling and sealing operations in one machine.

The significant advantages of the syringe filling method include the ability to accurately dose the solution (1-2 %) and a small time interval between filling and sealing (5-10 s), which allows for effective use of filling the free volume of the ampoule with

inert gas, which significantly extends the shelf life of the drug. When filling, an ampoule is introduced only necessary number solution, at this capillary ampoules It is not wetted by the solution and remains clean, which improves the sealing conditions of ampoules, which is especially important for thick and viscous solutions .

In the technology of ampoule filling in a jet of inert gases, the ampoule to be filled is pre-filled with gas, displacing the air, then the solution is supplied using a piston dispenser, and again — a jet of inert gas, after which the ampoule immediately enters the sealing stage (Fig. 14.8). The solution during filling practically does not come into contact with the surrounding environment of the room, which leads to an increase in the stability of many injection solutions.



Puc. 14.8. Scheme work machinery filling and sealing ampoules linear construction:

1 — loading ampoules; *2* — disjunctive screw;

3 — segmented transmission wheel;

4 — zone previous processing inert gas;

5 — zone filling; *6* — zone additional processing inert gas;

7 — preheating zone capillaries;

8 — sealing zone; 9 — removal pliers;

10 — transverse feed;

11 — storage device (unloading shop).

Currently, a number of designs of dosing elements have been created that operate without mobile parts, which allows completely to avoid pollution solution in the dosing process. Some foreign companies use peristaltic pumps, various membrane-type dispensers for this purpose. The introduction of a dose into an ampoule under pressure allows for additional filtration of the solution during filling directly at the time of filling, which makes it possible to guarantee purity, and when filtered using an ultrafilter, the sterility of the solution in the ampoule.

After filling the containers, the actual (withdrawn) volume of the solution is checked. In vessels with a capacity of up to 50 ml, the filling is checked calibrated syringe, in containers capacity 50 ml and more — with a calibrated cylinder at a solution temperature of 20±2 °C. The volume of the solution drawn from the ampoule with a syringe, after expelling air from it and filling the needle or after pouring into the cylinder, must be no less than the nominal volume.

Equipment for sealing containers

Sealing containers — the most responsible operation in the technological process, because poor quality blockage vials or Prolonged sealing of ampoules will lead to product shortages, and all the work spent on previous operations will be nullified.

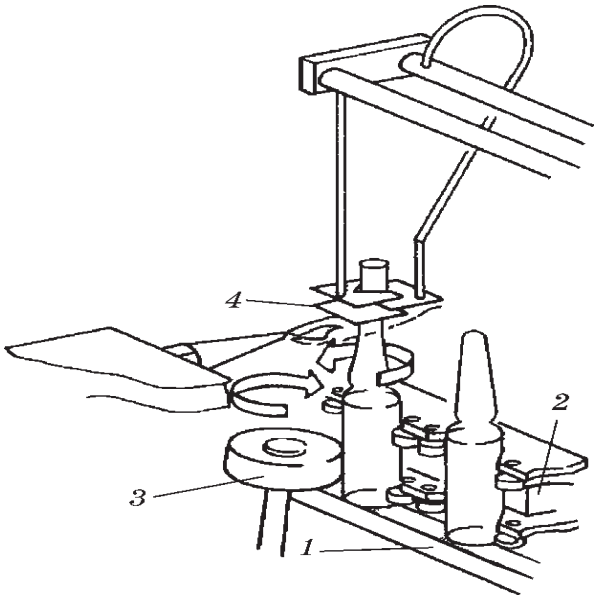
Currently, two methods of sealing ampoules using gas burners are used:

✦ *by capillary pulling* , when part of the capillary is unsoldered while pulling and the ampoule is sealed during the unsoldering process;

✦ *by melting the tips of capillaries* , when the tip of the capillary is heated in a continuously rotating ampoule, and the glass, softening, melts the capillary opening itself.

To heat the capillary evenly, the ampoule is rotated during sealing. The choice of sealing method is determined by the diameter of the capillary. When using syringe filling technology, when ampoules with a wide capillary or bell are used, the method of pulling back part of the ampoule capillary is used. In this case, the capillary of a continuously rotating ampoule is first heated, and then a part of the capillary is picked up with special

tongs and, pulling back, desoldered and discarded as waste (Fig. 14.9). At the same time, the torch flame is directed slightly to the side to burn through the glass thread formed at the desoldering point and to melt the sealed part. The sealing process is mainly carried out according to a rigid time cycle. In this case, the mass of glass introduced into the flame and to which the burner of the sealing unit is adjusted is of particular importance. If an ampoule with a capillary mass greater than the mass for which the burner is set is introduced into the flame of the burner, then during the time period allotted on the cycle diagram the glass will not have time to heat up sufficiently and the forceps will slip off the capillary when pulled back, i.e. such an ampoule will not be sealed. If an ampoule with a smaller capillary mass is introduced into the burner zone, the ampoule will heat up in a shorter period of time and overheat. The part to be desoldered will deviate from the ampoule axis, the forceps will not pick up the capillary, and the sealing will not be performed qualitatively. For qualitative sealing, the ampoules are specially sorted into groups during manufacture by capillary diameter, and the sealing operation is adjusted depending on the group of ampoules used in production. In a well-organized production marriage at use this way not exceeds 1%.



Puc. Scheme work soldering nodes ampoules method capillary retraction :

1 — ampoule filling lath; *2* — centering rail;

3 — pressure roller; *4* — filming locations tongs

Pull-off sealing ensures an attractive appearance of the ampoule and high quality due to the same thickness of the wall of the sealed part and the wall of the ampoule capillary. In recent years, other sealing methods have been developed that ensure high quality and productivity.

Researchers are looking for a method that would be insensitive to changes in the mass of the glass and to the geometric dimensions and shape of the ampoules. New schemes of the sealing process have been proposed, for example, to carry out the sealing operation with measurement of the glass temperature in the sealing zone. A design has been developed for sealing by the method pulling, which automatically performs the opening of the capillary when the necessary plasticity of the glass is achieved at the point of its heating.

Currently, a method of sealing with capillary pulling under the action of compressed air jets has been developed. It is devoid of the above-mentioned disadvantages, since there is no mechanical contact with the capillary during sealing. Sealing by the pulling method using compressed air jets allows for high-quality sealing of ampoule capillaries of both large and small diameters, and by its nature has a self-regulating process of heating and pulling the ampoule capillary.

For sealing ampoules with flammable and explosive solutions, sealing by heating using an electric resistance is used. The ampoule capillary is inserted from below into an electric nichrome heater, glass softens, and capillary delayed and melts. A promising method of sealing glass ampoules in modern automatic ampoule lines is *laser sealing* .

In cases where thermal sealing is not possible, the ampoules are sealed with plastic, such as polyvinyl butyrol.

A thermal method is used to seal containers made of polymer materials (ampoules, syringe-ampoules, and other products).

Sealing control (capping or sealing) is carried out all 100 % of containers for which four methods are widely used to determine their tightness.

The essence of the first method is that cassettes with ampoules (vials, etc.) are placed in a vacuum chamber with the capillaries down. A vacuum is created in the chamber, and the solution is poured out of the leaky vessels. Such containers are rejected.

Abroad, the method is known as called "crash test". The tightness of ampoules can also be checked using a colored solution of methylene blue (0.0005%). If the injection solution is subjected to heat sterilization, then the hot ampoules are placed in a vessel with a colored solution. When the ampoules are cooled sharply, a vacuum is created in the ampoules, and the colored liquid penetrates the inside of the leaky ampoules, which are rejected. If the parenteral solution is not subjected to heat, then a pressure of 100±20 kPa is created in the apparatus with the ampoules immersed in the colored solution, then it is removed. Ampoules or bottles with a colored solution are rejected.

To determine the tightness of ampoules with oil solutions, water or an aqueous solution of soap is used. When such a solution enters the ampoule, the transparency and color of the oil solution change due to the formation of an emulsion and saponification reaction products.

Both methods can be performed in the sterilizer chamber immediately after thermal sterilization or in a separate chamber.

The third method is based on on visual observed by by the luminescence of the gas medium inside the ampoule under the action of a high-frequency electric field of 20-50 MHz. Depending on the residual pressure inside the ampoule, different colors of the luminescence are observed. The determination is carried out at 20 °C and a measurement range from 10 to 100 kPa. According to this principle works high-voltage detector hermeticity ampoules companies –Rommelog "ag" (Switzerland).

The achievement of the latest progressive technologies at the stage of ampoule tightness control is the development by the company Ђausch + Strobel” (Germany) of a new machine, which completes the ampoule flow line. The machine has a horizontal conveyor made of a non-conductive material (Teflon). A high-voltage generator is located above the conveyor, which has four bit electrodes in in the form of pointed rods located above the edge of the conveyor. On the back side of the conveyor there is a contact pad in the form of a plate with an adjustable position, designed to drain the current. The ampoule, moving in the conveyor cell between the discharge electrodes and the drain plate, causes a discharge of a certain current strength to pass through its surface. If the ampoule has capillary cracks, punctures, microscopic holes in the neck of the ampoule or too thin walls, the discharge breaks through the ampoule, and not along its surface. This

causes an increase in the discharge current strength by tens of times, because the electrical conductivity of the solution is much greater than that of air or ampoule glass. The automation registers a sharp jump in current strength and automatically rejects the ampoule. Quality control of the work is carried out using a set of reference ampoules for the test. The use of this machine allows you to fully automate the tightness test operation, reduce the time of this operation by implementing the flow principle of testing.

14.1.1. Comprehensive automatic lines in production parenteral drugs.

It is well known that the use of automated flow lines allows to almost completely eliminate the contact of personnel with the products being manufactured, to reduce the risk of microbial contamination and to obtain a higher quality product. In the production of parenteral drugs, it is most expedient to use automated lines, which combine several technological stages in one set of equipment, which determine the quality of the resulting product.

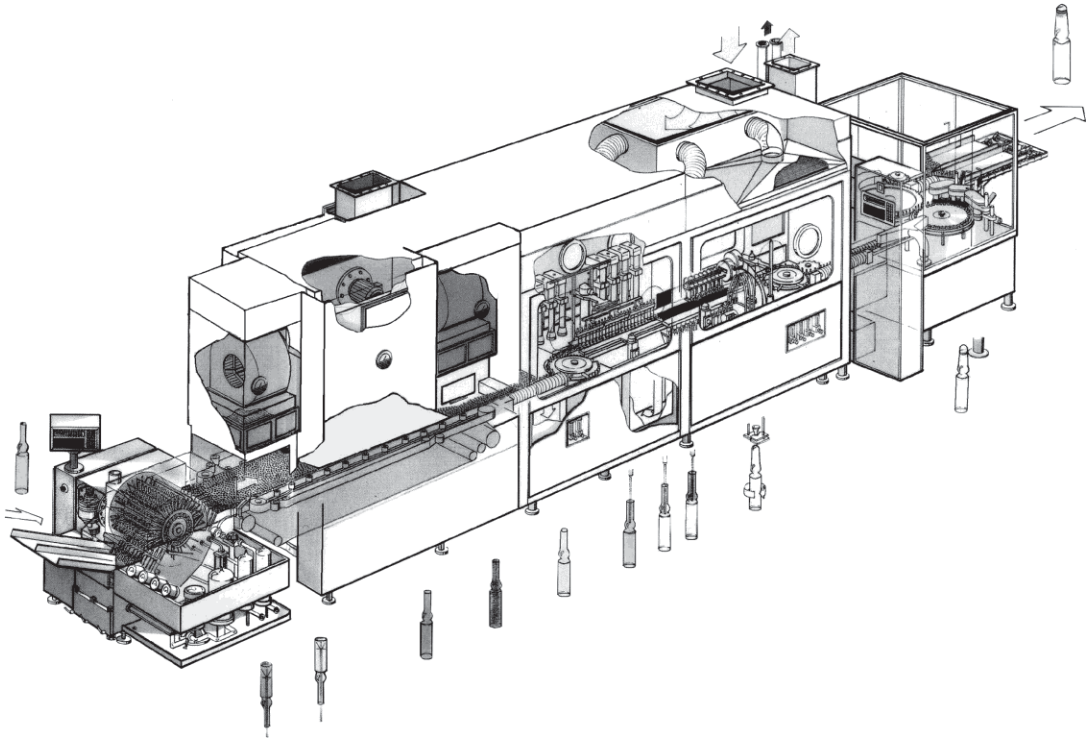
For the production of parenteral solutions, foreign lines are usually used, which are more productive and economical, use modern methods of preparing ampoules for filling, provide local areas with a high class of cleanliness and minimal risk of microbial and other types of contamination. They fully comply with the requirements of world standards and NVP.

Automatic lines ampoule

Complex automatic ampouleing line — This is a completely closed circuit that can be cleaned and sterilized, starting from the product tank and ending with the sealing of the ampoules, without dismantling individual parts. The line is equipped with systems for sterilization filtration of air, sterilization filtration of the solution immediately before filling, water recirculation, and all preparatory and production processes have a high level of automation. The line's productivity is from 10 to 30 thousand ampoules per hour. General view of the automatic ampoule filling line.

General appearance automatic lines ampoule solutions for injections using

insulating technologies



Such automated lines mostly consist of such functional units.

Machine washing machine for external and internal washing ampoules.

The machine operation consists of cycles of ampoule showering, ultrasonic treatment, syringe washing and air blowing of ampoules. The washing machine includes: a recirculation water pump; a filter for filtering recirculation water, an air filter; control and measuring instruments and a control panel.

The main differences between the syringe washing machine and domestic semi-automatic machines are: full automation of the process of internal and external washing of ampoules; use of ultrasound; emergency protection system (emergency valves, pressure relief channel, sound alarm). Special attention is paid to the separation of mechanical nodes (engine reducer, levers) from parts, which are in contact with solutions (purified water recirculation pumps, water filters, air filters, valves, etc.), for full compliance with GMP standards.

The machine is fed via a stainless steel belt conveyor onto which ampoules are loaded directly from boxes or metal cassettes. The intermittent movement of the chains determines the step-by-step movement ampoules through different Station zones: a bath with ultrasonic action, an external washing station, an internal washing station and

an air blowing station to the accumulator, where the ampoules are transferred for drying or sterilization.

All wash water passes through a filtration system capable of retaining particles from 1.0 to 0.22 microns. Air filters rated 0.2 microns are located in pipelines for supplying filtered compressed air and inert gas.

2. Drying and sterilization tunnel. Drying and depyrogenation of ampoules are carried out in a sterilization tunnel with a laminar air flow. The tunnel is divided into three zones: drying, sterilization and cooling. It is equipped with pressure regulators that constantly show the operation of the fans; resistance thermometers that show the drying temperature (180-220 °C) or sterilization (220—280 °C), outlet air temperature (20—23 °C); differential pressure sensor, which determines speed air in zone sterilization; automatic a regulator for measuring the speed of the belt to determine the time the ampoules spend in the sterilization zone; a device that registers changes in temperature and air speed, belt speed. The set includes an air filter, control and measuring instruments, and a control panel. The washing and drying or sterilization operations of the ampoules are carried out in parallel. The operation of the washing machine and the sterilization tunnel is controlled automatically from the control panel. The dried ampoules are fed to the accumulator, which is the connecting link between the sterilization tunnel and the filling and sealing machine. The accumulator ensures the supply of dried ampoules by turning them in a vertical direction and directs them to the syringe filling machine.

3. **Machine for nprcevogo filling and sealing ampoules.**

It has an internal local zone of class A with a surrounding environment of class B/C in accordance with GMP requirements. This is ensured by a continuous air flow through the use of a laminar module with a vertical laminar air flow, which creates a zone of increased pressure both in the area of the performed operations and on the transport devices. Laminar module consists of with pre-filter, filter fine cleaning from with an air purification degree of 99.995% (or higher) and a flow velocity of 0.40 m/s.

From the sterilization tunnel, the ampoules are transported by a conveyor to the ampoule filling and sealing station. The filling method is syringe, soldering - for with

help gas burners by delay capillaries ampoules. Productivity machinery depends from quantities dosing syringes that ensure high dosing accuracy (±0.01 for doses greater than 1 ml). All dosing syringes move synchronously. The solution is subjected to additional sterilization immediately before filling filtration with efficiency 99.99 %, which provides high degree of protection against microbial contamination. If necessary, the ampoules can be saturated with inert gas. The machine is equipped with a sterile air or inert gas filtration system, control and measuring devices, and a control panel.

Sealing of ampoules occurs in two stages: preheating of the stems, and then sealing of the capillaries using natural gas and oxygen. For uniform heating and stretching of the capillaries, the ampoules are constantly rotated.

The machine is equipped with an automatic speed regulator of the needle movement with the possibility of its blocking. When the speed of the conveyor needle decreases, which corresponds to an increase in the mass of ampoules on the connecting conveyor, a signal is sent to the micro-processing device using a potentiometer, which then reduces the speed of the sterilization tunnel needle and then the washing machine. Output accumulator — the final link of the automatic line. It is intended for removing sealed ampoules with solution from the ampoule sealing unit or for transferring them to inspection machines to determine the filling volume, ampoule tightness or control for mechanical inclusions. Currently, automatic ampoule filling lines of the companies “Strunk”, “MACOFAR”, “ROTA”, “Robert Bosch GmbH”, “Bausch + Strobel”, “Marchesini Group SpA” (Germany), “LAGERDE” (France), “Zanasi”, "IMA", "Marzocchi" Milan» (Italy), “Luxun” International Group” (China) and others.

Weights complex automatic line:

- combination of external and internal (syringe and ultrasonic) washing, presence of a water recirculation system (which significantly saves purified water consumption);
- For drying, sterilization and depyrogenation of ampoules, a tunnel with a laminar flow of hot and cooling sterile air is used;
- ampoules are filled by syringe using piston dispensers and with high dosing accuracy. The time interval between filling and sealing operations is

5-10 s;

- filling ampoules is happening in local zones class purity A, What guarantees minimal risk of solution contamination;
- foreseen possibility ampoule in currents inert gases;
- productivity lazy is from 15 to 30 thousands ampoules by hour;
- possibility equipment by machines for automated determination of mechanical inclusions, filling volume, ampoule tightness, application of coding rings, labeling machine, etc.

For filling and sealing of cartridges and syringes, lines similar to the automatic line “Inova VFVM 3000” of the company “Inova Pharma Systems GmbH” (Germany) with a capacity of up to 7200 ampoules are used in world practice. by hour, and also firm «Martin Sontag GmbH", "Bosch GmbH" (Germany).

Automatic filling lines and sealing vials

Automatic lines for the production of PLZ in glass vials or bottles mainly consist of the same basic functional units as and ampouleing lines. A description of the equipment for the preparation of vials and bottles is given in subsection 14.4.2.

A feature of the lines for the production of parenteral drugs in vials or bottles is automatic dosing machines of rotary or linear design with a rubber stoppering unit. For dosing solutions, suspensions or sterile powders into vials with a capacity of up to 10 ml, microdosing machines from well-known companies are used - ROTA", —Robert Bosch GmbH”, —Bausch + Strobel” (Germany), —EISAI" (Japan) and etc.

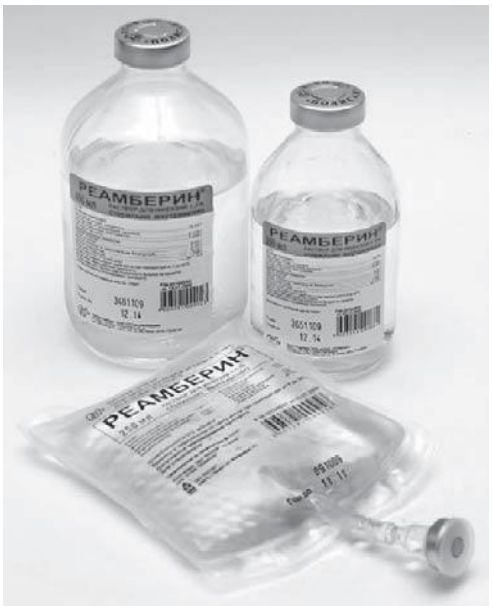
The next functional unit of automatic lines is an automatic machine for fixing metal caps, where the aluminum cap is rolled onto the neck of the vial or bottle. If the drug is not amenable to final sterilization, the line can be equipped with inspection machines for controlling mechanical inclusions and tightness (for example, models ATM18D and ATM18S of the company - Brevetti", - LIBRA", - SMR" (Italy), API 1000 from Bausch + Strobel (Germany), labeling and packaging machines.

The specified automatic lines have the same advantages as the ampouleing lines. Their use allows to increase the quality of preparation of vials and bottles, to carry out

additional sterile filtration of the solution before filling, to ensure high accuracy of infusion solution dosing, to exclude microbial contamination (due to the use of laminar flow and local zone of cleanliness class A), which will allow to obtain high-quality competitive products.

Equipment for filling and sealing polymeric containers

Flexible (soft) containers (Fig. 14.11) are polymer packages with a capacity of 100 to 1000 ml, heat-sealed around the perimeter. Such packaging has a number of advantages over traditionally used glass containers. Polymer containers — environmentally friendly, material (polyvinyl chloride, polypropylene) packaging — inert for many solution compositions. Weight of one container (500 ml capacity) — total 26 g, i.e. it is approximately in 10 times lighter by glass bottle. Others advantages packaging made of polymer material is convenient for transportation and storage, and can be used in emergency situations. Secondary vacuum packaging of polymer containers ensures the sterility of the surface of the inner container before its use. The presence of an inner container completely eliminates the possibility of contact of the solution with the environment during infusion.



Puc. Flexible containers

One with the most important advantages infusion solutions, What are issued in polymer containers, is a guarantee of the authenticity of the medicinal product. The

marking, which is automatically applied during production and cannot be washed off, contains information about the drug, data on control and the manufacturer. Drugs in such packaging are practically impossible to counterfeit due to the specifics of the technological process of production.

Flexible containers arrive at enterprises sterile in special packaging and do not require preparatory operations, which reduces the cost of the resulting products.

The technological process of filling and sealing polymer packaging for infusion solutions is carried out on automatic machines that are produced in warehouse production lines (for example, model Atlantic company —LEGRAND" (France) with a capacity of 500 doses per hour). This machine is designed for filling with solution, sealing with makrolon stoppers and aluminum caps of polymer containers with pre-applied marking. After filling and sealing, flexible packages can be subjected to gas or heat sterilization if necessary. at temperature 120 °C, under pressure 0.2 MPa for 30 min. The sterilization unit controls the tightness of containers. If final sterilization is excluded, the machine can be equipped with an automatic a device for checking for mechanical inclusions, a drop-jet marker (for applying the batch number and expiration date) and packaging machines for applying secondary hermetic packaging — multilayer polyethylene polyamide film, which guarantees the sterility of the inner container.

Now manufacturers flexible packages and drugs in polymeric containers are companies —LEGRAND", —LAGERDE" (France), —Medical Grade System MGS" (Italy), —Kobusch — Senge-wald", —PLUMAT" (Germany), —Luxun International Group" (China) and many others.

The pharmaceutical enterprise CJSC "RESTER" (Izhevsk, Russian Federation) specializes in the production of infusion solutions in polymer packaging. This enterprise operates a powerful container workshop, which fully meets the needs of its enterprise in primary polymer packaging and works under contract with other pharmaceutical enterprises to supply polypropylene containers at affordable prices. prices. Containers are made with polypropylene film - Propyflex" by welding with high-frequency currents in production premises of cleanliness class C. Marking in accordance with the ND and the trademark of the customer company are applied to the surface of the containers by embossing.

To polymeric packaging parenteral means hopes ***Syringe -ampoule,*** which is a tube with a capacity of 1-2 ml with an injection needle protected by a cap.

In the production of parenteral solutions in soft bags, plastic bottles, prefilled syringes and syringe ampoules, the “ *bottle pack* ” principle, or the “ *blowing-filling-sealing* ” technology (*Form-Fill-Seal*) , is used . This is a rational method of packaging parenteral solutions, in which the formation of the solution occurs during one continuous technological cycle. primary packaging from sterile (or non-sterile) thermoplastic granulate, automatic filling with sterile solution, sealing and application of the necessary marking, divisions, and code designations on the vessel using hot stamping.

The "blow-fill-seal" technology has significant advantages over traditional methods of aseptic filling of pre-made and sterilized ampoules and vials. First of all, it eliminates the entire cycle of auxiliary work and equipment for preparing vessels and closures for filling (washing, drying, sterilization, etc.). This method guarantees complete sterility of containers, since before forming the packaging, granules of polymer material that are in the extruder for several minutes under a pressure of 19.6-24.5 kPa and at temperature 160—230 °C, fully are sterilized. This principle of packaging of PLZ practically eliminates the need for final sterilization of products in primary packaging. Protection of packaging from possible counterfeiting is guaranteed by applying markings to containers using the hot (relief) embossing method.

The number of working and maintenance personnel for such an automatic equipment complex is significantly smaller, and the freed production space can be used for the production of other products.

A typical technological process for obtaining PLZ in polymer packaging includes the following main stages:

1) preparation polymer material before processing;
2) formation details and theirs processing;
3) filling and blockage vessels;
4) drafting details in nodes or products;
5) sterilization ready-made packaging with solutions (if necessary).

The described operations are carried out in the conditions of one automatic

complex of equipment, where it is possible to locally create aseptic conditions (local zone of cleanliness class A). Sterility of the solution is ensured by sequential sterile filtration through depth and membrane filters with a pore diameter of 0.45; 0.30 and 0.2 microns. This allows creating conditions of such technological purity that provides reliable protection of both the packaging itself and the medicinal product from microbial contamination and meets the modern requirements of good manufacturing practice.

Equipment for the “blow-out” technology filling — sealing”, used in the production of products to be sterilized at the final stage, must be installed in an environment of at least cleanliness class D. The same equipment used in aseptic production and having a type A zone with laminar air flow may be installed in an environment of at least cleanliness class C, and a shell corresponding to type A/B zones must be used.

METHODS STERILIZATION

One of the main requirements for a PLZ is sterility, which is achieved in various ways.

Sterilization (disinfection, sterilization) is understood as a set of physical, chemical and mechanical methods of getting rid of vegetative and inactive forms of microorganisms (H. Horn, 1984). Pharmacopoeias of leading countries of the world define ***sterilization*** as the process of removing microorganisms of all types, at all stages of development, from an object. The State Federal University of Ukraine defines sterilization as the absence of viable microorganisms .

Since the production of sterile dosage forms is subject to high requirements for microbiological purity (the degree of reliability of sterile parenteral preparations must be at least 10–6), not only the finished product, but also the equipment used, auxiliary materials, filters, solvents, and starting materials are subjected to sterilization. The choice of a particular sterilization method should be based on the economic feasibility and manufacturability of the processing, including the possibility of its full automation. The quality of the manufactured sterile products depends on the correctly selected sterilization method.

In most cases, product sterilization is preferably carried out in primary containers

(terminal sterilization). If terminal sterilization is not possible, aseptic production using sterilizing filtration is used. In all cases, the container and closures must ensure that the product remains sterile throughout its shelf life.

In the technology of industrially produced dosage forms, three groups of sterilization methods are currently used: *mechanical* , *chemical* , *physical* , or a combination thereof .

Mechanical methods sterilization

Sterilization filtration . Microbial cells and spores can be considered as insoluble formations with very small (1–2 μm) particle size. Like other inclusions, they can be separated from the liquid mechanically — by filtration through microporous filters. This method is included in the State Standard for sterilization of thermolabile solutions that are not subject to final sterilization and require aseptic production conditions.

According to the mechanism of action , microporous filter partitions used for sterilization filtration are divided into deep and surface (membrane) with a pore size of no more than 0.3 microns.

Filament filters are characterized by a complex mechanism of retaining microorganisms (sieve, adsorption, inertial). Due to the large thickness such filters particles are also retained smaller size, than pore size of the filter partition.

Membrane filters — These are thin (100-150 μm) plates made of polymeric materials, characterized by a sieve (surface) mechanism of retention of microorganisms and a constant pore size. To avoid rapid clogging of the filter, membranes are used in combination with prefilters, which have larger pores. When sterilizing large volumes of solutions, it is optimal to use filters of both types.

The use of depth and membrane filters ensures the necessary cleanliness, sterility and pyrogenicity solutions for parenteral application.

Sterilization filtration has advantages over thermal sterilization methods. For many solutions of heat-labile substances, it is the only available sterilization method. The State Food and Drug Administration recommends that sterilization filtration be performed immediately before the container filling operation .

Chemical sterilization methods

These methods are based on the high specific (selective) sensitivity of microorganisms to various chemical substances, which is determined by the physicochemical structure of their cell membrane and protoplasm. The mechanism of antimicrobial action of many such substances is still not sufficiently studied. It is believed that some substances cause coagulation of cell protoplasm, others —act as oxidants, a number of substances affect the osmotic properties of the cell, many chemical factors cause the death of the microbiological cell due to the destruction of the enzyme system. The basis of any variant of chemical sterilization is the interaction of a bactericidal substance with the components of the microbial cell or spore.

Chemical sterilization conditionally share on *sterilization solutions or substances* and *sterilization with gases* (gas sterilization).

Sterilization with solutions or substances . Sterilization with solutions (substances) of parenteral products that are mass-produced *is not used in factory conditions* (***!***), because the introduction of a foreign BA into the solution is undesirable due to the possible chemical interaction of the sterilization agent with the active components, as well as due to the possible side effects of this agent on the human body. Another fundamental limitation of this method is that almost any bactericidal substance has a certain selectivity and its effectiveness is manifested at high concentrations. or often in certain pH ranges that are unacceptable for living organisms. This type of sterilization is used to disinfect production facilities, various equipment, pipelines, and other equipment used in the production of sterile products.

Gas sterilization. A kind of chemical sterilization is the method of sterilization with gases. The advantage of the method is the possibility of sterilizing objects in plastic packaging (even with secondary packaging), permeable to gases and solutions with thermolabile substances. In a sealed chamber with an object, that is being sterilized, a sterilant is injected — a mixture of ethylene oxide and carbon dioxide in a ratio of 9:1. Carbon dioxide is added due to the explosive nature of ethylene oxide. For sterilization, the sterilant enters the apparatus under pressure up to 195 kPa at a temperature of 43-45 °C. Sterilization duration depends from permeability packaging, thickness layer material and lasts from 4 to 20 hours. Then the ethylene oxide is removed by blowing air (nitrogen)

or by evacuating the chamber.

For sterilization Donor material, solutions blood substitutes or blood-derived products, the sterilant β-propiolactone is widely used . Other sterilizing gases include ozone, bromomethyl, glutaraldehyde and some other gases.

Sterilizers from the companies “ETO” (Italy), “ETOXENOM” (Czech Republic), etc. operate on the principle of gas sterilization. During chemical sterilization with gases, all vegetative forms of microorganisms and molds die.

The main drawback of chemical sterilization methods is the need to free the sterilized object from residues of the sterilant and products of possible interaction. The widespread use of this method is hindered by the duration of sterilization, high cost, and the possibility of side effects of the chemical agent on the service personnel. However, for some drugs, this is the only reliable method of sterilization in modern conditions.

Use of preservatives .

The addition of antimicrobial preservatives can be conditionally attributed to chemical sterilization methods. The introduction of preservatives into solutions is carried out in cases where it is not possible to guarantee maintaining sterility. If this possible decrease sterilization temperatures or shortening the sterilization time.

The mechanisms of action of preservatives on microorganisms are very different and are determined by their chemical structure. The main result of this is the disruption of the vital functions of the cell, in particular the inactivation of the protein part of cellular enzymes. Depending on the degree of inactivation, either the death of the cell occurs or the slowing down of its vital functions.

Physical methods sterilization

Thermal sterilization. Today, thermal sterilization occupies a monopoly position among possible sterilization methods in pharmaceutical production. Depending on the temperature regime , it is divided into sterilization:

— couple under pressure (autoclaving);

— flowing steam;

— Tyndalization;

— dry heat.

Sterilization in pairs under pressure (autoclaving) — it sterilization

solutions resistant to heating, steam under pressure 111 kPa (1.1 atm) at a temperature of 119—121 °C. Under these conditions, not only vegetative but also spore-forming microorganisms die due to coagulation of cell protein.

This traditional method of sterilization has today an advantage over others. First, it allows sterilization of drugs in a final hermetic packaging, What excludes danger secondary contamination.

Secondly, thanks to long-term practice of use, it is equipped with fairly reliable equipment. And thirdly, today it is the most economical .

This method combines the effects of high temperature and humidity on microorganisms, killing the most resistant spores. Coagulation of protein substances under these conditions begins at a temperature of 56 °C.

Steam sterilization under pressure is carried out in sterilizers of various designs, cylindrical or square. Square-shaped, pass-through sterilizers have doors on both sides: one is used for loading non-sterile products, the other for unloading of sterilized. The autoclave body is heated by dull steam to prevent condensation in the working chamber. Then, hot steam is supplied to the chamber to displace air. The sterilization time begins to count from the moment the set pressure is reached according to the pressure gauge. Sterilizers are equipped with automatic control equipment, with the help of which the pressure and sterilization time are recorded on the control tape. The conditions for sterilization of products are specified in the technological regulations or other production documentation. Imported designs of sterilizers allow combining the operations of sterilization of the solution, checking the containers for tightness, washing them and drying in one technological cycle.

Sterilization of vegetable oils and fats in industrial conditions is carried out with steam under pressure of 101-111 kPa (1.0—1.1 atm) at a temperature of 119-121 °C for 2 hours.

Sterilization filtration units are also subject to autoclaving, filtering partitions and others auxiliary materials, used in the technological process of manufacturing parenteral

dosage forms. Among the disadvantages of the method, the impossibility of sterilization can be distinguished solutions, What contain thermolabile substances; danger working with steam under pressure; dehumidification of many materials during sterilization, etc.

Solutions of thermally unstable substances are sometimes ***sterilized with flowing steam*** at 100 °C (without air impurities and excess pressure). Saturated steam kills only vegetative forms of microorganisms and this method is ineffective if spore forms are present in the object.

For thermolabile substances, as well as for solutions in syringe ampoules, sterilization is sometimes carried out ***by the Tyndallization method*** **(** ***fractional sterilization*** **).** The essence of the method is to heat the solutions three times to 40-60 °C with breaks per day, during which the objects are thermostated at a temperature of 37±1 °C for the germination of spore forms into vegetative ones. This method is used extremely rarely today.

Dry heat sterilization **(** ***air sterilization*** **)** , carried out in air sterilizers or other devices of this type, also highly effective.

In this case, all forms of microorganisms die due to pyrogenetic decomposition of protein substances. However, the high heating temperature (160-200 °C), long exposure time (1-2 hours) and dry hot air have a destructive effect on the objects being sterilized, and therefore limit the possibilities of this method.

Parenteral solutions ***are not sterilized by dry heat*** (***!***), because due to the poor thermal conductivity of air, it does not provide rapid heating of solutions to the sterilization temperature, and prolonged heating leads to the decomposition of most medicinal substances. Some heat-resistant powders, oils, glass containers (ampoules, vials and necessary dishes), and auxiliary materials are sterilized by dry heat.

The best sterilizers have a laminar flow of sterile air heated to the required temperature, which improves the creation of a uniform temperature field and eliminates contamination from both the heated chamber walls and the air entering at the time of unloading the object.

Radiation sterilization . Radiant energy has a detrimental effect on the cells of a living organism, including various microorganisms. The principle of the sterilization

effect of this radiation is based on the ability to cause changes in living cells at certain doses of absorbed energy that inevitably lead to their death due to disruption of metabolic processes and protein coagulation. Source ionization ɣ-radiation serve long-lived Isotopes $^{60}Co_{27}$, $^{137}Cs_{55}$, accelerators electrons direct actions and linear electron accelerators. For bactericidal effect enough from 15 to 25 kGy, and the upper limit is necessary for the inactivation of spore forms.

Today, extensive experience has been accumulated in the use of this method, typical radiation doses necessary for reliable sterilization have been precisely established, radiation equipment has been developed for a high-performance sterilization process, and issues of safety of the installations for service personnel have been resolved. This method is superior in economic terms to aseptic preparation of solutions with sterile filtration, but is somewhat inferior to thermal sterilization. However, in the future it may approach it due to the inevitable decrease in the relative cost of isotopes as a by-product of nuclear power.

Ultrasonic sterilization . The passage of ultrasound (US) in a liquid medium is accompanied by alternating compressions, rarefactions and large alternating accelerations. Disruptions, so-called cavitation cavities, are formed in the liquid. At the moment of compression, these cavities collapse. The excess pressure created by the ultrasonic wave is superimposed on the constant hydrostatic pressure and can total several atmospheres in the bubbles. "Eggs" cavitation cavities can be bubbles gas, vapor in a liquid, solid particles and places of irregularities of a solid surface. High impulse pressures of cavitations lead to destruction of the integrity of the cell membrane of microorganisms, spore formations and other particles. It is important to establish optimal parameters of the sterilization process, since high impulse pressures can lead to mechanical destruction of ampoules. The sterilization sound frequency should be within 18-22 kHz.

Although this method is very effective, it has not found wide application due to the complexity of the hardware and possible complex chemical transformations of the components of the solutions. The issues of stability of components during ultrasonic sterilization have much in common with similar problems of radiation sterilization. To increase the stability of drugs under ultrasonic action, it is necessary to select such

conditions of sterilization processing that will ensure a decrease in the energy introduced into the system at those ultrasound frequencies that, simultaneously with sterilization, will not lead to the decomposition of the components of the drugs.

The method is most often used in the production of emulsions and suspensions for better dispersion of substances in them and at the same time obtaining sterile heterogeneous systems for parenteral use.

Sterilization by high and ultrahigh frequency currents. To date, there is no single point of view on the mechanism of inactivation of microorganisms by HF and microwave radiation. There is an opinion about an exclusively thermal mechanism of action of high frequency currents on biological objects. The principle of action of a high frequency field consists in its active action on the orientation of molecules of a substance. A change in the direction of the field causes a change in the orientation of molecules and absorption of part of the field energy by the substance. As a result, the substance rapidly heats up at all points of its mass. Less widespread is the idea that, in addition to thermal processes, the specific action of HF and microwave radiation affects the death of microorganisms.

With the help of microwave energy, it is possible to sterilize packaged finished products: eye ointments, pastes in tubes, medicines in blisters, powders, tablets, porous lyophilized masses that do not contain hydrophilic liquids. Sterilization of ampoule solutions and liquid dosage forms that are hermetically sealed is undesirable, because in a closed vessel there is an excess of vapor pressure of the evaporated liquid, which destroys it. As a result, depressurization occurs in the form of cracking of the walls of the ampoules or rupture of the sealing material.

The method has also not found wide application due to the complex design features of the hardware and the possibility of adverse effects of rapid short-term heating of the injection solution.

Sterilization by ultraviolet radiation . Due to the possible formation of toxic products and decomposition of biologically active components of parenteral solutions under the influence of UV radiation, ***the method has not found*** (***!***) its application for the sterilization of parenteral drugs. However, it is widely used for the sterilization of

powders, water for injection, auxiliary materials, the air environment of production facilities, technological equipment and other objects.

When sterilizing the air environment of production premises, special UV lamps (bactericidal ultraviolet lamps) are used as sources of UV radiation, which are manufactured in in the form of a tube made of special of uviol glass, capable of transmitting UV rays, with electrodes made of a long tungsten spiral coated with barium and strontium hydrocarbonates. The tube contains mercury and argon at a pressure of several hundred pascals. The source of UV rays is a mercury discharge that occurs between the electrodes when voltage is applied to them. The radiation of the UV lamp has a high bactericidal effect, because the maximum radiation of the lamp is close to the maximum of bactericidal action (254 nm).

For water sterilization, *devices with submerged and non-submerged UV radiation sources are used.* In the first type of devices, the UV radiation source (a bactericidal UV lamp covered with a quartz glass casing) is located inside the water pipe and is surrounded by water. This method of sterilization of large volumes of water for injection is the most economical .

In devices with non-immersed lamps, the latter are placed above the surface of the water being irradiated. Due to the fact that ordinary glass is practically impermeable to ultraviolet rays, the water supply in the places of irradiation is made of quartz glass, which significantly increases the cost of the device. Currently, the possibility of replacing quartz glass with polyethylene, which freely transmits UV radiation, has been developed.

As a positive factor, it should be noted that during water sterilization, there is no accumulation of peroxide compounds and under the influence of UV radiation, some pyrogenic substances that have entered the water are inactivated.

Sterilization infrared and laser radiation. Electronic sterilization .

These promising types of sterilization are practically not used today, although there are opportunities for this.

Radiation parenteral aqueous systems infrared (IR) radiation in the water absorption area (= 2.7 microns) can be an effective means of heating it and thus, in fact, another option for thermal sterilization. The presence of sufficiently powerful

sources of IR radiation allows us to hope for the possibility of creating equipment for high-performance technology. The advantage of this method over traditional autoclaving can be considered the possibility of abandoning dangerous in service and non-technological superheated steam. The method has proven itself well for the sterilization of glass primary containers.dangerous in service and non-technological superheated steam. The method has proven itself well for the sterilization of glass primary containers.

In principle, sterilization methods using laser and electron radiation are possible. When this can achieve high sterilization efficiency both by intensive heating due to the absorption of powerful radiation in water, and by selective absorption of radiation by macromolecules of microorganisms in multi-quantum processes. During electron irradiation, the product moves through a continuous or pulsating beam of high-energy electrons (□-radiation), which passes through the trajectory of the product movement. However, comprehensive studies of any specific system, the totality of which would provide a basis for the creation of industrial equipment using such sterilization methods, have not yet been conducted.

Biological indicators. These are standardized preparations of certain microorganisms used to assess the effectiveness of sterilization. They are a population of bacterial spores coated on an inert carrier. It is recommended that indicators be placed in areas least accessible to the sterilizing agent. These areas are determined empirically or based on previous physical measurements, if available. After completion actions sterilization agent carrier dispute transferred to culture medium, observing the rules of aseptic technique. If after incubation growth of sterilized reference microorganisms is observed, this indicates a poor-quality sterilization procedure.

PRODUCTION MEDICATIONS IN ASEPTIC IN M OVAH

The production of many parenteral drugs requires the creation of special aseptic conditions. The concept of " *aseptic* " includes a set of measures that minimize the possibility of microorganisms or mechanical inclusions entering the drugs at all stages of the technological process. The creation of aseptic conditions is an unbreakable chain of mandatory measures that complement each other. An error made at one stage can nullify all the work done.

To ensure aseptic conditions, it is necessary to take into account the sources of microbial contamination of drugs. These, as mentioned earlier, include production premises, ventilation air supplied, auxiliary materials, medicinal substances, solvents, equipment used, as well as working personnel and their failure to comply with production discipline.

Aseptic conditions for the production of sterile preparations are ensured in production facilities. zones with class purity AND and surrounding its environment class B. Purity class And intended for the production of products, when the risk of contamination must be completely eliminated, such drugs are not further sterilized in the final packaging. The contamination level must be less than 0.1% with a confidence level of 95%.

Validation of a process under aseptic conditions should include simulation of the process using culture media. The process simulation should simulate as closely as possible the routine operation under aseptic conditions and include all subsequent critical steps of the manufacturing process. The process simulation should be repeated at specified intervals and after any significant change in the equipment or process. The manufacturing process operations that may be performed under aseptic conditions include: opening of sterile raw materials, materials, sterile primary containers and closures; mixing or dissolving of ingredients; sterile filtration of the solution through a sterile filter with a pore size of 0.22 μm (or smaller); filling and sealing.

Preparation of injection solutions that cannot be heat sterilized.

Compliance with all aseptic conditions is especially important in the production of medicinal products. for parenteral use, which are not subject to sterilization in the final packaging. This applies to the preparation of injection solutions from thermolabile substances (barbamyl, adrenaline hydrochloride, euphylline, aminazine, diprazine, hexamethylenetetramine, antibiotics or other preparations of microbiological origin, enzymes and hormones, preparations obtained from human blood or plasma, etc.).

Solutions ***of hexamethylenetetramine*** at normal temperature are relatively stable and have a bactericidal effect. When the temperature increases, hexamethylenetetramine undergoes hydrolysis with the formation of formaldehyde and ammonia, therefore, the

preparation of its 40% solution is carried out under aseptic conditions (purity class A) without thermal sterilization. The medicinal substance used for the preparation of the injection solution must be of higher quality than the pharmacopoeial one. It must not contain amines, ammonium salts and paraform.

Aqueous solutions ***of aminazine*** and ***diprazine*** are easily oxidized even by short-term exposure to light, forming red-colored decomposition products. Antioxidants and sodium chloride are added to obtain stable preparations. — for isotonizing solutions. Manufactured under strictly aseptic conditions without heat sterilization.

The process of filtering through bacterial filters plays an important role in the technology of preparing injection solutions that are not subject to heat sterilization, in which microorganisms are removed from the solution, thereby ensuring its sterility and pyrogen-freeness. Sterile filtration is achieved by using depth and membrane filters. Preparations prepared under aseptic conditions may contain antimicrobial preservatives in appropriate concentrations. All incoming raw materials, solvents, materials, primary packaging must be sterilized in advance or their microbiological contamination must be minimal.

Lyophilized forms for parenteral administration. Currently, the production of lyophilized drugs is expanding.

Freeze drying (***cold sublimation***) — one of the effective ways to increase the stability of unstable and thermolabile LRs, such as antibiotics, enzymes, hormones and other biologically active fluids. For some drugs, this is the only possible method of production. When drying by sublimation, conditions are created under which substances undergo minimal chemical transformations, thereby reducing the number of destabilizing factors and increasing the stability and quality of the drug. Lyophilized drugs are porous powders containing a small amount of water and placed in sterile containers. Injectable solutions of lyophilized substances are prepared directly at the patient's bedside using a sterile solvent, which is included in the package. When shaken with the specified volume of the appropriate sterile liquid, the lyophilized substances quickly form a solution free from mechanical inclusions, which must meet the requirements set forth for the PLZ.

The lyophilization process is carried out under aseptic conditions and is divided

into four stages:

- preparation of material for sublimation (filling ampoules, vials, beam molds, etc. with aqueous solutions);
- freezing prepared material;
- actually sublimation drying;
- processing lyophilized product (blockage vials, sealing of ampoules or further distribution of the lyophilisate).

Material, designed for sublimation drying, after for filling containers under aseptic conditions, frozen so that the maximum possible surface is formed with the maximum layer thickness 1 cm. The freezing temperature depends on the type of material being dried and can range from –20 to –60 °C. The frozen material together with the containers is placed in a sublimation chamber, which is hermetically sealed. A vacuum is created in the chamber within the range of 0.133—13.33 Pa and heat is supplied at the same time. These conditions are ideal for sublimation of water vapor without increasing the temperature of the dried material and without the vapor turning into a liquid state.

1935 is considered the beginning of the industrial use of this method in world practice. Previously, the method of sublimation drying was patented in 1921 by Lappa Strazhenetsky, although the active use of the method began in the 60s and 70s of the last century. At the same time, the sublimation apparatus KS-30 (later models LZ-9, LZ-45) of the Frigera enterprise (former Czechoslovakia), the series of TG-5, TG-15, TG-50 installations of the Khokhvakum firm (former GDR), equipment of the firms Yusifruy (France), Leybold (Germany), Edwards, Brizio Base (Italy) were developed. Currently, equipment for freeze-drying is supplied by many firms, including —Secfroid" (Switzerland), — Martin Christ" (Germany), — Luxun International Group" (China), and others.

Sublimation plants consist of a cooling unit, a vacuum pump, a sublimation chamber (sublimator), a condenser, a heating system, a control system and a process control system. Since lyophilization has become an industrial production process, the attention of equipment manufacturers has been primarily focused on the economy of production, increasing the productivity of equipment and expanding the possibilities of

using this method to obtain high-quality drugs .

The latest designs of freeze dryers are more productive, have automatic loading and unloading of the product, and the usual cooling system is replaced by cooling with liquid nitrogen. Such dryers are manufactured by the companies “Tofflon” (China), “Martin Christ” (Germany), “Kyowa Vacuum Engineering, LTD” (Japan) and some others.

Emulsions and suspensions for injections.

Currently, a significant number of suspensions and emulsions for parenteral administration are used in medical practice. Suspensions for injection are administered subcutaneously, intramuscularly, intraarticularly (intrasynovially), they have a prolonged effect. LR. The range of suspensions is quite wide: suspensions of hydrocortisone acetate 2.5 %, zinc-corticotropin, various insulin suspensions etc. Emulsions are mostly represented by fat emulsions for parenteral nutrition, which will be considered in the following sections.

The technological process of obtaining suspensions and emulsions for injections does not differ significantly from the general technological scheme of production of other pharmaceutical preparations, but has its own characteristics. Suspensions are prepared under aseptic conditions by dispersing a sterile medicinal substance in a sterile filtered solvent. To improve the quality of the resulting product, in some cases, ultrasonic action is used, which contributes to additional grinding and dispersion of the medicinal substance in the solvent, and on the other hand, provides the medicinal form with sterility. Under these conditions, the particle size is reduced to 1-3 microns, and such suspensions and emulsions are theoretically can be suitable for introduction even in bloody it's true. To increase stability in the production technology of suspensions and emulsions, co-solvents, stabilizers, emulsifiers, and preservatives are used.

Emulsions for injection should not show any signs of separation. Suspensions for injection may contain a precipitate which should disperse rapidly. at shaking, forming suspension. Suspension, What formed must be stable enough to provide the required dose upon administration.

Materials for activating higher education students during lectures: questions, situational tasks, etc.:

Question:

1. What types of contamination are parenteral drugs divided into?
2. What is filtering?
3. Indicate the **types** of filtration in the production of parenteral solutions.
4. What types of fabrics are used in depth filters?
5. What is membrane filtration?
6. What do you understand by sterilization filtration?
7. What are the stages of filling and sealing primary packaging?
8. What equipment used for sealing containers ?
9. What is a complete automatic ampoule line?
10. What are flexible (soft) containers?
11. What sterilization methods do you know?
12. What conditions are required for the production of parenteral drugs?
13. In what way? Do they administer suspensions for injections?

General material and methodological support for the lecture

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

Questions for self-control:

1. How are the principles of filtering characterized ?
2. How are flexible (soft) containers used ?
3. What are sterilization methods used for?

List of sources used:

1. A textbook for independent work of students of the Faculty of Pharmacy for the licensing exam "Step 2. Pharmacy" / V.Yu. Anisimov, O.I. Belyaeva, G.G. Vidavska, V.O. Helmboldt, A.V. Zamkova, I.V. Lytvynchuk, A.V. Nikitin, B.V. Prystupa, I.B. Petkova, Ya.V. Rozhkovsky, S.B. Strechen, L.M. Unguryan, N.S. Fizor Odessa: Odessa

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Access mode 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:

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- Encyclopedia of Pharmaceutical Technology: 3-d Ed. / ed. by J. Swarbrick. – New York; London: Informa Healthcare, 2007. – 4128 p.

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- State Pharmacopoeia Ukraine / State enterprise « Ukrainian scientific officinal center qualities medical " means " - 2nd ed . – Kharkiv : State enterprise « Ukrainian scientific officinal center qualities medical means ", 2015. – T. 1. – 1128 p .
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- State Pharmacopoeia Ukraine / State enterprise « Ukrainian scientific officinal center qualities medical " means " - 2nd ed . – Kharkiv : State enterprise « Ukrainian scientific officinal center qualities medical means ", 2015. – T. 3. – 732 p .
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Lecture No. 4

Topic: Industrial production Ophthalmic dosage forms. Technology of manufacturing eye drops, lotions, sprays, soft drugs, inserts. Ear dosage forms.

Relevance of the topic: Drug technology (industrial drug technology) is one of the fundamental technological sciences. It consists of several key aspects that are important for modern medicine and patients: Efficacy and safety - Modern technologies allow the production of drugs with high efficiency and safety for patients. Accurate dosing, quality control and the absence of impurities make drugs more effective and safe. Innovations in the medical field: 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 treatment. Minimization of side effects:

Technologies allow the development of drug formulas that minimize side effects and negative effects on the body. This provides more comfortable and safe treatment for patients. Fast production and delivery process: The use of modern technologies allows the acceleration of the production process of drugs, which is especially important in a rapidly changing medical environment, such as the spread of diseases or epidemics. Personalized treatment: Technologies allow for the development of medicines that take into account the individual characteristics of the patient, leading to a personalized approach to treatment and increasing its effectiveness. Cost-effectiveness and accessibility Improved manufacturing technologies can reduce production costs, making medicines more accessible to a wider range of patients, ensuring cost-effectiveness in healthcare.

Thus, the use of modern pharmaceutical manufacturing technologies is an important factor in improving the effectiveness of treatment, patient safety, and the overall state of public health.

Purpose: The discipline provides, on the basis of general knowledge and principles, regularities of factory production technology, to form in students knowledge about: theoretical foundations, acquisition of professional skills and abilities in the preparation of dosage forms, phased 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 facilities and personnel. To get acquainted with the main stages of industrial production of dosage forms and the discipline "Drug Technology", to give a characteristic of ophthalmic dosage forms and requirements for them. To get acquainted with the prospects for the development of medicinal products in ophthalmology.

Basic concepts:

eye medications — These are sterile liquid, soft or solid preparations intended for application to the eyeball and/or conjunctiva or for introduction into the conjunctival sac.

Eye drops — The most common dosage form in ophthalmology. They are sterile aqueous and oily solutions or suspensions containing one or more active substances intended for instillation. in eye.

Ophthalmic suspensions — the finest suspensions of LR powders in an aqueous

or oily dispersion medium.

Eye lotions — These are sterile aqueous solutions intended for wetting and rinsing the eyes.

Eye sprays — This is a metered (or metered) aerosol that contains solutions for in injection in eye.

Lecture plan and organizational structure:

No. 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* Defining learning goals. Providing positive motivation. *Main stage* Presentation of lecture material. Plan: 1. Eye medicinal forms. 2. Classification of dosage forms and requirements for them. 3. Eye drops 4. Ophthalmic suspensions 5. Problems of eye drop production. 6. Eye lotions 7. Eye sprays 8. Ophthalmic soft drugs 9. Eye ointments 10. Eye drops 11. Quality control of ophthalmic dosage forms.	I II III	Combined lecture Slides	1% 2% 90%

	12. Prospects for the development of medicines for use in ophthalmology. 13. Auricular dosage forms.		Bibliography, questions,	
III	*Final stage*		assignments.	
4.	Lecture summary, general conclusions.			2%
5.	The lecturer's answers to possible questions. Tasks for student self-study.			3% 2%

Structural and logical diagram of the lecture content.

1.Eyes medicinal forms

2. Classification of dosage forms and requirements for them.

2.1 Ophthalmic medications.

2.2Principles of sterility and stability

2.3 Principles of isotonicity and isohydricity

2.4 Principle of prolongation of action

3. Eye drops

4. Ophthalmic suspensions

5. Problems of eye drop production.

6. Eye lotions

7. Eye sprays

8. Ophthalmic soft drugs

9. Eye ointments

10. Eye drops

10.1 Modern classification eye inserts .

10.2 Dissolvable eye inserts based on natural polymer

10.3 Insoluble ophthalmic inserts.

10.4 Diffusion ophthalmic inserts.

10.5 Osmotic ophthalmic inserts.

10.6 Biosoluble ophthalmic inserts

10.7 Minimums

10.8 Eye films

11. Quality control of ophthalmic dosage forms.

12. Prospects for the development of medicines for use in ophthalmology.

13. Auricular dosage forms.

Content of the lecture material (lecture text)

Eye medicinal forms

Among the diverse range of therapeutic agents used by modern medicine, eye medications occupy a special place, and their production is The subject of a separate section of pharmaceutical technology. This is explained both by the unique features of the human organ of vision (the uniqueness of its structure and properties), and by the specific mechanisms of absorption, distribution, and interaction of medicinal substances with various tissues and fluids of the eye.

The vulnerability of eye tissues, a large number of diseases of the human visual organs (eyelid and orbital abscesses, anioma, blepharitis, glaucoma, trachoma, cataracts and a number of other diseases), the social component (the exceptional role of the eye in ensuring working capacity and quality of life) have necessitated the creation and constant improvement of drugs used in ophthalmological practice.

No less important tasks — creation of simple, convenient, aesthetic, informative and cost-effective packaging of ophthalmic drugs, which will allow them to be stored in a sterile and chemically stable state for a long time, and at the time of use to ensure the speed and ease of administration of the drug.

CLASSIFICATION EYE MEDICAL FORM TA REQUIREMENTS FOR THEM

According to the definition of the State Federal University of ***Applied Sciences, eye medications*** — These are sterile liquid, soft or solid preparations intended for application to the eyeball and/or conjunctiva or for administration into the conjunctival sac. Ophthalmic drugs are classified as follows:

- eye drops;
- eye direct messages;
- eye sprays;
- eye soft medical means;
- eye inserts.

In addition, they also include **: *ophthalmic injections* ; *eyelid ointments intended for use on the outer surface of the eyelid* ; *liquids for treating contact lenses.***

Nowadays, the requirements for drugs used in ophthalmological practice have increased significantly. Modern pharmaceutical codes, specifications of various countries, and the State Pharmaceutical University do not make a significant difference between drugs for the treatment of eye diseases and parenteral drugs. Both should be as free from mechanical and microbial contamination as possible.

Eye medications should be: sterile, stable, isotonic (osmolar or osmolal), to contain accurate dosage LR, not have visible to the naked eye, mechanical contaminants, some of which must have a prolonged effect and be easy to apply.

The principle of sterility and stability. The need to manufacture ophthalmic dosage forms under aseptic conditions is due to the fact that they are applied to the conjunctiva of the diseased eye. Under normal conditions, tears The liquid contains a special antibiotic substance — Lysozyme (according to the modern classification of enzymes it is called "muramidase"), which is capable of lysis of microorganisms that have entered the conjunctiva. In most eye diseases, the amount of lysozyme in the tear fluid decreases, as a result of which the eye becomes insufficiently protected from the action of microorganisms, therefore the use of non-sterile drugs can lead to serious consequences, sometimes even to loss of vision.

Microbial contamination is unacceptable not only from a sanitary and hygienic point of view, but also from the standpoint of maintaining the chemical stability of drugs, since inoculation with microorganisms accelerates the decomposition of drugs under the action of bacterial enzymes and leads to their deterioration as a result of various reactions (oxidation, reduction, polymerization, etc.). In this regard, the conditions for conducting the technological process of manufacturing ophthalmic medicinal products and all preparatory operations should be the same as during the preparation of other sterile medicinal products. Modern requirements for the production of sterile products with observance of the rules of Good Manufacturing Practice are given in Chapter 14.

The role of aseptic conditions is especially important in the manufacture of ophthalmic medicinal products that are not subject to thermal sterilization, as well as those containing heat-labile medicinal substances (sprays, gels, suspensions, etc.). When heated, the processes of crystallization, flocculation and coalescence are sharply intensified. Compliance with the rules of asepsis - the only way to ensure the proper quality of such medicines.

On practices thermolabile substances in aseptic conditions dissolve in a pre-sterilized solvent or in an ointment base in a sterile reactor, adding preservatives and stabilizers as necessary. To ensure sterility, some solutions are filtered through filters capable of retaining microorganisms. Filling of the primary container and sealing should also be carried out under aseptic conditions. These manipulations are carried out in special areas (modules, boxes, etc.), where the degree of cleanliness corresponds to class A or B.

Ophthalmic medications containing heat-stable substances, prepared in class C or D production facilities with mandatory sterilization (thermal, gas or radiation) in the final packaging.

Preservatives are added when sterility cannot be guaranteed during use of the dosage form. or then, When to prevent microbial contamination others by means impossible . But the choice of preservative must be scientifically justified and validated in order not to harm the patient and ensure the high quality of the drug .

Principles of isotonicity and isohydricity. Isotonicity — a necessary condition for the preparation of LF for eye treatment. It is known that both hypertonic and hypotonic

solutions are poorly tolerated by patients. In both cases, these phenomena are accompanied by a strong feeling of pain, therefore an important technological task has been realized — manufacturing ophthalmic preparations whose osmotic pressure would correspond to the osmotic pressure of tear fluid, which normally equals approximately 730 kPa.

Methods for determining and calculating the isotonic concentration, as well as the osmolality (osmolality) of solutions are given in Chapter 14 of the textbook. Solutions with an osmolality equivalent to sodium chloride concentrations in the range of 0.6—2.0 do not cause pain to a healthy eye. %, which corresponds to 220-680 mOsmol/L.

The pH of the solution is of great importance when using ophthalmic LF. The average pH value of the tear fluid — 7.4. Ophthalmic agents with such a pH value are the most favorable in terms of tolerance by the body. However, drugs with a pH of 5.8 to 9.0 are also relatively comfortable. Ophthalmic agents with other pH values cause severe tearing, burning sensation, and itching. Buffer solvents (phosphate, borate-acetate, citrate-phosphate, etc.) are used to regulate the pH value of eye drops, aiming to ensure both a therapeutic effect and good tolerance of the drops during instillation.

The principle of prolongation of action **.** The biological availability of ophthalmic drugs depends to a large extent on the time of contact of the drug substance with the tissues in the anterior segment of the eye . Increasing the duration of action of the API allows you to reduce the dose and frequency of use of the drug , and quickly neutralize side effects . Prolongation of the action of the LR is of great importance in the treatment of many diseases , as it provides a stable concentration of active ingredients at the therapeutic level over a long period of time .

Among the *methods of prolongation* are : the use of viscous solvents , *the* addition of biosoluble polymeric substances to the composition , or the development of new drug forms with *a* regulated rate of release of active substances .

EYES DROPS

Eye drops — The most common dosage form in ophthalmology. They are sterile

aqueous and oily solutions or suspensions containing one or more active substances intended for instillation. in eye. Instillation is being carried out drip in a way on the cornea of the eye or in the conjunctival sac of the lower eyelid. In some cases, to ensure the stability of the eye drops, they can be be released in a dry, sterile form, which is dissolved or suspended in the proposed sterile liquid immediately before use.

Eye drops — The simplest form of administration of LR in the diagnosis, prevention and treatment of eye diseases. Instillations of eye drop solutions are simple and can be easily performed by patients themselves.

As solvents for eye drops, highly purified water or water for injection, sterile fatty oils (peach, almond, etc.), and vaseline oil are used. Buffer solvents are widely used to increase the stability and therapeutic activity of medicinal substances, as well as to reduce the irritating effect of eye drops.

Basics requirements, that are related to quality eye drop, — sterility, a certain pH and osmotic pressure, quantitative content of the API, absence of mechanical inclusions, viscosity, transparency, absence of toxic and irritating effects — are described in all leading pharmacopoeias of the world.

A necessary condition for the production of eye drops is stability, since multi-batch production requires that the shelf life of the drugs be quite durable. The main causes of instability of aqueous eye drops: hydrolysis of LR, their oxidation and contamination of solutions with microorganisms. Stabilization factors include: the introduction of stabilizers (boric acid, sodium hydroxide or bicarbonate, sodium tetraborate, sodium citrate), buffer solutions, antioxidants (sodium sulfite and metabisulfite), preservatives.

The disadvantages of eye drops include the fact that when they are introduced into the conjunctival sac, the LR is quickly washed out by the tear fluid and as a result — a significant part of the drug is absorbed and does not have a therapeutic effect. To achieve the necessary therapeutic effect, it is necessary to increase the number of instillations to 5-8 per day, and sometimes more. As a result, resistance of the eye microflora to the administered antibiotics and sulfonamide drugs often develops; sometimes allergic reactions are observed.

With the aim of prolonging the action of LR in eye drops, attempts have been made

to increase the viscosity of solutions by using natural oils (sterile peach, almond), but these solvents have not gained significant popularity for various reasons. Their disadvantages include the formation of a fatty film, incomplete release of substances, and increased lacrimation. The recommended viscosity of eye drops should be within 15-30 mPa•s at 37 °C, and the refractive index is 1.334-1.338.

A long time ago with goal prolongation actions eye drop use

Biosoluble polymeric materials of synthetic origin - polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), polyacrylamide and other materials. Aqueous solutions of methylcellulose (MC) in concentrations of 0.5–2 have become widely used. %, which have high viscosity and a refractive index (1.336) close to that of water (1.334), which is of significant importance to ensure normal vision. However, MC delays the processes of corneal epithelium regeneration, and in some cases causes irritation of the eye tissues, which is why there has been a tendency to reduce the production of eye drops using MC. Other cellulose derivatives are also used to prolong the action of eye drops. — carboxymethylcellulose, as well as its salt sodium CMC, methyloxypropylcellulose, which are well soluble in water and easily mix with tear fluid.

To increase the viscosity of aqueous eye drops, 1.5% PVA is used. It does not irritate the mucous membrane of the eye, does not violate the integrity of the corneal epithelium and accelerates the epithelialization of the eroded cornea, and also promotes the healing of ulcers and burns of the cornea. PVA solutions can be injected into an open eye wound. PVA is compatible with most LRs and preservatives. The viscosity of its solutions is lower than that of cellulose derivatives, which has a positive effect on the eye, since a thinner film is formed on its surface. a film that does not interfere with normal vision.

The use of PVP and PVA causes a slight decrease in surface tension and provides longer contact of the substances dissolved in them with the tissues of the eye. In order for the medicinal solution to be evenly distributed over the cornea, its surface tension should be close to 31 mN/m. Surface The tension of tear fluid at 32.1 °C (average corneal temperature) is 46.29 mN/m.

A necessary condition for drops — absence of vegetative and spore forms of viable

flora, since the mucous membrane of the eye is easily infected. Sterility of eye drops is easily achieved by observing the rules of asepsis during preparation, as well as sterilization. Sterility of eye drops can be achieved by applying methods of heat, chemical or radiation treatment, often in combination with sterilization filtration.

The probability of microbial contamination of ophthalmic dosage forms increases significantly with their repeated use, which requires frequent opening of the packaging and measuring the solution with a pipette. Already when opening the bottle and first use, the drops are inoculated with microflora. In this regard, along with heat treatment and sterilization filtration, preservatives with bactericidal or bacteriostatic action are introduced into their composition.

The following preservatives are used for eye drops: phenylethyl alcohol (0.3—0.5 %), benzyl (0.9 %), nipagin (0.025-0.05 %), nipazol (0.03-0.08 %) and their mixture (0.18 and 0.2 % respectively), sorbic acid (0.05—0.2 %), chloramphenicol (0.15%), salts quaternary ammonium compounds — benzalkonium chloride, ethony chloride, cetylpyridinium chloride, chlorhexidine (in concentrations of 0.005—0.01 %), merthiolate (0.005 %) and other substances .

When studying preservatives, it was found that many of them are irritating to the eyes. Therefore, in each specific case, one should not only consider the compatibility of the preservative with the API, but also the possibility of using it in one or another pathological process of the organ of vision. Preventing microbial contamination of drugs without the use of preservatives is possible only through the use of disposable packaging, the characteristics of which and the features of the production technology will be given below. The technology for manufacturing eye drops almost completely repeats the general technology for producing parenteral solutions in vials.

Ophthalmic suspensions — the finest suspensions of LR powders in an aqueous or oily dispersion medium. They are obtained *by the dispersion method* , when the suspension is formed as a result of a gradual decrease in the degree of dispersion of the initial insoluble substance (i.e., its grinding), or *by the condensation method* , when the formation of the suspension occurs as a result of an increase in the degree of dispersion of the initial material, which was previously in the ionic, molecular or colloidal degree of dispersion. In the case of overcoming the sedimentation instability of the suspensions and

preserving fine particles in them, the resulting preparations are not felt by the patient and have the same therapeutic effect as eye drops.

Recently, in industrial conditions, *an ultrasonic method* of dispersing components has been used to obtain ophthalmic suspensions, in which the size of the particles formed can reach 3-10 microns, and ultrasonic sonication leads to sterility of the dosage form. To increase stability in the production of suspensions, co-solvents, stabilizers, and preservatives are used.

Sometimes, for the preparation of eye drops and lotions from unstable substances, ***sterile powders are used*** , which are dissolved in a sterile solvent immediately before use. In this case, the powders should dissolve easily and without residue in the appropriate solvent, not contain irritating or traumatic components to the eyes, and the resulting solution should meet all the requirements for eye drops. Most often, this dosage form is obtained in factories under aseptic conditions and packed in sterile vials with tamper-evident closure.

Problems production eye drops in optimal packaging.

The problem of packaging of ophthalmic drugs requires constant attention due to the fact that its irrational choice, inconvenience of use, the influence of the primary packaging material on the drug can lead to a decrease in the quality of the product and significant losses of medicinal substances and materials.

The primary packaging must guarantee the impossibility of infection of the eye drops and the eye during repeated use of the drug, and its design must exclude the possibility of immersing the eye pipette in the solution, the use of which leads to contamination of the solution.

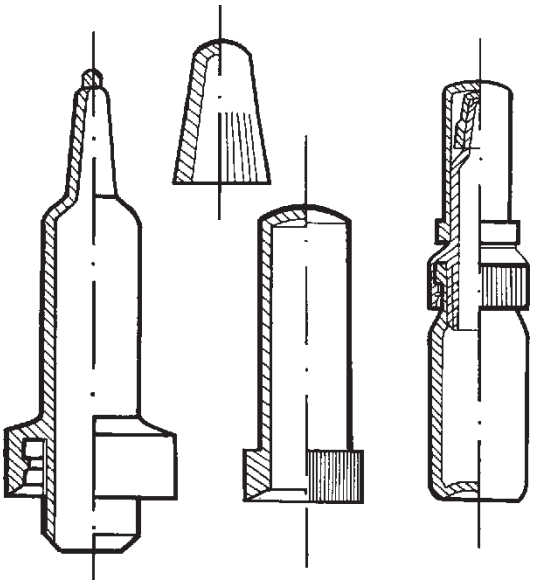


Figure 15.1. General view of a plastic pipette stopper

Research by scientists and manufacturers has identified two main areas in the technology of eye drop production, which are determined by the type of packaging.

A common type of primary packaging for eye drops is a glass bottle with a capacity of 5-10 ml. ml, sealed with a rubber stopper and a metal cap, with a special dosing device attached to it (Fig. 15.1). After opening the bottle, the patient independently fixes the polymer dropper.

Vials equipped with screw-type pipettes with a central or forced dropper have enjoyed some success, but they also have some drawbacks. For example, there is a risk that the pipettes may come into contact with the surface of contaminated objects. and infect the solution; children can easily open the bottle; a glass bottle can be subjected to leaching, and a significant volume of the bottle contents cannot be used for 3-5 days, which leads to irrational use of LR or microbial contamination of the solution. Rubber stoppers can also pose a certain risk due to the possible migration of rubber components into the solution of ophthalmic drugs before their use. More details about the types of primary containers for eye drops are given in Chapter 2 of the textbook.

Technology production eye drops in glass vials consists of the following main stages and operations:

- preparation production (preparation production premises, air,
- equipment, personnel and workwear and other measures); preparation primary

containers and clogging means;

preparation solution (in case need stabilization, isotonization or introduction of preservatives) and its sterilization filtration;

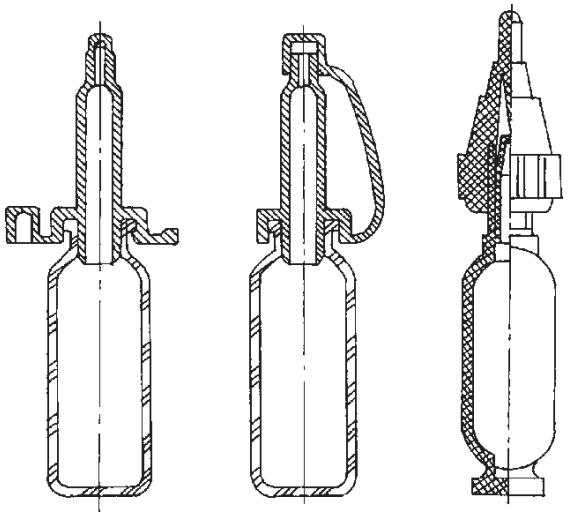
- filling vials and theirs sealing;
- thermal sterilization vials with solution;
- marking vials; packaging finished products.

By such technology works equipment foreign firms Germany

(Bosch, Rota groups), India (Kleinzides, Fortune), Italy (Pharmomak), Russia (VIPS-med, Sakta NPF) and others, which produce automatic technological lines that provide the entire range of operations for the preparation of glass containers, stoppers and caps, pouring solutions, sealing vials and their subsequent packaging in group packaging. Installation of such equipment should be carried out in clean rooms of certain cleanliness classes. The use of automatic lines guarantees high quality of the resulting product, sterility, almost complete automation of processes, minimal personnel participation, etc.

Recently, a second direction in the production of ophthalmic solutions has been identified and has begun to develop rapidly - in polymer containers. Polymer packaging allows to isolate the drug from harmful environmental factors at the production stages and reliably ensure its sterility and stability, and to deliver the drug directly to use without violating its tightness. Polymer containers for ophthalmic drugs means (tube- or dropper bottle) are made of one or several polymers that do not contain substances harmful to the body that can be extracted from them by liquids.

A dropper tube is a polyethylene container with a capacity of most often 1.5±0.15 ml for packaging, transportation, sterile storage and instillation of aqueous solutions of eye medications (Fig. 15.2). It consists of a body that is sealed under aseptic conditions after filling with a sterile solution, and a protective cap with a piercing device.



Types dropper tube

Currently, in Ukraine, some pharmaceutical factories use ***the technology BFS (Blow-Fill-Seal) "blowing — filling — sealing"*** in the production of ophthalmic drugs in polymer packaging. The equipment for this technology is a complex equipment of special design, in which containers are formed from thermoplastic granulate during one continuous technological cycle, filled and then sealed within one automatic complex.

The introduction of this technology into the production of ophthalmic drugs in polymer packaging of various configurations guarantees complete sterility of products and meets modern GMP requirements. Almost all foreign manufacturers produce eye drops using this technology.

Using the specified technology allows:

✦ exclude laborious stage preparation (washing, drying or sterilization) of primary packaging and closures;

✦ to manufacture cases while simultaneously filling them with sterile solution in Class A zone in within one complex equipment with an environment not lower than class C;

✦ minimize the time between solution preparation, filling, and sealing of the case (1-2 s), which leads to increased stability and quality of the drug;

✦ exclude thermal sterilization as destabilizing factor;

✦ to mark the primary packaging by embossing directly during the blowing of the

case by using molds equipped with marking inserts;

- ✦ much to lower cost drug, because the cost of polymer packaging is significantly lower than glass packaging;
- ✦ eliminate the possibility of drug falsification thanks to the original marking on case polymer packaging.

General technology production eye solutions in polymer bottles or dropper tubes consists of the following stages:

- ➢ formation protective caps (lid);
- ➢ production polymeric sterile buildings;
- ➢ preparation solution and its sterilization filtration;
- ➢ filling buildings and theirs sealing;
- ➢ marking buildings droppers (vials);
- ➢ drafting buildings and caps (lid);
- ➢ packaging ready products.

The resulting tube- or dropper bottles with solution subjected to visual inspection for the absence of mechanical inclusions and a random check is carried out for all indicators — 5 % of containers from each series. Polymer packages are placed in single-use cases or foil, 5-10 pieces in cardboard packs or in contoured polyvinyl chloride film.

EYE LOTIONS

Eye lotions — These are sterile aqueous solutions intended for wetting and rinsing the eyes, as well as for soaking materials applied to the eye. They must meet all the requirements for ophthalmic dosage forms. Ophthalmic solutions used in surgical procedures and for first aid should not contain antimicrobial preservatives and should be available only in single-dose containers.

Aqueous solutions of eye drops, produced in multi-dose containers, must contain antimicrobial preservatives in the necessary concentrations, except in cases where the drug itself exhibits sufficient antimicrobial activity. The selected preservatives must be compatible with other ingredients of the drug and maintain effectiveness throughout the entire period of use of the eye drops. A multi-dose container may contain no more than

200 ml of eye drop solution and is used in stationary medical institutions.

Eye drops may contain excipients to ensure isotonization, viscosity, creation or maintenance of the necessary pH value, increase the solubility of active substances, and stabilize the drug. These substances, in the concentrations used, should not negatively affect the effectiveness of the drug and should not cause local irritation.

To this one w groups eye medical means trace to take away ***liquids for Contact lens treatment*** . These are sterile, moisturizing and disinfecting aqueous solutions used to preserve, clean and facilitate the application of contact lenses or contact glasses of ophthalmic devices used for eye examinations.

The technology for producing eye lotions and lens treatment fluids is similar to the production of eye drops in bottles.

EYES WITH PRESENTATION

Recently, a new pharmaceutical form for the treatment of ophthalmological diseases appeared across the border - eye sprays.

Eye sprays — This is a metered (or metered) aerosol that contains solutions for in injection in eye. Solutions for injection should be gentle, comfortable, and hygienically flawless for outpatient treatment, as they are applied to the eye in a contact-free manner.

For small volume ***metered aerosols*** (20-50 ml) nitrogen and nitrogen dioxide are used as a carrier. In order for the precisely dosed release of the contents to reach the eye without a jet, the propellant pressure should not be higher 210 kPa at 20 °C. Sterility of such LF is more difficult to achieve than other dosage forms for the eyes. Quaternary ammonium compounds should not be used as preservatives due to undesirable slight foaming during spraying.

Aerosol particles are well adsorbed on the mucous membrane, which ensures rapid absorption of the medicinal substance. The use of sprays and aerosols is painless, and due to the high dispersion of particles, their use allows you to significantly increase the therapeutic effectiveness of drugs.

The technology for producing eye sprays and aerosols is similar to that for producing pressurized preparations (Chapter 13 of this textbook).

EYES M 'WHICH APC MEDICINE With AC BOTH

Ophthalmic soft drugs — These are homogeneous sterile ointments, creams or gels intended for application to the conjunctiva of the eye. They may contain one or more active substances dissolved or dispersed in a suitable base. Ophthalmic soft drugs also include eyelid ointments, which are used to lubricate the outer surface or edges of the eyelid.

Eye ointments must meet the following quality indicators: sterility, lack of irritant effect, necessary therapeutic effect, stability, uniform distribution of LR or its solution in the ointment, soft consistency, rapid formation of the thinnest film on the eyeball, good contact with the eye and no sticking of the eyelids. The pH of the ointment must correspond to the pH of the tear fluid, otherwise tearing occurs and APIs are quickly washed out.

An important criterion in the technology of manufacturing eye ointments is consistency. Eye ointments should be soft and in the temperature range of 15-50 °C to exhibit stable viscosity. At a temperature of 30 °C, the viscosity of the ointment should be 0.3-1.0 Pa•s. The necessary consistency is provided by ointment bases, which are divided into ***hydrophobic*** **,** ***hydrophilic*** **(** ***water-washable*** **,** ***water-soluble*** **) ,** ***and adsorptive.*** The ointment base should not have foreign inclusions and impurities; it must be sterile, neutral, and easily and evenly distributed on the mucous membrane of the eye and conjunctiva.

What hydrophobic bases use vaseline alloys, which does not contains reducing agents, and anhydrous lanolin in various ratios. Suggested bases containing lanolin processing products: basis, What consists of from alcohols woolen wax, ceresin, Vaseline oil and petroleum jelly in a ratio of 4:24:60:10, as well as hydrolin (hydrogenated lanolin) and other substances.

Along with hydrophobic ointments, hydrophobic gels with silica, stearates or polymers as gelling agents are also being developed. However, they have not yet received due recognition because After antimicrobial heat treatment, a significant change in their viscosity is observed.

An alternative to hydrophobic bases are hydrophilic bases, such as hydrogels (jellies), PEG-based gels, emulsion and hydrophilic bases on methylcellulose gels, oil-in-water emulsions. Dosage forms obtained on hydrophilic bases also have disadvantages. Ointments on hydrophilic bases do not initially cause burning in the eye, but they cause an unpleasant sensation of "sand" and have the ability to stick the eyelids together after drying. Their residence time in the conjunctival sac is shorter than that of hydrophobic ointments, which provides a shorter duration of therapeutic action. The use of PEG-based eye ointments is limited due to the irritating effect caused by high osmolarity.

Recently, when studying the biopharmaceutical characteristics of eye ointments, it was found that the efficiency of LR release increases when using ophthalmic emulsion-type bases compared to aqueous drops. The release of API depends on their distribution between the oil and water phases of the emulsion ointment base, and the diffusion of LR from the base .

Traditional ophthalmic topical LFs have low bioavailability due to rapid elimination of LR, absorption on the conjunctiva, partial elimination of the dose through lacrimation and normal tear flow. To enhance the therapeutic effect, either the concentration of active substances or the frequency of instillations can be increased, which is often impractical. This leads to the conclusion that the action should be prolonged, which, on the one hand, will increase the contact time between the drug and the cornea and improve the therapeutic effect, and on the other hand, reducing the number of instillations will contribute to comfort in use.

One with approaches for software necessary time release The API currently practiced consists of the use of viscous preparations, most often of the hydrogel type. **Hydrogels** — These are polymers that have the ability to swell in water or aqueous solutions and form a jelly-like structure. The improvement of the technology of eye ointments will be facilitated by the targeted search for new ointment bases. Currently, ointments with anti-inflammatory drugs (cortisone, dexamethasone, actovegin, solcoseryl), antibiotics and antiviral substances (gentamicin, tetracycline, chlorsig, zovirax, virolex), vitamins (B_2, B_6, B_{12}, A, E, D), antiglaucoma drugs (pilogel, betaxolol suspension, etc.) are prepared on the basis of carbopol gel (a cross-linked copolymer of acrylic acid).

Technology obtaining eye ointments typical and covers such stages:

- production preparation (preparation of production premises, air, equipment, personnel, workwear);
- preparation medical substances and ointment foundations;
- obtaining multicomponent ointment foundations;
- introduction medical substances in basis;
- homogenization ointments;
- packaging, packaging and marking ready products.

Eye ointments should be prepared with the strictest adherence to the rules of asepsis; heat-stable medicinal and auxiliary substances should be pre-sterilized, and medicinal substances insoluble in the ointment base should be ground to a minimum degree of dispersion, which ensures high bioavailability and the absence of discomfort when applying the ointment. The features of changing the technology for obtaining eye ointments are indicated in a separate ND.

For packaging of eye ointments, sterile metal tubes with a varnished inner surface are used to prevent contact of the metal with the medicinal substance. Polymeric materials are also increasingly used for packaging a single dose of ointment. The content of the tube should not exceed 5 g, they should be hermetically sealed to prevent microbial contamination.

Eyeliners — recently a very rare dosage form. In ophthalmological practice they are used for cauterization of mucous membranes. Eye pencils are obtained by melting the base and active ingredients with subsequent pouring into special molds, where they solidify and, losing moisture, harden.

OPHTHALMOLOGICAL LIKA PC ЬKI BC AND B KI

A significant achievement in the field of ophthalmic pharmaceuticals — is the creation of ophthalmic medical inserts. Ophthalmic inserts — This is an alternative form of prolonged-release eye medications.

Ophthalmic inserts are sterile solid or soft preparations intended for insertion into the conjunctival sac. Their size and shape are specifically designed for ophthalmic use. They usually consist of a matrix in which either the LR is incorporated or the active substance is surrounded by a membrane that controls its release rate. The active substance

should be well soluble in physiological fluid and released over a certain period of time.

Ophthalmic inserts can be used for local or systemic therapy. Their main task is to increase the contact time of the drug and the conjunctiva. They have significant advantages over traditional ophthalmic LF.

Ophthalmic drug inserts allow for precise, controlled dosing of LRs, prolonging their action as a result of the gradual dissolution of the insert in the tear fluid and increasing the time of contact with the eye surface, reducing the number of drug administrations, increasing its therapeutic concentration in eye tissues, reducing the course of treatment by 2-3 times, and also providing treatment in conditions where other methods of drug administration are difficult or **impossible.**

Modern classification eye inserts built on their solubility:

soluble, insoluble and biosoluble.

Dissolvable ophthalmic inserts. This class is the oldest. Since the inserts are completely soluble, there is no need to remove them from the application site, which has a positive effect on the patient. Dissolvable inserts are quite well studied and evaluated by *in vitro* and *in vivo tests* . However, they are characterized by such disadvantages as a high rate of tear fluid penetration into the insert; blurred vision caused by solubilization of the components; insufficient contact with the surface of the eye due to their structure, because they are dry and smooth.

Depending on ***the nature of the polymers used,*** soluble eye inserts are divided into those obtained on the basis of:

— natural polymers;

— synthetic or semi-synthetic polymers.

For the first time, ***soluble eye inserts based on a natural polymer*** — collagen were developed by S. M. Fedorov in the form of a bandage after eye surgeries. Since then, scientific research has been mainly aimed at improving the mechanism of drug release and methods of their introduction into the insert. Such systems make it possible to reduce the number of complications and accelerate the healing of damaged eye tissues. The kinetics of drug release from inserts of this type should be compared with the kinetics of

drug release from hydrophilic contact lenses.

The advantages of ***soluble eye inserts based on synthetic and semi-synthetic polymers*** are simple design and materials traditionally used in ophthalmology, easy production technology (slow evaporation, extrusion, compression or pressing in molds).

The release of active ingredients from such systems is characterized by two distinct phases: the first corresponds to the penetration of tear fluid into the insert, which causes diffusion of the substance and the formation of a gel layer around the pores of the insert. This external gelation causes a second phase, which corresponds to a decrease in the release rate, which continues to be controlled by diffusion.

Insoluble ophthalmic inserts. This group of ophthalmic inserts is classified as in such method: a) *diffusion systems* ; b) *osmotic systems* ; in) *hydrophilic contact lenses* . Basic blemish insoluble inserts - the need for mandatory removal after use.

Diffusion ophthalmic inserts consist of a central reservoir and the API placed in it. The reservoir is constructed of special semipermeable or microporous membranes, due to which the LR diffuses at a certain rate. The release from such systems is controlled by the tear fluid, which penetrates the membrane and helps to achieve the necessary internal pressure, which allows you to control the release of substances from the reservoir.

The reservoir may consist of glycerin, ethylene glycol, propylene glycol, water, a mixture of methylcellulose with water, sodium alginate, polyvinylpyrrolidone, polyoxyethylene stearate, fatty acids. Microporous membranes can to be made with polycarbonates, polyvinyl chlorides, polyamides, polysulfones, polyethers, polyvinyl acetates, polyurethane, acrylic resins, cellulose esters, cross-linked polyethylene oxide, polyvinylpyrrolidone, polyvinyl alcohol.

The rate of release of LR from such systems is characterized by three phases. The initial rate is usually high, which corresponds to the achievement of an equilibrium state between the reservoir and the surface of the eye. Then the rate decreases to some constant value, which corresponds to a uniform rate of release of substances. In the third phase, there is a final decrease in the rate of release, which corresponds to a decrease in the amount of active substances.

Osmotic ophthalmic inserts consist of a central part surrounded by a peripheral

part. The central part can consist of a simple reservoir or two different compartments. In the first case, the reservoir consists of LRs distributed in a polymer matrix. The water-permeable matrix can be made of copolymers of ethylene vinyl ethers, plasticized polyvinyl chlorides or polyamides, polyisobutylene, polyethylene, cross-linked polyvinylpyrrolidone, polyurethane.

The reservoir together with the LR may contain dissolved excipients to create osmotic pressure. For this purpose, sodium chloride, sodium and potassium sulfates, calcium sulfate, potassium hydrogen phosphate, magnesium chloride or sulfate, lithium chloride, calcium lactate, magnesium succinate, tartaric acid, acetamide, sorbitol, mannitol, glucose and lactose are used.

Otherwise, the active substance and substances to create osmotic pressure accommodate in two different departments. Tank from API surrounded by an elastic impermeable membrane, and the reservoir with auxiliary substances is surrounded by a semipermeable membrane.

The peripheral part of the osmotic inserts contains a film of insoluble semipermeable polymer based on, for example, derivatives of acetylcellulose, ethylene vinyl acetate, polyesters of acrylic and methacrylic acids, polyvinyl alkyl esters, polystyrene. The nature of the release of medicinal substances from osmotic inserts is different and depends on their structure.

Currently, the ***hydrophilic contact lens class*** is developing the fastest. Contact lenses are a coherent system — a covalently cross-linked hydrophilic or hydrophobic polymer, the structure of which allows it to retain water, aqueous solutions of LR or solid components. The polymer network consists of repeating units of the same or different monomers, which form long chains. These chains are connected by internal bridges, or cross-links, which are responsible for the coherent structure of the system. Such cross-linked systems do not dissolve, but can swell by absorbing water.

The great advantage of contact lenses is that they are the only class of ophthalmic dosage forms capable of simultaneously correcting refractive errors of vision and providing treatment for certain eye pathologies.

The use of contact lenses as LR delivery systems is complicated by two reasons.

First, during application, the patient's hands are in constant contact with the lenses, which leads to a high risk of contamination and frequent rinsing procedures, which causes loss of medication. Second, it relatively high price. Ago prospects development Contact lenses as carriers of medicinal substances are related to solving issues related to the creation of lenses for permanent wear throughout the entire treatment period.

Biosoluble ophthalmic inserts are a matrix with homogeneously dispersed LR, which is included or not included in a hydrophobic layer. This layer is impermeable to active substances. The main components of this type of inserts are the so-called biosoluble polymers, i.e. materials that are exposed hydrolysis chemical connections and, therefore, dissolution. Biosolubility here is determined as

property material for for a long time disintegrate on components parts or to stand out from structures because of actions on him environment eye. This process not should do toxic actions on eye. It is difficult to control the release of medicinal substances from biosoluble eye inserts. However, various methods of release control have been proposed today: the use of new promising biosoluble materials; changing the composition by introducing various excipients to increase or decrease the erosion rate of the insert (as a rule, anionic surfactants accelerate the erosion process, cationic ones slow it down). Successful bioerosive materials for ophthalmic use are polyorthoesters and polyorthoecarbonates. When releasing drugs from such systems, the contact of the agent with the tear fluid is very important, including surface bioerosion of the matrix. But the main advantage of these bioerosive polymers is the possibility of modulating their erosion rate by modifying their final structure during synthesis.

Modern ophthalmic inserts belong to the third generation of drugs, but the history of their development began with the creation and improvement of minims, lamellae, and eye films.

Minimums — This is a small reservoir made of high-polymer material, designed for a small amount of liquid (4-12 drops) or ointment (about 0.5 g) medication. The minims shape allows you to easily open it, squeeze out 1 drop of solution or 100 mg of ointment, shake to clean the outlet, and then apply a few drops of solution or a portion of ointment to the mucous membrane in the conjunctival sac of one or both eyes.

Minims are manufactured abroad by many pharmaceutical companies on special molding machines. Granulated high-pressure polyethylene is used as the starting material, which is sterilized with ethylene oxide and fed for automatic filling using a dosing machine with a sterile solution or ointment containing the appropriate LR. After filling, the minims are sealed under aseptic conditions or sterilized again with ethylene oxide, packed in foil or other materials on which the necessary data is applied (name of the drug, dose, expiration date, series, method of use, etc.).

Single-use ophthalmic LF, intended for placement in the conjunctival sac, are ***lamellae*** — small gelatin oval disks with a diameter of 3 mm, which contain in the gelatin mass various LRs used in ophthalmological practice. The original ophthalmic LF for single use should be called ***ophthalmic films*** — oval-shaped plates (average mass 0.015 g and in size 9.0□4.5□0.35 mm), which are made with biosoluble and a polymer compatible with eye tissues and medicinal substances. They are intended for the introduction of these substances into the conjunctival cavity in viral, bacterial, allergic and other eye diseases, as well as for accelerating reparative processes after eye damage. Eye films are used to replace frequent instillations of eye drops and prolong the action of LR by extending the time of their contact with eye tissues. The solubility of the films is determined by the composition of the base and can be 35—90 The industry has mastered the production of eye films with sulfapyridazine sodium, neomycin sulfate, florenal, dicaine, pilocarpine hydrochloride, kanamycin, and other drugs.

C O N TPO L HOW TO EYE MEDICAL FOPM

Eye drops, according to the State Pharmacopoeia and pharmacopoeias of leading European countries, are controlled for the following quality indicators: *opuc* ; *identification* ; *transparency* ; *color* ; *pH* ; *incidental impurities* ; *volume of container contents (for multi-dose containers)* ; *sterility* ; *mechanical inclusions* ; *quantitative determination of active* medicinal products is possible due to the constant expansion of the range based on original substances, the search and study of new excipients, the improvement of manufacturing technologies, and the equipping of manufacturers with advanced technological equipment, which would allow the production of new high-quality drugs that have high bioavailability, stability during storage, and are distinguished

by simplicity and convenience for patients when used.

Auricular dosage forms .

Ear medications are liquid, soft or solid drugs intended for instillation, spraying, inhalation or application into the ear canal or for rinsing the ear. In addition to the active substances and the solvent, they may contain excipients intended to regulate tonicity or viscosity, create or stabilize the required pH level, increase the solubility of the active substances, ensure stability or provide appropriate antimicrobial properties. Excipients should not adversely affect the action of the drug and have a toxic or undesirable irritant effect. *Ear drops and aerosols* are solutions, emulsions or suspensions containing one or more active substances in appropriate solvents and intended for introduction into the ear canal, do not exert dangerous pressure on the eardrum. They can also be introduced into the ear canal (without creating dangerous pressure) using a turunda impregnated with the drug. Emulsions may delaminate, but should easily transform into an emulsion when shaken. Suspensions may form a precipitate, which is quickly resuspended when shaken, forming a suspension that is stable enough to provide the required dose when administered. 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* are medicinal products in the form of aqueous solutions with a pH level that corresponds to physiological limits, intended for cleaning the external auditory canal.

Materials for activating higher education students during lectures: questions, situational tasks, etc.:

Question:

1. How? How are eye medications classified?
2. What are the basic principles of sterility and stability?
3. What are the basic principles of isotonicity and isohydricity?
4. Name the main methods of prolonging the action of drugs.
5. How? Is eye drops instilled?
6. How are eye suspensions obtained?
7. What is the common type of primary packaging for eye drops?

8. What are eye drops?
9. Describe eye sprays.
10. How can you characterize eye-softening medications?
11. What are eye drops?
12. What is the classification of eye inserts?
13. What are the types of eye inserts?
14. What are ***minima?*** ?
15. What indicators are used to control the quality of eye drops?
16. What is the classification of oral dosage forms?

Quality control of substances and antimicrobial preservatives.

In eye drops, which contain substances that provide a certain viscosity, *viscosity is additionally controlled* .

For eye drops in the form of oily (oil) solutions, *the taste* and *smell of the food are additionally controlled* .

For eye drops in the form of suspensions, the *particle size is additionally controlled* ; the presence of particles of size over 90 microns. A reusable container should contain no more than 10 ml of the drug.

Eye drops should be clear, free of particles, and sterile. The shelf life of the product after opening the container should be stated on the label of multi-dose containers, which should not exceed four weeks.

Eye soft medical resources must answer requirements general article "Soft drugs for topical use". Additionally, eye ointments are controlled by the following quality indicators: *mass of container contents* , *metal particles* , *sterility* , *container tightness* . *For eye ointments, the bases of which contain triglycerides of fatty acids, the taste* and *bite* are additionally controlled . Soft eye medications containing dispersed solid particles must withstand *particle size tests* (particles larger than 90 microns are not allowed).

For ophthalmic medicinal inserts, compliance with the requirements of the article “Uniformity of the active substance content in a unit dose of a medicinal product” is monitored, determining; *the dose of the active substance released per unit time* ; *sterility* , *solubility* (for soluble and biosoluble inserts); *physicochemical properties* (transparency,

integrity, surface roughness, elasticity, strength and other indicators).

PROSPECTS DEVELOPMENT MEDICAL RESOURCES FOR USE IN OPHTHALMOLOGY

The prospects for the development of drugs for use in ophthalmology are associated with the development and production of new-generation ocular therapeutic systems (OTS) with controlled release and targeted delivery of active substances to the area of pathology. Saturation of the pharmaceutical market with ophthalmological products

General material and methodological support for the lecture.

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

Questions for self-control:

1. How are the principles of sterility and stability characterized ?
2. How are eye drops used ?
3. What are minima used for?
4. What are the methods of quality control of eye drops?

List of sources used:

1. A textbook for independent work of students of the Faculty of Pharmacy for the licensing exam "Step 2. Pharmacy" / V.Yu. Anisimov, O.I. Belyaeva, G.G. Vidavska, V.O. Helmboldt, A.V. Zamkova, I.V. Lytvynchuk, A.V. Nikitin, B.V. Prystupa, I.B. Petkova, Ya.V. Rozhkovsky, S.B. Strechen, L.M. Unguryan, N.S. Fizor Odessa: Odessa National Medical University. 2020. - 240 p.

Access mode 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 of higher. educational. pharmaceutical institutions (pharmac. faculties) / E.V. Gladukh, O.A. Ruban, I.V. Saiko and others. - Kh.: NPhU: Original, 2016. - 632p. : Named after. - (Series "National textbook")

2. Workshop on industrial technology of medicines, specialty "Pharmacy" / Edited by Ruban O.A. - Kh .: National University of Physics and Technology, 2015. - 374 p.

3. INDUSTRIAL technology of medicines : a teaching aid for independent work of students / O. A. Ruban , V. D. Rybachuk , L. M. Khokhlova etc. – KH.: NATIONAL UNIVERSITY OF PHYSICS AND TECHNOLOGY, 2015. – 120 p.

- Excipients in the production of medicines: a manual for students of higher pharmaceutical schools / O. A. Ruban , I. M. Pertsev, S. A. Kutsenko, Yu. S. Masliy; edited by I. M. Pertsev. – Kh.: Zoloti storyny, 2016. – 720 p.
- Technology of industrial drug production: a textbook for students of higher education institutions: in 2 parts / V. I. Chuyeshov, E. V. Gladukh, I. V. Sayko and others – 2nd ed., revised and supplemented – Kh.: National University of Physics and Technology: Original, 2012. – Part 1. – 694 p.
- Technology of industrial drug production: a textbook for students of higher education: in 2 parts / V. I. Chuyeshov, E. V. Gladukh, I. V. Sayko and others – 2nd ed., revised and supplemented – Kh.: NPhA: Original, 2013. – Part 2. – 638 p.
- Modern pharmaceutical technologies: teaching aids for laboratory classes of undergraduates of full-time, evening and correspondence forms of study in the specialty 8.110201 "Pharmacy" / edited by O. A. Ruban. – Kh.: Publishing house of the National University of Physics and Technology, 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 Ukraine / State enterprise « Ukrainian scientific officinal center qualities medical " means " - 2nd ed . – Kharkiv : State enterprise « Ukrainian scientific officinal center qualities medical means ", 2015. – T. 1. – 1128 p .
- State Pharmacopoeia Ukraine / State enterprise « Ukrainian scientific officinal center qualities medical " means " - 2nd ed . – Kharkiv : State enterprise « Ukrainian scientific officinal center qualities medical means ", 2014. – T. 2. – 724 p .
- State Pharmacopoeia Ukraine / State enterprise « Ukrainian scientific officinal center qualities medical " means " - 2nd ed . – Kharkiv : State enterprise « Ukrainian scientific officinal center qualities medical means ", 2015. – T. 3. – 732 p .
- On medicinal products: Law of Ukraine of 4.04.96 No. 123/96 // Bulletin of the Verkhovna Rada of Ukraine. – 1996. – .№ 123.

Lecture No. 5

Topic: Extractive preparations. Stages of extraction. Requirements for extractants) – 2 hours.

Relevance of the topic: Drug technology (industrial drug technology) is one of the fundamental technological sciences. It consists of several key aspects that are important for modern medicine and patients: Efficacy and safety - Modern technologies allow the production of drugs with high efficiency and safety for patients. Accurate dosing, quality control and the absence of impurities make drugs more effective and safe. Innovations in the medical field: 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 treatment. Minimization of side effects: Technologies allow the development of drug formulas that minimize side effects and negative effects on the body. This provides more comfortable and safe treatment for patients. Fast production and delivery process: The use of modern technologies allows the acceleration of the production process of drugs, which is especially important in a rapidly changing medical environment, such as the spread of diseases or epidemics. Personalized treatment: Technologies allow for the development of medicines that take

into account the individual characteristics of the patient, leading to a personalized approach to treatment and increasing its effectiveness. Cost-effectiveness and accessibility Improved manufacturing technologies can reduce production costs, making medicines more accessible to a wider range of patients, ensuring cost-effectiveness in healthcare.

Thus, the use of modern pharmaceutical manufacturing technologies is an important factor in improving the effectiveness of treatment, patient safety, and the overall state of public health.

Purpose: The discipline provides, on the basis of general knowledge and principles, regularities of the technology of factory production, to form in students knowledge about: theoretical foundations, acquisition of professional skills and abilities in the preparation of dosage forms, stage-by-stage 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 facilities and personnel. To get acquainted with the main stages of industrial production of dosage forms and the discipline "Technology of Medicines", consider the features of extraction of plant raw materials with a cellular structure, stages process extraction, requirements for extractants, various extraction methods.

Basic concepts:

Infrared drying - makes it possible to carry out the process in large volumes at high speed (duration - from 30 to 200 min, depending on the type of material).

Acoustic drying - based on the action of intense ultrasonic waves on the material, is suitable for drying raw materials with any initial moisture content and is characterized by a high degree of preservation of BAS in the dried material.

Molecular diffusion — This is the process of transferring a distributable substance (DSP) due to the chaotic movement of the molecules themselves in a stationary medium.

Extractant - must be able to penetrate cell walls, selectively dissolve the "necessary" medicinal substances inside the cells, after which the dissolved substances,

together with the extractant, must pass through various membranes and go beyond the plant material.

Electroplasmolysis — processing of raw materials with low and high frequency electric current.

Rectification (from Latin *rectification* — correction, cleaning) — the process of separating a mixture of liquids that are miscible and have similar boiling points into individual components and purifying them.

Lecture plan and organizational structure:

No. No. .p.	**The main stages of the lecture and their content.**	**Goals in levels of abstraction.**	**Type of lecture, lecture equipment.**	**Time allocation.**
	2	**3**	**4**	**5**
. . I .	*Preparatory stage* Defining learning goals. Providing positive motivation. *Main stage* Presentation of lecture material. Plan: 1.Extraction drugs 2. Theoretical foundations of extraction. 3.Features extraction vegetable raw materials with cellular structure. **4.** Stages process extraction. 5. Requirements for extractants 6. Extraction liquefied gases. 7. Recovery of extractants from spent	I II III	Combined lecture Slides	1% 2% 90%

II .	raw materials. 8. Rectification. *Final stage* Lecture summary, general conclusions. The lecturer's answers to possible questions. Tasks for student self-study.		Bibliography , questions, assignments.	2% 3% 2%

Structural and logical diagram of the lecture content.

1. .Extraction drugs

2. Theoretical foundations of extraction.

3.Features extraction vegetable raw materials with cellular Structure.

3.1 Infrared drying

3.2 Acoustic drying.

3.3 Molecular diffusion.

3.4 Convective diffusion.

4. Stages process extraction.

4.1 Extraction using a pulsed magnetic field.

4.2 Extraction by electropulse action.

4.3 Extraction using electroplasmolysis.

5. Requirements for extractants

6. Extraction liquefied gases.

7. Recovery of extractants from spent raw materials.

8. Rectification (from Latin *rectification* — correction, cleaning) .

Content of the lecture material (lecture text)

Extractive drugs

The use of medicinal plants as healing agents has been known since ancient times. For many centuries, people have used various plants and selected the most effective ones from them. The first medicinal agents were produced in the form of dried herbs or extracts from raw materials of plant and animal origin, which were obtained using wine, oils and fats. Since the beginning of the 19th century, most plants have been carefully studied in order to isolate active components.

Many researchers have made a significant contribution to the development of extraction preparations, thanks to which herbal preparations appeared and were improved. and tinctures and extracts from LRS (which were called galenic) still occupy a worthy place in pharmacotherapy. Galenic preparations should be considered as a specific group of medicines, since they are not chemically individual substances, — These are complex complexes of substances. Extracts containing a complex of substances often act somewhat differently than a separate chemically pure substance isolated from it. Therefore, the therapeutic effect of galenic preparations is due to the entire complex of BAS contained in them, strengthening, weakening or modifying the effect of the main substances.

At the end of the 19th century, new herbal preparations appeared, called novogalenovymi, which are extracts from medicinal plants, completely or partially freed from accompanying substances, which is why they were also called ***maximally purified. preparations*** (MOP). These are also total preparations, but with a narrow spectrum of action on the body, due to which they have their own characteristics. Deep cleaning of extracts increases their stability, eliminates side effects of related substances (resins, tannins, etc.), allows them to be used for injection. By isolating individual biologically active components from the total MOS, ***preparations of individual substances are obtained .***

Thus, extraction preparations from medicinal plant raw materials can be divided into three groups by composition:

1) ***total (galenic) drugs*** ;
2) ***total maximally cleaned drugs (new Galenic)*** ;

3) ***drugs individual substances*** .

The last one sometimes some authors allocate yet one group preparations - ***combined*** (complex), containing, along with BAS obtained from plants, other LR of various chemical nature (vitamins, trace elements, hormones, etc.). Today, phytochemical substances obtained by extraction are included in the composition practically all dosage forms: tablets, injectable solutions, ointments, suppositories, oil and alcohol solutions, syrups, etc. The production of herbal medicines is carried out in specialized workshops of pharmaceutical enterprises, in pharmacies only water extracts (infusions and decoctions) from LRS are produced. The specificity of herbal production depends on the raw materials, the nature of the active components, the presence of accompanying substances, close in nature and physical properties to BAS and which are in a certain chemical or physical connection with them. These factors determine the choice of technology for their production. *Herbal medicines are obtained from fresh plants* (natural and condensed juices and extracts) and dried raw materials (tinctures, extracts, maximally purified preparations and individual substances). LRS is represented different parts of plants: these are grass, leaves, roots and rhizomes, flowers, inflorescences, fruits, seeds, bark, etc. The basis of the production of extraction preparations is the process of extracting raw materials, which is determined by the laws of mass transfer. extraction in system « ***solid body — " Riduna "*** and in system ***" riduna " — " Riduna ",*** or liquid extraction.

The most widely used extraction method in pharmaceutical production is the “solid-liquid” extraction system. liquid", where the solid is the medicinal plant raw material or raw material of animal origin, and the liquid is the extractant. Liquid extraction is required for the purification of extracts in the production of highly purified preparations and for the isolation of preparations of individual substances.

THEORETICAL O C NO B I EC C TRAGU B ANNYA

In pharmaceutical production, a significant number of drugs are obtained by the process of extracting BAS from plant, animal or microbiological raw materials that have a cellular structure. In general, the structure of plant, animal and microbial cells has much in common, but there are also differences that determine different technological

approaches to extracting substances contained in the cell. All cells consist of cytoplasm, which contains organelles (mitochondria, core, nucleolus, lysosomes, endoplasmic reticule, Golgi complex, etc.). Cell organelles are separated from the cytoplasm by membranes about 7.5 nm thick, which have a three-layer or mosaic structure. The cytoplasm is a colloidal system in which the dispersion medium is water, and the dispersed phase is proteins, nucleic acids, lipids and carbohydrates. The cytoplasm with its structures forms the living part of the cell - the protoplast, which is surrounded by a cell membrane. In plant cells, the cell membrane — it is dense, elastic, multi-layered cellulose shell, which surrounds and protects cellular membrane. Animal cells have a thin elastic membrane consisting of polysaccharides and glycoproteins. In addition to the protective and mechanical function, the membrane has filtration and ion exchange properties due to the existence of cell pores, the diameter of which varies from 0.35 to 0.8 nm. The pores have the structure of a long winding tubule. Membranes participate in the regulation of biochemical processes in the cell, increasing or decreasing permeability. The degree of permeability of a plant cell is determined by the state of the membrane, cell membranes, cytoplasm, and so on. The membranes surrounding the cytoplasm and organelles that are located in her. If protein compounds these membranes denature, then the main resistance to mass transfer will be provided only by the cell membrane.

The process of isolating BAS from raw materials with a cellular structure is the basis for the production technology of many drugs and dosage forms, such as as tinctures, extracts, juices, and also hormones, enzymes, antibiotics , etc.

A significant contribution to the theory and practice of extracting medicinal raw materials was made by IN. WITH. Father, M. AND. Borisov, M. F. Komisarenko, IN. M. Kovalev, V. AND. Litvinenko, AND. F. Makarevich, N. P. Maksyutina, AND. AT. Muravyov, A. G. Natradze, V. D. Ponomarev, A. P. Prokopenko, V. T. Chernobai and many others.

Features extraction vegetable raw materials with cellular

structure

The peculiarities of extracting BAS from materials with a cellular structure are related to the fact that on the way to the substances contained in the cell is the cell wall, the structure and physiological state of which can be different. A living plant cell has a

parietal layer of protoplasm of a certain thickness, tightly pressed to the shell. This layer of protoplasm leaves a special imprint on the properties of the cell wall as a partition separating the cell sap inside the cell from the fluid outside the cell. As long as the protoplasm is alive, the cell wall is a semipermeable partition that does not allow substances dissolved in the cell sap to pass outside. In this case, only the penetration of the extractant into the cell is possible due to the phenomenon of osmosis.

A dried (dead) cell behaves completely differently. As a result of plasmolysis and the death of protoplasm, the cell wall loses its character as a semipermeable partition. She begins to pass substances into both sides (dialysis phenomenon), i.e. the cell membrane acquires the properties of a porous partitions, through which one can to diffuse BAR, whose molecules do not exceed the size of the holes.

Currently, the vast majority of extractive preparations are obtained from dried plant materials, i.e. dehydrated **by natural or thermal extraction** . During drying, fresh plants lose water. Protoplasm shrinks and is transformed on relatively not a large lump, the cell sap turns into a dry residue, and the interior of the cell is usually filled with air. BAS in dried raw materials are found in the form of dry conglomerates in the cell cavity or adsorbed on its walls.

Recently, **microwave dehydration technology has been used to dry plant materials** , which is based on the action of an intense electromagnetic field of ultrahigh frequencies (MHF) on the product. The main difference between microwave dehydration and traditional drying methods is the volume of heating. Heat penetrates the raw material not from the surface, but is generated inside the material itself and distributed throughout its volume. Due to this, moisture is removed, the raw material is dried, and at the same time - equalization of humidity throughout the product. Processing of plant material by microwave drying allows you to obtain a high-quality product in a short time without losing heat.

Among the newest methods, infrared and acoustic drying should be mentioned. ***Infrared drying*** using infrared radiation makes it possible to carry out the process in large volumes at high speed (duration - from 30 to 200 minutes, depending on the type of material).

Acoustic drying , based on the action of intense ultrasonic waves on the material, is suitable for drying raw materials with any initial moisture content and is characterized by a high degree of preservation of BAS in the dried material.

Extracts obtained from dried medicinal raw materials are not always equivalent to freshly harvested plants in terms of the qualitative and quantitative composition of BAS. Studies by many scientists show that during harvesting, drying and storage during the year, the content of biologically active substances decreases several times. A feature of preparations from fresh plants is that they contain the entire complex of BAS that are part of the raw materials in their most natural state. Therefore, it is advisable to obtain preparations from fresh plants by pressing or extracting raw materials. Extracts of substances from fresh plants by the method of extracting raw materials are obtained if the raw materials are low-juicy and pressing is not effective enough. IN such cases necessary condition there are thin grinding of raw materials, since a living cell is in a state of turgor and the cell wall does not allow BAS to escape.

When obtaining preparations from fresh plants, the cells can be dehydrated with high-concentration ethyl alcohol, which is very hygroscopic and, when in contact with a plant cell, dehydrates it, causing strong plasmolysis. Killing cells of animal origin is achieved by the same methods: drying or dehydration with organic solvents (alcohol and acetone). When preparing preparations from fresh plant and animal raw materials, the cells of which are not dehydrated, *the leaching of cell sap* from destroyed cells and open pores occurs rather than the extraction process. When choosing a technology for extracting BAS, it is also necessary to take into account their location in the cell, chemical structure, properties and concentration of active substances, etc.

The extracted material contains a wide variety of chemical compounds, many of which have a therapeutic effect on the human body. Such compounds are commonly called *medicinal substances, or BAP.* Along with them, other substances are extracted that do not exhibit a pharmacological effect, and sometimes even cause undesirable side effects and affect the stability of BAP. These substances are called *ballast.* There are also those that do not have their own pharmacotherapeutic effect, but contribute to the dissolution and extraction of BAP, potentiate the activity and stability of medicinal substances. Such substances are called *concomitant.*

The main goal of the production of extraction preparations is the maximum extraction of BAS from the cell with a minimum content of basic substances in the extract, which is achieved by studying the theoretical foundations of the extraction process and, as a result, the correct choice of the extraction method and purification of the resulting extract.

Extraction of medicinal raw materials — A complex mass exchange process, determined by the basic laws of mass transfer, consists of several separate processes that are closely intertwined: *diffusion* ; *osmosis* ; *dialysis* ; *dissolution* ; *desorption of substances* .

Extraction of substances from solid materials is the process of separating a solid into soluble and insoluble parts using an extractant. Unlike the dissolution process, when the transition of a substance into a solution occurs completely, during extraction it is carried out partially, forming two phases: a solution of substances in the raw material and a solution of extract substances in the extractant, which washes the raw material. The transition of substances from one phase to another is carried out as long as they have a difference in concentration, which is *the driving force of the extraction process* . The limiting state of mass transfer is the achievement of equilibrium of the system, equalization of the rate of transition of substances from one phase to another. The rate of mass transfer is proportional to the driving force of the process, and the transfer of substances into the extractant is carried out by molecular and convective diffusion.

Molecular diffusion — is the process of transfer of a diffusible substance (DMS) due to the chaotic motion of the molecules themselves in a stationary medium. It is characterized by the molecular diffusion coefficient D , which is derived from Einstein's equation:

$$D = \frac{RT}{N_0} \cdot \frac{1}{\frac{kT}{6\pi\eta r}} = \frac{RT}{6\pi\eta r N_0},$$

where R is the universal gas constant, 8.32 J/(grad•mol); T is the absolute temperature, K; N0 is Avogadro's number (6.06•1023); η is the viscosity of the solution, H•s/m2; r — radius diffusing particles, m; k = R/N0 — became Boltzmann.

The molecular diffusion coefficient characterizes the ability of a given substance to penetrate due to diffusion into a stationary medium and, as can be seen from the equation, increases with increasing temperature and decreases with increasing viscosity of the medium and size of diffusing particles of the substance. Therefore, the smaller the radius of the diffusing particles, the faster the diffusion occurs. Thus, solutions of proteins, mucus, pectins and others with large molecules are characterized by very low diffusion coefficients. Substances with small molecular sizes (which are more often BAS) diffuse much faster.

Convective diffusion. Characterized by coefficient convective diffusion . It shows what number substances transmitted through 1 m ^{2} of the phase contact surface into the medium for 1 s at a concentration difference between the layers equal to unity. The convective diffusion coefficient is determined experimentally and depends on the hydrodynamic conditions of the process.

Convective diffusion can be *free* (natural) and *forced* . Free diffusion occurs due to the difference in density of the extractant and solution, changes in temperature, and the hydrostatic column of the liquid. Forced convective — occurs when the system is stirred by agitators, pumps, vibration, etc. The rate of convective diffusion is 10 ^{12} times higher than molecular diffusion, therefore it is of great practical interest, since it contributes to the intensification of the mass transfer process.

Stages process extraction

The process of extracting dried plant materials begins with the penetration of the extractant into the material, wetting of substances inside the cells, then their dissolution and desorption, then diffusion through the openings of the cell membrane, and ends with the mass transfer of substances from the surface of the material to the solution.

Penetration extractant within vegetable material occurs through macro- and microcracks, through intercellular passages, holes, numerous capillaries, filling cells and other voids in the raw material. Such penetration of the extractant is called

endoosmosis , i.e. movement through a porous partition. Cell membranes have diphilic properties, with hydrophilicity prevailing. The process of penetration of the extractant into the cell is determined by the degree of hydrophilicity of the material, the nature of the extractant, the number and size of the holes in the cell wall. The greater the affinity of the extractant with the material, the faster it wets the walls of the capillaries, penetrating into the raw material, until the forces of capillary rise and the force of gravity of the hydrostatic column of liquid (extractant) in the capillary are balanced. The penetration of the extractant into the capillaries is hindered by the air contained in them. To intensify process use previous vacuuming raw materials, supplying the extractant under high pressure or replacing the air in the pores with a readily soluble gas.

The process of wetting substances is closely related to the penetration of the extractant into the raw material and also depends on their affinity. To facilitate the wetting of dried cell contents, it is sometimes recommended to add a surfactant in a concentration of 0.01-0.1 %, which provides a reduction in surface tension at the interface of phase separation.

After penetrating into the cells, the extractant interacts with the substances contained in them: substances soluble in the extractant dissolve; IUDs that swell indefinitely swell and peptize (desorption and dissolution); IUDs that swell only to a limited extent swell, thereby forming gels. A concentrated solution of substances dissolved in the extractant is formed inside the cells. Then, molecular transfer of dissolved substances occurs. Dissolved substances are first transferred to the extractant located in the intercellular space, then into an extractant that fills micro- and macrocracks, and then — on the surface of the pieces of material and into the extractant that washes the raw material.

During the extraction process, mass transfer occurs, characterized by the transition of one or more substances from one phase (raw material) to another (extractant). Transfer of substances from raw material with a cellular structure to the extractant — This is a complex process in which three main stages can be distinguished:

1) "internal diffusion", which includes all phenomena of substance transfer

within raw material particles;

2) substance transfer within the immediately adjacent diffusion layer (substance transfer is carried out according to the law of free diffusion);

3) transport of matter by a moving extractant (convective diffusion). Mass transfer dissolved in cellular juice substances through The openings of cell walls into intercellular spaces have their own characteristics. First of all, the presence of a porous partition, intercellular space and cell passages reduces speed diffusion. Further, through holes partitions Only substances that do not exceed the size of the holes can pass through. The number of cell layers membranes, quantity and the diameter of the holes is not are permanent, and fluctuate in wide within in different species raw materials. Finally, there are yet one significant feature — phenomenon desorption, which observed in the cell after the extractant penetrates it. Since the substances within cells tied by force attraction, then necessary, first for everything, overcoming these adsorption forces. Mechanism of diffusion through the cell membrane, according to the theory of equilibrium sorption such: molecules substances sorbed on membrane, diffuse through it and desorb from its other side. In this case, the rate of diffusion of the substance through membrane is limited by the concentration gradient and the characteristics of the membrane itself. After the substances are removed from the cell, their diffusion actually becomes molecular diffusion, but limited by the narrow lumens of the openings and the length of the capillary passages. In addition, additional resistance arises due to the collision of particles with the walls of the openings.

The overall process of transferring substances from material particles to the extractant is expressed main equation mass media:

$$S = K \bullet F \bullet \Delta C \bullet \tau, \qquad (7.2)$$

where S is the amount of substance that diffused, kg; K is the mass transfer coefficient, m2/s; F is the phase separation surface, m2; ΔC is the difference in substance concentration, kg/m3; τ is the diffusion time,

The extraction process depends on **many factors** , the most important of which

are including: hydrodynamic conditions, phase separation surface, concentration difference, process duration and extraction method, extractant viscosity, temperature. In addition, the completeness and speed of extraction are influenced by: addition of surfactant, nature of raw material loading, selection of extractant, porosity and voids of raw material, leaching coefficient, action of vibrations, pulsations, electric pulse discharge in a liquid medium, crushing and deformation of raw material in the extractant.

Knowledge of the theoretical foundations of extraction enables the technologist to properly conduct this production process and thereby ensure the most complete and shortest possible extraction of BAS.

REQUIREMENTS TO EXTRAGENTS

The extractant plays a particularly important role in the extraction process. It must be able to penetrate through the cell walls, selectively dissolve the "necessary" medicinal substances inside the cells, after which the dissolved substances, together with the extractant, must pass through various membranes and go beyond the plant material. If the extractant is chosen incorrectly, other compounds can be obtained instead of BAS.

To ensure complete extraction of active ingredients and maximum extraction speed, a number of requirements are imposed on the extractant:

- selectivity (selective solubility), that is, maximum dissolve BAS and minimally - ballast substances;
- chemical and pharmacological indifference, i.e. it should not chemically react with BAS and change their pharmacological properties;
- minimal toxicity, i.e. the extractant must be pharmacologically indifferent (if it has negligible toxicity, it is completely removed from the resulting extract);
- ability prevent development microflora in extractor hood;
- high wetting ability, which ensures good penetration through the holes of the material and cell walls;
- volatility (preferably with a low boiling point and the ability to regenerate);

- low cost, accessibility;
- safety of use (with minimal fire and explosion hazard). Of two equivalent extractants, the less fire-hazardous one is chosen,

affordable, less toxic, etc. If the extractant does not meet the specified requirements, then mixtures are used, such as acidified water, alcohol with water, ether with alcohol, alcohol with chloroform, etc.

Water (H_2O) — one of the most acceptable extractants, which has a number of advantages: penetrates well through cell membranes that are not impregnated with hydrophobic substances; dissolves and extracts many substances better than other liquids; is pharmacologically indifferent; easily achieves the required chemical purity; is non-flammable, explosion-proof; affordable.

But as extractant has and number negative parties: not dissolves and not extracts hydrophobic substances; does not have antiseptic properties, as a result of which microorganisms can develop in aqueous extracts, which can cause spoilage of the obtained extract; in the presence of water, hydrolytic cleavage of many substances occurs, especially at high temperatures; in an aqueous environment, enzymes can cleave some BAS and etc.

Ethanol (C_2H_5OH) — Colorless, transparent, mobile liquid with a characteristic odor and a burning taste. Hygroscopic, miscible with water, as well as with ether and chloroform in any proportions. Density of rectified alcohol 0.808-0.812, absolute — 0.789 g/cm ^{3} (at 20 °C). The boiling point of anhydrous alcohol is 78.39 °C. It ignites easily, is flammable, temperature outbreaks 13 °C. More full characteristic and methods for producing ethanol are given in Chapter 6.

Alcohol as an extractant is a good solvent for many compounds that are not extracted with water (fats, alkaloids, chlorophyll, glycosides, essential oils, resins, etc.); has antiseptic properties (microorganisms and fungi do not develop in alcohol-water solutions with a concentration of more than 20%); the higher the alcohol concentration, the lower the possibility of hydrolytic decomposition of substances; alcohol inactivates enzymes; it is quite volatile, therefore alcohol hoods light thicken and are drying out to powdery substances, to preserve thermolabile substances, evaporation and drying are carried out under vacuum.

The most commonly used extractants include: ***acetone, ethyl ether, chloroform, dichloroethane, methylene chloride, methanol, vegetable oils*** , etc.

Promising for extraction are recently proposed *liquefied gases* ***: carbon dioxide, propane, butane, liquid ammonia, nitrogen, chlorofluorocarbons*** **(** ***hydrocarbon derivatives*** **)** , etc. etc. Liquefied carbon dioxide extracts essential oils, fatty oils and other hydrophobic substances well. Hydrophilic substances are well extracted by liquefied gases with high dielectric constant (ammonia, methylene chloride, methylene oxide, etc.). Extraction by liquefied gases is carried out under pressure, with the removal of which the extractant evaporates, and the extracted substances remain in their pure form.

Numerous studies conducted at the State Research Center for Chemical and Pharmaceutical Research (Kharkiv) have proven that chlorofluorocarbons are quite promising extractants. — liquefied gases of chlorofluorocarbon derivatives of methane, ethane, propane and butane. Under normal conditions, these are gases, and at excess pressure they are colorless, easily mobile liquids, the viscosity of which is significantly lower than the viscosity of organic solvents. Chlorides are non-toxic, chemically indifferent to BAS and structural materials of devices, do not form explosive mixtures with air, and are fireproof. Chlorides extract essential and fatty oils, tocopherols, sterols, carotenoids, terpenoids, coumarin derivatives, chlorophylls, alkaloids and other natural substances. It has also been established that chlorides do not extract water-soluble substances (polysaccharides, proteins, phenolic compounds, etc.), therefore, the meal after treatment with chlorides should be used for extraction with polar solvents.

The last one sometimes all more value in BAS extraction with of plant raw materials becomes liquefied carbon dioxide (CO_2). Its viscosity is 14 times less than water, five times less than ethyl alcohol. The boiling point is in the range from -55.6 to +31 °C.

The use of $CO2_{as}$ an extractant has many advantages: it is physiologically not a cause for concern (it is found in carbonated beverages, and in some cases is the end product of human metabolism); sterile and bacteriostatic; non-flammable and non-explosive, so there is no need for special devices against flash and explosion in the technological cycle; safe for the environment, it does not produce wastewater and

waste solvents, thereby eliminating the usual additional costs; for production purposes it can be obtained in large quantities, its reserves in liquefied form are an indicator of the state of the art; chemically it shows complete indifference to raw materials, active substances, and equipment materials.

If conditions are created under which the pressure and temperature parameters exceed the parameters of the so-called critical point, the gas passes into a supercritical state. *Supercritical* gas is characterized by faster mass movement compared to traditional liquid organic solvents. Despite a somewhat lower density compared to a liquid, the dynamic viscosity of compressed gases corresponds more to the values of the normal gaseous state. The diffusion coefficient of a supercritical gas is more than ten times higher than that of a liquid.

Therefore, supercritical gas can penetrate the extracted material, absorb and transport dissolved substances in principle better than a traditional extractant. The use of carbon dioxide allows it to be completely and gently separated from the extract and material, unlike traditional extractants, the removal of which is not always complete. The energy consumption for the regeneration of the extractant is in many cases less than in traditional extraction. And the excess pressure in the system prevents the penetration of oxygen during extraction, which prevents oxidation processes. Supercritical gases have a high extraction capacity and, under appropriate conditions, sufficient selectivity; A simple change in the pressure and temperature parameters (both during extraction and in the separation process) allows you to regulate the concentration of substances in the extract. And the possibility of using a modifier in the extraction process allows you to significantly increase the solubility while preserving, and in some cases , increasing the selectivity of their therapeutic activity. Therefore, the use of this method requires thorough research in each specific case.

Extraction using a pulsed magnetic field. This method is based on the action of a magnetic pulse on plant raw materials. In a magnetic pulse extractor, a movable electrically conductive membrane oscillates under the action and with the frequency of the electromagnetic field, which transmits the pulsed motion to the extractant. As a result of its oscillatory motion, a flat pulse of alternating pressure is formed, which promotes extraction - cavitation occurs in the extractant.

Advantages of the method — the possibility of conducting the process with a small ratio of raw materials and extractant (1:4), the absence of moving metal parts of the equipment, a 10-fold reduction in microbial contamination of the processed raw materials, and a 1.5-2-fold reduction in energy consumption.

Extraction by electropulse action. The use of electropulse discharges allows to accelerate extraction from raw materials with a cellular structure. Electric discharges create conditions for a very rapid course of intracellular diffusion, while the molecular transfer of substances is replaced by convective. For this purpose, a pulsed electroplasmolysis device is used (Fig. 7.8).

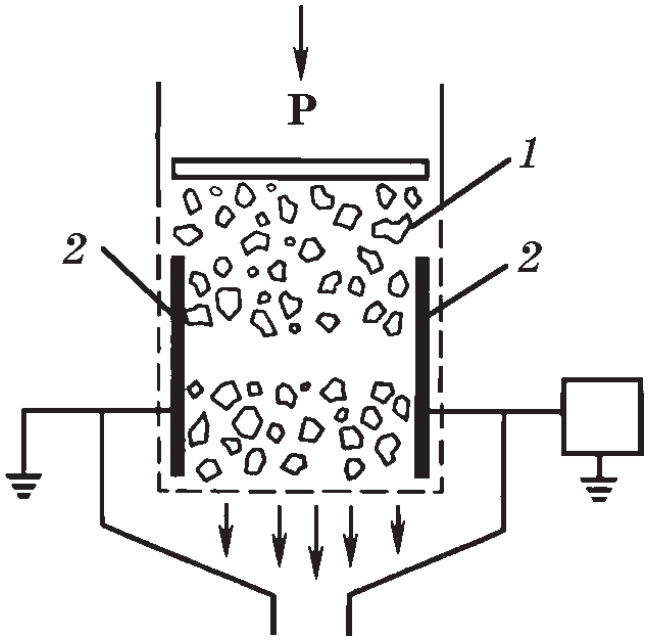


Figure 7.8. Scheme pulsed electroplasmolysis

Inside the extractor with raw materials *1* , electrodes *2 are placed* , to which a high or ultrahigh frequency pulse current is applied. Under the action of a high-voltage pulse discharge, shock waves arise in the extracted mixture, which create ultrahigh pulse pressure and powerful cavitation processes.

As a result, intensive mixing of the processed mixture occurs. (from speed hundreds meters away second), thinning or the adjacent diffusion layer completely disappears and convective diffusion increases. The occurrence of shock waves promotes the penetration of the extractant into the cell, which accelerates intracellular diffusion. Due to the spark discharge, plasma cavities are formed in the liquid, which,

expanding, reach the maximum volume and close. In a short period of time, a large amount of energy is released in a small space and a micro-explosion occurs, which partially destroys the cellular structures of the plant material. Thus, BAS are washed out of the destroyed cells. This method is quite promising, although it is not without some drawbacks: the possibility of mechanical cracking of molecules; significant noise from hydraulic shocks; the cost of the product is higher than in the methods of maceration or percolation.

Extraction using electroplasmolysis and electrodialysis. ***Electroplasmolysis*** — processing of raw materials with low and high frequency electric current, resulting in plasmolysis of protoplasm. The essence of the method is the destructive effect of the current on the protein-lipid membranes of tissues while preserving the integrity of cell membranes. Electroplasmolysis gives the greatest effect when obtaining preparations from fresh plant and animal raw materials. At the same time, the resulting extracts are enriched with active substances and contain only a small amount of accompanying substances. The electroplasmolysis with moving electrodes has two horizontal roller electrodes that rotate towards each other, to which an electric current with a voltage of 220 V is supplied. Fresh raw materials enter the gap between the rollers from the hopper, the juice is collected in the receiver. The time for processing raw materials with electric current is fractions of a second. The juice yield increases by 20-25 % compared to traditional methods.

Electrodialysis is used to accelerate extraction from plant and animal raw materials. The driving force of the process is the difference in concentrations of the extracted substances on both sides of a semipermeable partition, the role of which in raw materials with a cellular structure is performed by cell membranes. Under the action of electric current, the electrical potentials of the surface of the raw material change, its wettability improves, and the movement of BAS ions in the cell cavity and in the capillaries of cellular structures accelerates. As a result, the internal diffusion coefficient increases.

Extraction by this method is carried out in an apparatus (Fig. 7.9) from an electrically non-conductive material (tree, plastic) with conical bottom from stainless

steel, over which steel is attached perforated plate *1* , which serves as a cathode. Pre-wetted raw material is loaded onto a plate covered with filter material *2 3* , and the lid drops on top of it *4* with built-in graphite anode *5* . The electrodes are connected to a DC source. current 15 A, density on cathodes — 0.6 A/m ^{2} , voltage — 0.8 V/cm.

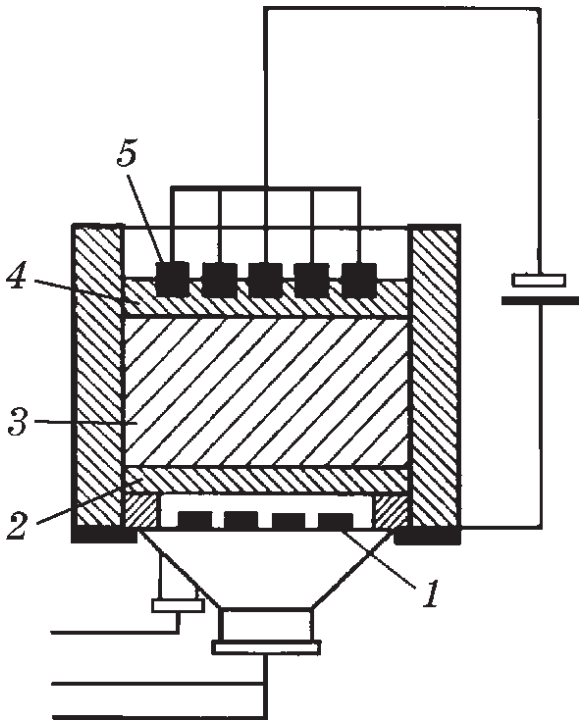


Diagram of a device using electrodialysis

With continuous supply of extractant, the time required to obtain the product is half that of other extraction methods. The yield of BAS in this case increases by almost 20%.

Interesting in a way intensification mass transfer there are **fluidization extraction system** , which occurs during the pressure decrease in the extraction object due to the boiling of the extractant at lower temperatures. In the process of boiling, steam bubbles, forming and moving with practically equal speeds throughout the raw material layer, create (in contrast to various kinds of vibrations) the same conditions at all its points. As a result, a new phase appears, which differs in density from the main interacting phases and promotes more energetic movement of particles and liquid. The extraction process is carried out in column-type apparatuses with a pseudo-fluidized layer, which are distinguished by their simple structure and small by mass. Pseudo-saturation of the system allows to significantly accelerate the process while

simultaneously increasing the degree of extraction of BAS. This method is widely implemented in the sugar industry, but, unfortunately, it is underestimated in the pharmaceutical industry .

Thanks to such methods (hydrodynamic cavitation and fluidization of the extraction system), the extraction time is reduced several times, the yield of the target product is increased, the extractors do not have mechanical mixing devices, and the existing extraction equipment is quite suitable for implementing the processes.

Recently, *microwave technologies have been widely used in industrialized countries* to accelerate and increase the completeness of the extraction of BAS from plant and animal raw materials.

At mechanical way imposition on environment oscillating force fields, the acceleration of the diffusion mechanism of mass transfer becomes optimal in the region of fairly **low oscillation frequencies** (3-50 Hz) at small particle sizes. External diffusion processes are accelerated here due to magnification speed flow around stream liquids inertially calm particles, formation alternating pressure, cavitation, strengthening capillary effect and intensification intradiffusion processes in plant tissues. The effect of low-frequency vibrations can be attributed to to pulsating methods of dissolving substances, combined with natural convection, direct flow around, gravitational or inertial methods. In industrial conditions, the raw material and the extractant contained in the extractor are can subject **high-frequency** (1.5-20 Hz) processing. IN poly high frequencies electromagnetic waves at dielectric increases when heated desorption substances, is happening decrease degree hydration (solvation) molecules extracted substances, rather is happening coagulation of protein compounds. As the size of solvated molecules decreases, the coefficient their free diffusion, substances rather pass through holes cellular shells, that is, is growing mass transfer substances in the system "cell — extractant.

Extracts obtained **under the action of a microwave field** have qualitatively new chemical and biological properties, which are significantly higher than those of analogues. This technology allows obtaining a new type of extracts (oil extracts of valerian root, capsicum, Japanese sophora, etc.), which are difficult to obtain by traditional methods. In addition, material and energy costs, production costs and the

duration of the microwave extraction process are significantly reduced .

Extraction of raw materials using cryogenic technologies. Recently, the use of cryogenic technologies for the production of herbal medicines has been of increasing interest. This technology makes it possible to prevent the destruction of BAS throughout the entire production process, since there is no heating and oxidation of the raw materials. At the same time, such biochemical processes as lipid peroxidation, denaturation and dissociation of protein molecules, pigmentation, which irreversibly change the properties substances, What contained in raw materials. Cryogenic Processing fresh plant raw materials allows you to preserve the native structure of not only the vitamins contained in it, but also molecular complexes with a wide range of microelements necessary for humans.

The production process begins with rapid freezing of raw materials in cryotunnels in the presence of liquid nitrogen or argon, since freon compressor freezers, which carry out continuous blowing of raw materials with cold air, remove low-molecular components. Then the raw materials are subjected to multi-stage cryogenic processing. At the first stage, its cryogenic grinding is carried out in special cryogenic mills in liquid nitrogen vapor at temperatures from -100 to -200 °C to particles of 20-30 microns in size. Cryo-refinement sharply increases the specific surface area of the fractions being processed and increases the efficiency of the subsequent processing stage. — cryosublimation fractionation, which The cryopreserved frozen raw material is divided into two fractions: water and dry. The water fraction is, in fact, low-molecular plant juice. Special sublimation installations with a multi-stage circuit are used to obtain it. The cryogenic panels of the main desublimator in these installations are cooled to a temperature of -196 °C, which allows esters, amino acids, vitamins, trace elements and other molecular complexes with high biological activity to be condensed on them. The practical application of this fraction opens up new horizons in the technology of medicinal products.

Extraction liquefied gases

Extraction by generated gases — one of the promising methods of extracting material containing volatile and unstable substances, such as essential oils, cardiac

glycosides, phytoncides, plant hormones, lipophilic BAS. When using as an extractant the generated butane, butanepropane, nitrogen, ammonia, carbon dioxide, chlorofluorocarbons (CFCs), argon and other substances with a boiling point lower than room temperature, there will be no oxidation, decomposition, loss of valuable substances and their properties during evaporation, since these extractants evaporate at room temperature. The quantitative yield of DR in extraction with generated gases reaches 88-98%, which is higher than in known extraction methods.

Now exist technologies receiving haldons such drugs, as sea buckthorn oil, rosehip oil, carotolin, apomelin, sorbilin, etc., for the production of which special extraction plants have been created.

The installation, which is intended for the extraction of natural compounds from plant raw materials using **liquefied gases (chladons) as extractants** , is shown in Fig. 7.10. It is a closed system and operates according to the following scheme: to the extractors *1* through the loading hatch using vacuum is supplied crushed raw materials. From systems The air is removed by vacuuming and filled with gaseous refrigerant from cylinder *2* until working pressure is created.

It was noticed that with an increase in the particle size of the raw material, the yield of extractive substances decreases sharply, therefore, it is advisable to grind plant material using combined methods to particle sizes of 0.1–0.2 μm.

Many extracts obtained using liquefied gases are characterized by a higher content of BAS and resistance to microbial contamination. This is especially true for raw materials containing polyphenolic compounds, alkaloids, and glycosides.

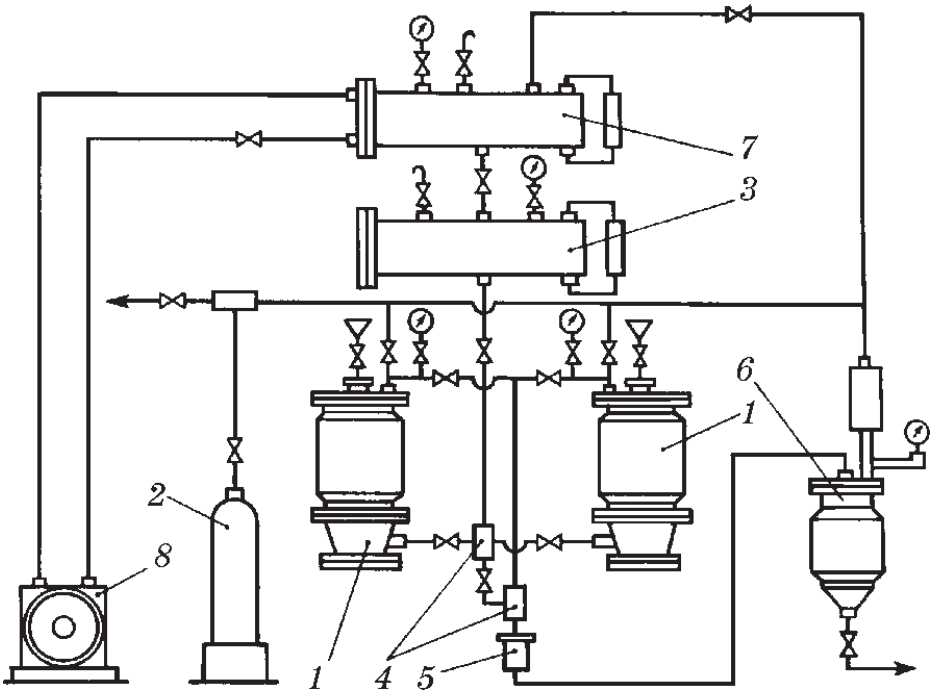


Figure 7.10. Scheme installations extractions BAR with haldons

After reaching pressure equilibrium, liquefied refrigerant is fed into the extractors *1* from pressure vessels *3.* The solvent passes through the raw material layer, extracts soluble components and flows into the evaporator through filter *5. 6.* The pressure in the evaporator is much lower than in the extractors and collection, volume The extractant becomes gaseous and enters the condenser. *7* , which is cooled by a refrigeration unit *8* . The extractant is condensed and returned in liquid form to the pressure vessels *3* , and from there it is again fed to the raw material. Thus, the solvent is in a closed cycle and is used many times. The resulting product remains in the evaporator, from where it is periodically drained. The extraction process is carried out at an operating pressure of 1.0-6.6 MPa (depends on the saturated vapor pressure of the extractant) and a temperature of 20-25 °C.

Extraction technology using liquefied gases allows you to significantly reduce the duration of the process, reduce the consumption of raw materials and materials, and improve the quality of the resulting herbal preparations.

Currently, a method **of extracting plant raw materials with liquid carbon dioxide** (in subcritical areas) at room temperature (not higher than 28 °C) and pressure 6.6-7.0 MPa in continuous extraction plants. Pre-crushed plant material is loaded into mesh baskets, which are placed in containers. The latter move into a chamber where

the raw material is impregnated with liquid carbon dioxide. The saturated raw material passes into another chamber where a reduced pressure is maintained. As a result sharp changes pressure diluted gas, What contained in raw materials, changes its state of aggregation sharply, while the liquid instantly boils, breaking the raw material into the smallest particles. Carbon dioxide vapors are removed through a cyclone. The raw material crushed in this way passes into the extractor, where countercurrent contact of the raw material with the solvent coming from the collectors takes place. The resulting extract is directed through the filter into the distiller *, from which the vapors go back to the condenser, and the extract is periodically removed through the lower valve. After extraction, the spent plant raw material is moved to the chamber, where the remains of diluted* CO_2 are evaporated from the meal with water vapor. The remaining carbon dioxide in the meal, is discharged through a cyclone for liquefaction into a condenser, where it is converted back into a liquid and then fed to the material. Next, the containers with the meal are unloaded. For processing vegetable raw materials liquid carbon dioxide also A battery of percolators connected in series is used. The extraction process begins with the grinding of the raw material to a very fine or fine powder. The dry plant material is loaded into the extractors, sealed, is being created pressure gaseous CO_2 to 6.0-7.0 MPa, then liquid carbon dioxide is supplied from above in a volume three to six times the amount of raw material and is infused at room temperature from 15 min to 1.5-3 h, depending on the properties of the raw material and active substances. The extract is filtered and fed into the evaporator, the extractant evaporates at room temperature (warm water 25-40 °C is fed into the steam jacket). Gaseous CO_2 is pumped through a pipeline into the condenser, where it is converted back into a liquid and then fed to the material. After the raw material in the first extractor is exhausted, the second one is connected, and the first one is filled with a new portion of raw material, etc.

In subcritical areas (at pressures below 73.8 atm), carbon dioxide is used in a liquefied state. This, in addition to some differences in technological equipment, means a reduction in the spectrum of extracted BAS (in comparison with supercritical parameters), as well as a significant increase in the time required to carry out one extraction cycle (4 hours or more). In essence, this is a variant of liquid extraction (similar to water-alcohol), but with a "more elegant" solvent. With all its positive

qualities, subcritical $CO2_{extraction}$ has the same drawbacks as traditional extraction processes. At a certain temperature increase, which ultimately leads to intensification of the process and allows for a higher yield of the final product, a reaction medium is created from water vapor and carbon dioxide, in which structural changes occur in some BAS of plant raw materials.

Supercritical parameters (pressure above 73.8 atm at almost any temperature range) complicate the system, since the extractant must not only be brought to supercritical conditions — We need a flow with certain parameters that would allow us to work with it not only in liquid or gaseous states, but also to use transitional states (from liquid to gaseous and vice versa), the possibilities and properties of which have not yet been sufficiently studied. However, scientists are already obtaining interesting practical results. The most supercritical (or even near-critical) parameters dramatically change the selectivity of carbon dioxide as an extractant, which allows the process of supercritical (SC) extraction to be regulated by small changes in temperature and pressure, ensuring the most complete extraction of BAS when extracting natural raw materials of plant origin.

Although carbon dioxide is used in both processes, the extractant behaves differently in them. This can be explained by the different density of the extractant, and not by pressure or temperature alone. Moreover, with an increase in temperature in the subcritical region, a sharp decrease in the dissolving power of carbon dioxide is observed, which is a function of pressure and temperature. In fact, when the extraction temperature is increased in the subcritical region, the steam extraction method is started, since carbon dioxide simply boils.

The technological process ensures the processing of a wide range of raw materials with a controlled concentration of the necessary BAS, makes it possible to extract both solid and liquid raw materials, and also allows processing raw materials of animal origin. Extraction of solid raw materials takes place in extractors in batches, while liquid raw materials are extracted continuously in countercurrent columns.

European Database of Organizations (DASFAF — Developments and Applications of Supercritical Fluids in Agricultural and Fisheries) confirms that today the most popular in the world is supercritical fluid CO_2 extraction, which is an

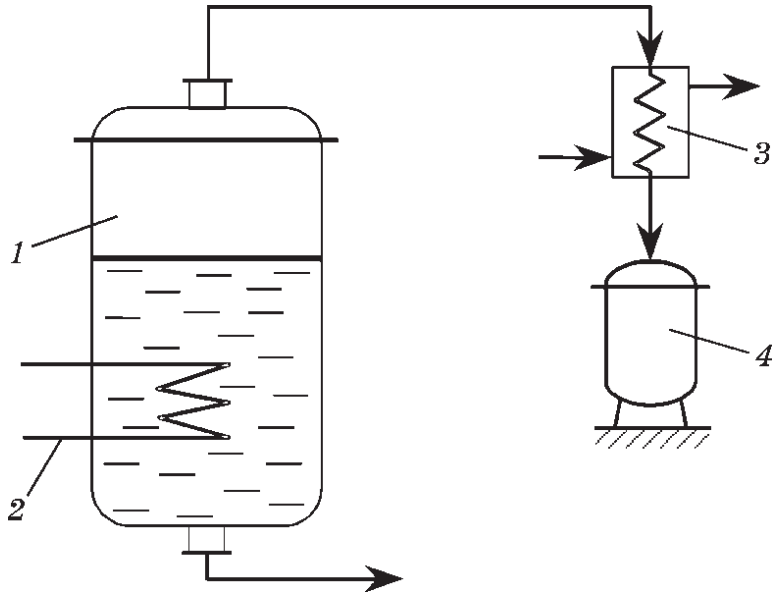
important branch of high-pressure technology. Moreover, this process is highly profitable, more technological and allows you to obtain a wide variety of products, unlike subcritical CO_2 extraction, where the process is poorly controlled and allows you to obtain only CO_2 extract with the sum of extracted substances.

RECUPERATION EXTRACTING AGENTS WITH PROCESSED RAW MATERIALS

In the spent plant raw materials - meal — Two to three volumes of extractant are retained relative to the mass of the raw material. This extractant ***is recovered*** (from the Latin ***recuperatio*** — return, recovery), that is, it is extracted by various methods and returned to production. Ethanol can be recovered from the meal in two ways: methods: washing with water and steam distillation.

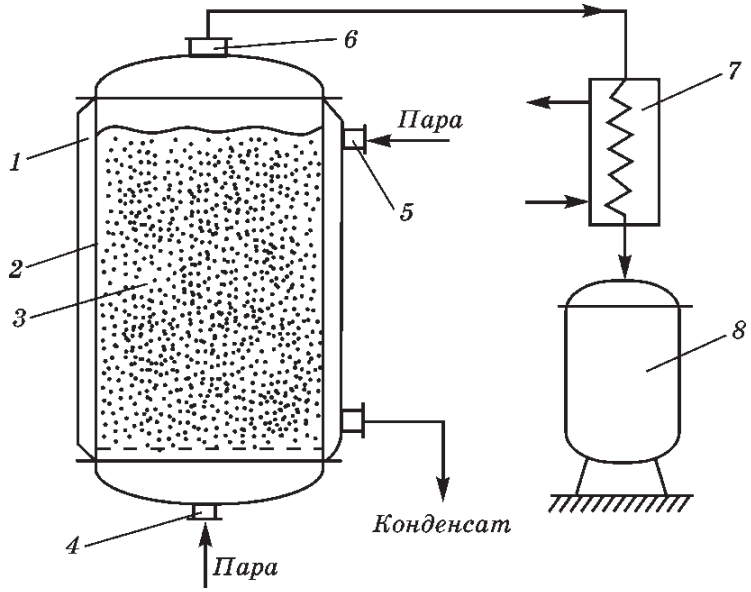
In small pharmaceutical enterprises, ethanol recovery from meal is carried out **by the method of water washing** . After pressing, the meal is poured into vessels with water and left to infuse for 1.5 hours. In this case, ethanol diffuses from the raw material into the water. After that, “washing waters” are obtained at the percolation rate, the amount of which depends on the concentration of the extractant. Thus, for the recovery of 70% ethanol, almost five volumes of washing waters are obtained in relation to the raw material, for 40% ethanol, approximately three volumes are obtained. These waters contain 5-30% ethanol and a significant number ballast substances. They there are muddy liquids, have the smell of volatile substances of plant material, deteriorate during storage.

Ago washing water (primary recuperate) are subjected to downtime distillation in special installations for the purpose of strengthening and purifying ethanol. The washing water in the vessel *1* is heated to boiling by an electric heater *2* , gas or any other heat carrier available to the enterprise. The resulting alcohol and water vapor enter the condenser *3* , from which the condensate enters the distillation collector *4.* In this case, the resulting distillate (secondary recovery) contains a maximum of 80 % of alcohol, which can be used to dilute strong ethanol during the preparation of the extractant. The average yield of alcohol in regeneration by the specified method is approximately 50% of the amount of ethanol remaining in the meal.



Scheme installations simple distillation

In large pharmaceutical plants, the recovery of the extractant from the meal is carried out in percolators after complete draining of the extract **by distillation. with water steam** (Fig. 7.12). For acceleration process recovery simultaneously uses "dead" and "hot" steam. "Deaf" steam is supplied in shell *1* percolator *2* through fitting *5* . "Severe" couple is fed through the lower fitting *4* and mixed with the raw material *3* . As a result of this supply of the coolant, the raw material is quickly heated. The ethanol contained in the raw material boils and is removed from the upper part of the percolator through the pipe *6* together with water vapor. The mixture of alcohol vapor and water goes into the heat exchanger *7* , from which the condensate enters the distillation collector *8* .



Puc. 7. Scheme recovery extractant from meal by steam distillation method

Distillation alcohol, received in process processing vegetable material with a "pungent" vapor, is a clear liquid with a faint odor. The ethanol content in it is about 55-65 %. Approximately 95% of the alcohol remaining in the plant material is regenerated by this method.

The resulting distillate is used as an extractant if its concentration meets the requirements. At other concentrations, the distillate is used in the preparation of an extractant for the raw material of the same name, since the aromatic compounds of the raw material are distilled together with ethanol. Recoveries and distillates containing 30-40 % ethanol and above, can be fortified and purified by distillation.

Rectification (from Latin *rectification* — correction, cleaning) — the process of separating a mixture of liquids that are miscible and have similar boiling points into individual components and purifying them.

To carry out the rectification process, rectification units of continuous and periodic types are used. As a rule, such units consist of a rectification column, a distillation cube, a reflux condenser, a condenser-refrigerator and a collector. The main part of any unit is a rectification column — a cylindrical apparatus 15–30 m high, with a diameter of 1 to 6 m.

Depending on the internal structure, columns are divided into packed, mesh, cap, film, rotary, drop-jet, etc. Their main function — ensuring the greatest contact of the vapor of the low-boiling component rising from below with the liquid phase flowing from above.

The distillate is fed into a distillation cube heated by a "dead" steam or heating elements, and brought to a boil. The resulting vapors rise into a distillation column, which is irrigated with reflux, where the separation of low-boiling and high-boiling components, solidification, and purification from impurities take place. Next, the alcohol vapors enter the dephlegmator, from where they enter the collector in the form of condensate after cooling.

IN result rectification ethanol recuperators receive purified ethanol and fortified

to a maximum concentration of 97.1%.

Materials for activating higher education students during lectures: questions, situational tasks, etc.:

Question:

1.What are the features? extraction vegetable raw materials with cellular structure?

2. What is the infrared drying process?

3. What is the basis of acoustic drying?

4. What is the process of molecular diffusion?

5. What can be convective diffusion?

6. What are the stages? process extraction ?

7. What is the extraction method using a pulsed magnetic field based on?

8. What mechanism is used in electropulse extraction?

9. What is extraction using electroplasmolysis?

10. What opportunities does the technology of extracting raw materials using cryogenic technologies provide?

11. What does the extraction method consist of? liquefied gases?

12. What is the process of recovering extractants from spent raw materials?

13. What is the rectification process used for ?

General material and methodological support for the lecture:

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

Questions for self-control:

1. What are the features of the infrared drying process ?

2. What is the process ? extraction ?

3. What are the features of the extraction method? liquefied gases?

4. How to explain the process of recovering extractants from spent raw materials?

List of sources used:

1. A textbook for independent work of students of the Faculty of Pharmacy for the licensing exam "Step 2. Pharmacy" / V.Yu. Anisimov, O.I. Belyaeva, G.G. Vidavska, V.O. Helmboldt, A.V. Zamkova, I.V. Lytvynchuk, A.V. Nikitin, B.V. Prystupa, I.B. Petkova, Ya.V. Rozhkovsky, S.B. Strechen, L.M. Unguryan, N.S. Fizor Odessa: Odessa National Medical University. 2020. - 240 p.

Access mode 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 of higher. educational. pharmaceutical institutions (pharmac. faculties) / E.V. Gladukh, O.A. Ruban, I.V. Saiko and others. - Kh.: NPhU: Original, 2016. - 632p. : Named after. - (Series "National textbook")

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Lecture No. 6

Topic: Extraction methods (maceration, re-maceration, percolation, flow extraction, circulation extraction.). Extraction with liquefied gases. -2 hours.

Relevance of the topic: Drug technology (industrial drug technology) is one of the fundamental technological sciences. It consists of several key aspects that are

important for modern medicine and patients: Efficacy and safety - Modern technologies allow the production of drugs with high efficiency and safety for patients. Accurate dosing, quality control and the absence of impurities make drugs more effective and safe. Innovations in the medical field: 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 treatment. Minimization of side effects: Technologies allow the development of drug formulas that minimize side effects and negative effects on the body. This provides more comfortable and safe treatment for patients. Fast production and delivery process: The use of modern technologies allows the acceleration of the production process of drugs, which is especially important in a rapidly changing medical environment, such as the spread of diseases or epidemics. Personalized treatment: Technologies allow for the development of medicines that take into account the individual characteristics of the patient, leading to a personalized approach to treatment and increasing its effectiveness. Cost-effectiveness and accessibility Improved manufacturing technologies can reduce production costs, making medicines more accessible to a wider range of patients, ensuring cost-effectiveness in healthcare.

Thus, the use of modern pharmaceutical manufacturing technologies is an important factor in improving the effectiveness of treatment, patient safety, and the overall state of public health.

Objective: to get acquainted with the main stages of industrial production of dosage forms and the discipline "Drug Technology", to describe extraction methods and describe the current state of the pharmaceutical industry.

Basic concepts:

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

Percolation (from Latin Percolation - filtering through ...). Filtering an extractant through plant material in order to extract substances soluble in the extractant.

However , the extraction of which consists in the stepwise advancement of a

pure extractant from a more depleted raw material to a less depleted one.

Circulating extraction.

Lecture plan and organizational structure:

No. 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* Defining learning goals. Providing positive motivation. *Main stage* Presentation of lecture material. 1. Production of extraction preparations . 2. Theoretical foundations of extraction . 3. Features of extraction from plant raw materials with a cellular structure . 4. Stages of the extraction process and their quantitative characteristics .	 I II III	 Combined lecture Slides Bibliography ,	 1% 2% 90%

	5. Main factors affecting the completeness and speed of extraction . 6. Requirements for extractants . 7. Maceration 8. Percolation . 9. Flow-through extraction 10. Circulation extraction *Final stage*		questions, assignments.	
III 4. 5. 6.	Lecture summary, general conclusions. The lecturer's answers to possible questions. Tasks for student self-study.			2% 3% 2%

Structural and logical diagram of the lecture content

1. Classification methods extraction.
2. Theoretical foundations of extraction .
3. Features of extraction from plant raw materials with a cellular structure .
4. Features of extraction methods and their quantitative characteristics .
5. Main factors affecting the completeness and speed of extraction .
7. Maceration
8. Percolation .
9. Flow-through extraction.
10. Circulation extraction.

Content of the lecture material (lecture text)

EXTRACTION METHODS

Classification methods extraction

All existing extraction methods are classified into static and dynamic according to the nature of the process. In static methods, the raw material is periodically poured with an extractant and left to infuse for a certain time. In dynamic — Continuous change of the extractant or raw material and extractant is assumed.

Depending on the periodicity of the process, *periodic processes* are distinguished : — when the supply of raw materials (extractant and plant material) to the extraction apparatus is carried out periodically and *continuously* (with continuous supply of raw materials).

By achievement state equilibrium — *equilibrium* and *unbalanced.*

By quantity degrees equilibrium distinguish *single-stage* and *multi-stage* methods.

In the direction of flow of extractant and raw material - *co-current* (extractant and material in the same flow) and *counter-current* (active movement of the extractant and plant material towards each other).

By completeness cycle — *from completed* and *unfinished cycle* .

By distribution raw materials — with equal distribution of LRS and unequal distribution **.**

By speed process extraction raw materials — *fleeting* and *slow-moving* methods **.**

Choice method extraction dictated efficiency production and depends on the properties of the extractant and plant material.

Maceration and remaceration

maceration method (from the Latin *maceratio* — maceration), or ***infusion*** , was previously very widespread. However, maceration in its "classical" version does not meet the requirements of production intensification and is used only in special cases.

Maceration. The crushed raw material with the calculated amount of extractant

is loaded into the maceration tank and infused at a temperature of 15- 20 °C, stirring periodically. If no specific time is specified, the infusion is carried out for 7 days. Nowadays, the infusion for each type of raw material is established by studying the kinetics of extraction. After infusion, the extract is drained, the residue is squeezed. The extracted raw material (meal) is washed with a small amount of extractant, squeezed again and the extract is added — to the one that was drained earlier, after which the entire extract is settled and brought to the required volume with an extractant.

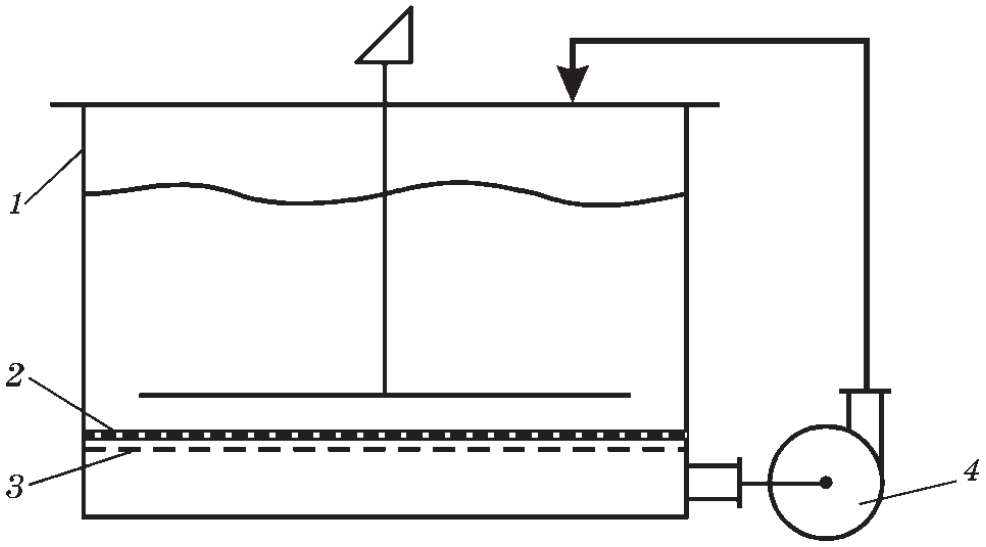
The advantage of this method is its simplicity. Disadvantages include incomplete extraction of active substances, excessive duration of the process, high content of ballast substances in the extracts (NAS, pectins, mucus, proteins, etc.), and laboriousness (double pressing and washing of the meal).

This method is ineffective. New forms of maceration with maximum dynamization of all types of diffusion are being developed and introduced. In order to intensify the extraction of the material, the process is carried out using re-maceration (stepwise infusion), maceration with forced circulation of the extractant, centrifugal extraction in rotating maceration tanks (centrifuges), etc. A significant acceleration of free diffusion in the extractant that washes the raw material is achieved by using vibration. and pulsations of the mixture of crushed raw materials and extractant.

Re-maceration , or **fractional maceration** . In this method, the total amount of extractant is divided into 2-4 parts and the raw material is successively infused with the first part of the extractant, then with the second, third and fourth, each time draining the extract. The infusion time depends on the properties of the plant material. In the infusion process, the plant material swells and absorbs from one to three parts of the extractant, therefore a slight excess of the extractant is used. The use of press extractors is recommended. for forced removal hoods from raw materials. Such The extraction process allows for more complete depletion of the raw material in a short time, since a high concentration difference is constantly created in the raw material and the extractant.

Maceration with forced circulation of the extractant. Carried out in a maceration tank *1* (Fig. 7.1) with perforated bottom *3* , on which the filter material is placed *2* and LRS. The extractant is pumped through the raw material using pump *4* until an equilibrium concentration is reached. In this case, the infusion time is reduced

several times. By forced circulation of the extractant, fractional maceration is also carried out. In this case, a more complete depletion of the raw material is achieved at the same extractant consumption .



Scheme of a maceration tank with extractant circulation

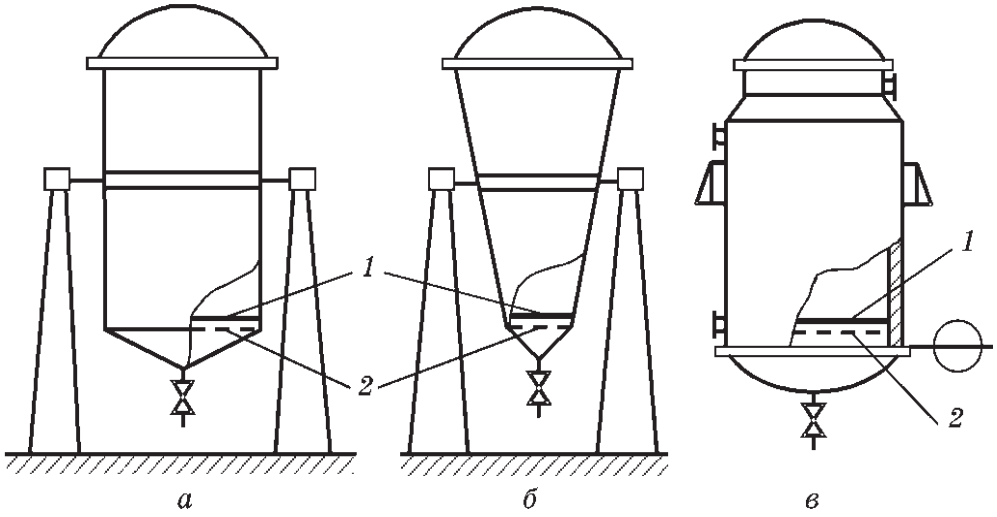
Among others ways intensification maceration trace to name: extraction with simultaneous *grinding of the curd in the extractant medium* using high-speed mixers, a rotary pulsation apparatus (RPA); re-maceration, accompanied *by pressing of the curd on hydraulic presses or rollers* . In the latter case, the process is repeated until equilibrium concentrations are reached. The method allows to reduce the loss of active substances and extractant, since a small volume of extract remains in the meal, and the finished extract contains a high amount of extractive substances

Percolation

Percolation (from Latin *percolatio* — filtering through), i.e. filtering the extractant through the plant material in order to extract the substances soluble in the extractant. The process is carried out in tanks of various designs, which are called percolator-extractors. They can be cylindrical (Fig. 7.2, *a*) or conical (Fig. 7.2, *b*) in shape, with a steam jacket (Fig. 7.2, *c*) or without it, can be turned over or self-drained. They are made of stainless steel, aluminum, tinned copper and other materials. There is a perforated mesh at the bottom of the percolator *2* , on which one placed filtering material *1* (burlap, cloth, etc.), and load the raw material. Cylindrical percolators are convenient when unloading raw material, conical —ensure uniform extraction .

The percolation method includes three stages that occur sequentially one after

the other: *soaking the curd, steeping, and percolation itself* .



Scheme percolator- extractors

Soaking of raw materials (swelling) is carried out outside the percolator. More often, maceration tanks or other vessels are used for this, from which it is convenient to unload the soaked raw materials. For soaking, 50 to 100% of the extractant is used relative to the mass of the raw materials. After mixing, the raw materials are left for 4-5 hours in a closed vessel. During this time, the extractant penetrates between the particles of plant material and into the cells, the raw materials swell and increase in volume. At the same time, the dissolution of substances inside the cell begins.

In production conditions, soaking is sometimes combined with infusion, but if the raw material is capable of swelling significantly, the soaking stage must be carried out in a separate vessel, since due to the large increase in volume in the percolator, it can become very compressed and not let the extractant through at all.

Infusion — the second stage of the percolation process. The swollen material is loaded into the percolator on a perforated bottom with optimal density so that as little air as possible remains in the raw material. The density of the raw material is of some importance, since optimal compaction will facilitate extraction, but transverse unevenness of the extractant movement may occur, which will ultimately slow down the extraction process. If the raw material is capable of caking easily, it is laid in layers, shifting it with special sieve-like pads. It is covered with filter material on top, pressed with a perforated disc and poured extractant Yes, that maximum to displace air. Can Load the material into a bag of filter material that fills the entire capacity of the

percolator. The bag is tied and a wick is placed in the upper part. The raw material is poured with extractant until a “mirror” is formed - a layer, the height of which above the raw material should be approximately 30-40 mm, and the infusion is carried out for 24 hours (for easily extracted raw materials) or 48 hours (for difficultly extracted raw materials). During this time, an equilibrium concentration will be achieved. For some types of raw materials, the infusion time may be shortened.

Percolation itself — uninterrupted passage of the extractant through the layer of raw material and collection of the percolate. In this case, the draining of the percolate and the simultaneous feeding of the extractant to the top are carried out at a speed not exceeding 1/24 or 1/48 of the working capacity of the percolator per 1 hours Saturated extract is being squeezed out of vegetable material by the stream fresh extractant and a difference in the concentrations of the extracted substances in the raw material and the extractant is created. The percolation rate must be such that the diffusion of the extracted substances into the extract has time to occur.

The stages of percolation during the production of extracts do not differ in any way from percolation in the production of tinctures. The difference lies only in the collection of finished extracts. When preparing tinctures, percolation is completed by obtaining five or ten volumes (depending on the properties of the raw material) of the extract. on relation to the mass loaded raw materials. For liquid extracts hood divide on two portions. First portion in number 85 % of the raw material mass is collected in a separate vessel. Then the percolation is continued in another vessel until the raw material is completely exhausted. In this case, 5-8 times (relative to the mass of raw material loaded into the percolator) is obtained. more weak hoods, which one are called "vacation". This one "release" is evaporated under vacuum at a temperature of 50-60 °C to 15 % relative to the mass of raw material loaded into the percolator. After cooling, this condensed residue is mixed with the first portion of the obtained product and an extract is obtained in a ratio of 1:1.

Repercolation

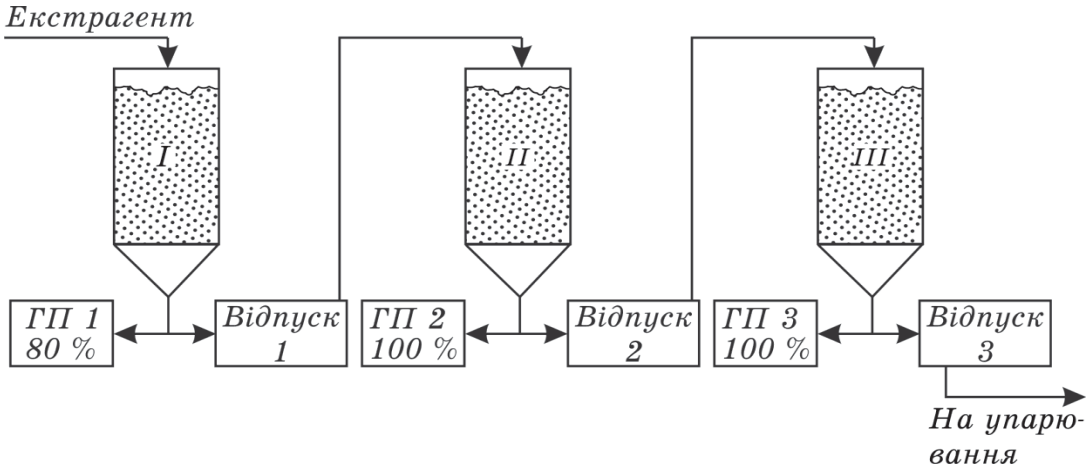
Repercolation **,** i.e. *repeated (multiple) percolation* , allows you to maximize the solvent capacity of the extractant and obtain concentrated extracts when the raw material is completely exhausted. In all cases, the process is carried out in several percolators (from 3 to 10), which work in connection - the so-called battery of

percolators. The heavier the raw material is extracted, the greater the number of percolators is included in the battery. In the battery, the finished product is drained from the "main" percolator, in to whom always fresh raw material, and fresh extractant serve in "tail" percolator, where most exhausted raw material. Extractor hood with "tail" The percolator processes the raw material in the front percolator, and so on throughout the battery — In the following percolators, the raw material is extracted by the extracts obtained from the previous ones. Thus, from the first to the last percolator in the battery, a countercurrent movement of the extractant is carried out. As the raw material is depleted, the position of the "main" and "tail" percolators changes.

There are different options for repercolation: with the division of raw materials into equal and unequal parts, with a completed and incomplete cycle, etc. Some of them allow you to obtain concentrated extracts without further evaporation .

Repercolation with the distribution of raw materials into equal parts, with a completed cycle, is carried out in a battery of percolators. Number of percolators in the battery depends on the properties of the raw material: the harder the raw material is extracted, the greater the number of percolators installed in the battery.

The raw material, divided into equal parts, is loaded into percolators (Fig. 7.3). In the percolator The *raw* material is soaked for swelling, which lasts 2-6 hours, after which the extractant is added to the percolator (to the "mirror") and left to infuse for 24 hours.



Scheme repercolations with distribution raw materials on levels parts, from finished cycle

Then percolate into a separate vessel and get 80 % of finished product (*FP) 1* —

80 %) of the mass of raw materials in this percolator. Percolation is continued until the raw materials are completely exhausted into another vessel - “dispense *1* ” is obtained. This dispense *1* is used to soak, infuse and percolate the raw materials in the percolator. *II* , from which the finished product is obtained (*FP 2* — 100 %) in an amount equal to 100% of the mass of the raw material in this percolator, and release *2* . Release *2* carry out soaking, infusion and percolation of raw materials in percolator *III* , from which the finished product is obtained (*FP 3* — 100 %) in an amount equal to 100 % of the mass of the raw material in this percolator, and the release is *3* .

This process is carried out in each subsequent percolator, if there are more than three of them. The output of the last percolator is evaporated (concentrated) to 20 %, which is missing from the finished product drained from the first percolator. If this receive on 300 kg raw materials rare extract: 80 + 100 + 100 + 20 = 300 liters (kg), i.e. in a ratio of 1:1.

Repercolation with distribution of raw materials into equal parts, with an incomplete cycle (Fig. 7.4). The first portion of raw materials intended for for loading, pre-soaked with equal or half the volume of extractant relative to the mass of raw material. After swelling for 2-4 hours, the material is placed in percolator *I* and infused for 24 hours with a double volume of extractant relative to the mass of raw material.

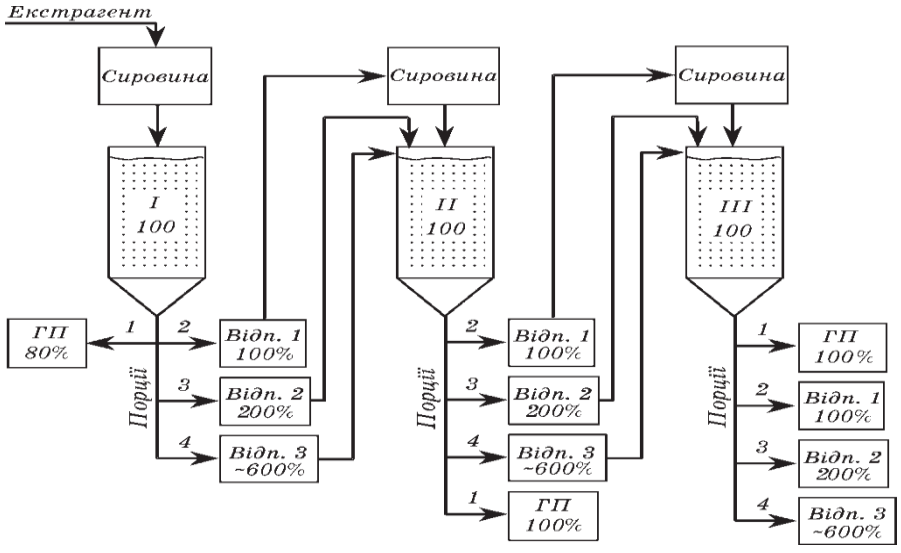


Рис. 7. Scheme re-circulation with distribution raw materials on equal parts, with an unfinished cycle.

After the specified time, percolation is carried out until the raw material is completely exhausted, with the extract being divided: first portion in quantity 80 %

of the mass of raw material considered as the finished product; second portion (less concentrated extract) — in an amount equal to the mass of the raw material and intended for soaking the raw material for the percolator *II* ; the third portion (release *2*) — in double the amount relative to the mass of raw materials and the intended for infusion raw materials in percolate *II* ; Thursday portion (discharge) *3*) — in an amount that is approximately six times the mass of the raw material and is intended for extraction (percolation) of the raw material in percolator *II* . From the percolator *II* get 100 % of the finished product (*FP*) from the mass of the raw material in the percolator and collect the allowances for working with the raw material in the next percolator. From the last percolator, 100% of the finished product and allowances are obtained, which are used to process the next batch of similar raw material. All portions of the finished product obtained from each percolator are combined.

Repercolation with the division of raw materials into unequal parts. According to the US and German pharmacopoeias, the starting raw materials are loaded into percolators in the ratio of 5:3:2 and 5:3.25:1.75, respectively, and extracted. The percolate is collected in two stages without further evaporation of the extracts. These methods are used by small-scale production to obtain a small amount of product, since in the above modifications of repercolation the raw materials are not completely exhausted.

Repercolation with circulating exchange. This method allows you to reduce the extraction time due to circulating mixing in each percolator during the infusion process using a centrifugal pump. As the raw material in percolator *I is depleted, percolator II* becomes the tail (i.e., fresh extractant will be fed into it), and the main — the former first, from which the depleted raw material (meal) was unloaded and fresh material was loaded.

The method allows for maximum depletion of the raw material in each percolator, reducing the extraction time to a minimum, since when the extractant circulates, reaching equilibrium concentration occurs faster.

Countercurrent extraction

The essence of the countercurrent extraction method is the stepwise advancement of pure extractant from more depleted raw materials to less depleted ones. The most depleted plant material is extracted with pure extractant, and the concentrated extract is

collected from the extractor from the newly loaded raw materials. The countercurrent principle of feeding raw materials and extractant, the continuous movement of not only the liquid but also the solid phase contribute to achieving a high concentration difference, convective diffusion of substances in the extractant layer and the creation of an effective extraction surface, which greatly intensifies the process.

This type of extraction is carried out in various ways: in *a battery of extractors* , when the raw material is stationary and only the extractant moves; in *continuous extractors* , where the raw material and the extractant move towards each other. The method of countercurrent continuous extraction is used for mass production, associated with with the processing of large quantities of LRS.

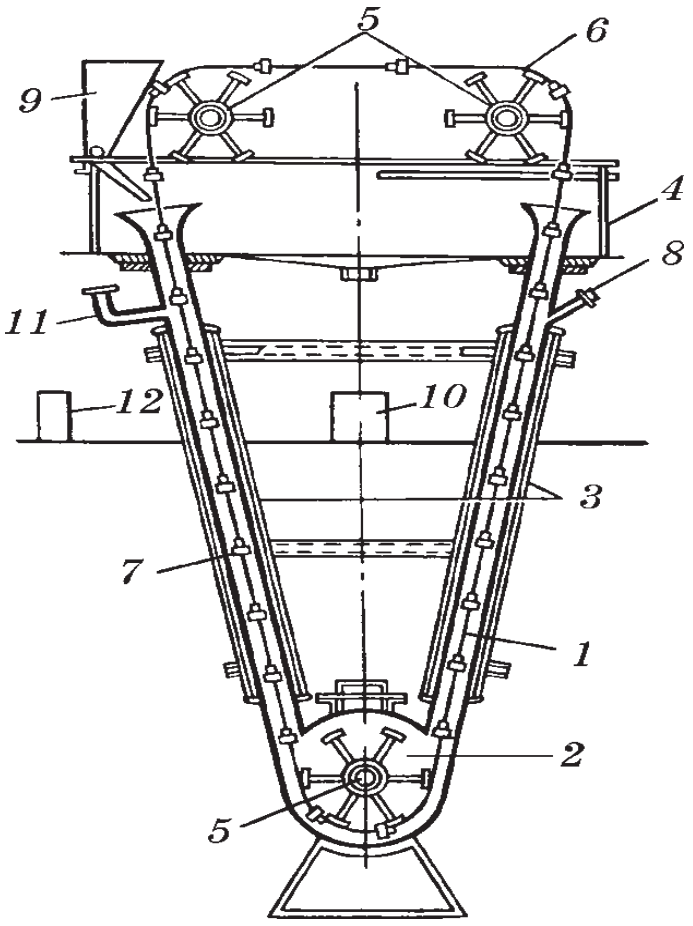
Continuous countercurrent extraction with replacement of raw material and extractant.

Plant material using transport devices — augers, buckets, discs, belts, scrapers or spring-blade mechanisms — moves towards the moving extractant. The raw material, which is continuously fed into the extraction apparatus, moves countercurrently to the extractant. In this case, the fresh raw material comes into contact with the extractant saturated with extractive substances, which becomes even more saturated, since the concentration in the raw material is even higher. The exhausted raw material is extracted with a fresh extractant, which extracts the remaining extractive substances even more completely. According to the theory of extraction, this method is the most effective, because at each moment of the process and in any cross-section along the length (or height) of the apparatus there is a difference in the concentrations of BAS in the raw material and the extractant, which allows with the greatest yield and the smallest expenses conduct process. Except that, continuous The processes are amenable to automation, which allows you to avoid labor-intensive work of loading and unloading raw materials from extractors.

Extraction is carried out in extractors of various designs: ***horizontal screw, vertical screw, disc, spring-vane*** etc.

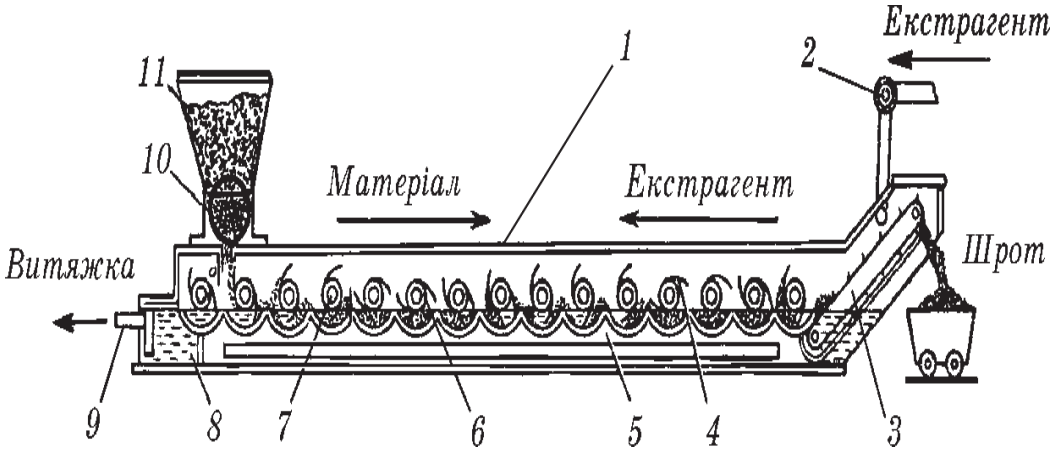
The disc extractor consists of two pipes *1* , located at an angle and connected at the bottom by a chamber *2* . The pipes are equipped with steam jackets *3.* The upper ends of the pipes enter the trough *4 with two rotating sprockets 5* installed in it , through which the cable *6 passes* . Perforated discs *7 are mounted on the cable* . The cable with

the discs passes through inclined pipes and the lower chamber with a sprocket *5* . The sprockets are driven by an electric motor. Before starting work, the extractor through the cartridge side *8* is filled with extractant. The cable with the discs starts moving and at the same time from the bunker *9* raw material is fed to the discs of the moving cable. The raw material is lowered from the loading point downwards, passes through the lower chamber, then rises along the second pipe, where it is unloaded into the trough *4* and then directed into the collector *10* . At the same time, through the branch pipe *8* at a certain speed the extractant is fed. The saturated extract is discharged from the extractor through the nozzle *11* , equipped with a filter mesh, and accumulates in the collection *12* .



Scheme disk extractor

Spring-blade extractor (Fig. 7.6) consists of a body *1* , divided into sections. Each section has a shaft *7* with a drum *6* , on which two rows of spring blades are mounted *4*. Each shaft is set in motion. In the bottom of the device there is a heating chamber *5*. The exhaust gases are collected in the chamber *8* and are discharged through the nozzle *9*. The ground, prepared material from the bunker *11* using a feeder *10* enters the first section of the extractor, where the extractant is located. Here, the raw material is immersed in the extractant with the help of spring blades and moves further, pressing against the wall of the section, where partial separation of the extractant occurs. If exit blades from sections they straighten up and The wet raw material is transferred to the next section. So the raw material passes to the second, third and subsequent sections and goes straight to the conveyor. *3* . Extpagent from patpubka *10* is fed to the exhausted material, which moves along the conveyor, after which it enters the last section, moves countercurrently to the raw material and is collected in chamber *8*. Testing of the extractor on various plant raw materials (licorice and valerian roots, mountain ash and wormwood grass) showed that the exhaustion of the raw material in it ends in 75-120 min and can be carried out in a wide temperature range.

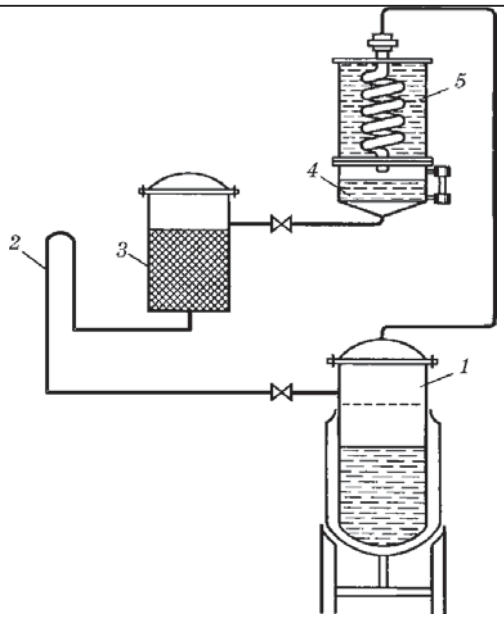


Scheme spring-blade extractor

The advantages of this extractor include the fact that the raw material is subjected to mechanical action, which significantly increases the yield of extractive substances. Disadvantages — a large number of rotating shafts in the device, which complicates its maintenance and increases electricity losses.

Circulating extraction

The method is based on multiple extraction of LRS with the same portion of a volatile extractant. The extraction unit operates in a closed cycle, continuously and automatically, according to the principle of a Soxhlet apparatus (Fig. 7.7). It consists of interconnected interdependent Cuba *1* , extractor *3* , condenser refrigerator *5* , collector condensate *4* .



Scheme circulatory apparatus type Soxhlet

Volatile organic solvents with low solubility are used as extractants. temperature boiling,- ether ethyl (34.5 °C), chloroform (61.3 °C), methylene chloride (40.0 °C) or mixtures thereof. Ethyl alcohol (even 96 %) is unsuitable here, as it will adsorb moisture contained in the raw material and change its concentration, which will cause changes in the boiling point and extraction capacity.

The raw material is loaded into the extractor *3* , filled with extractant slightly below the loop of the siphon tube *2* and left to infuse. At the same time, a small amount of extractant is poured into the evaporator *1.* After the infusion from the collector *4,* as much extractant is fed into the extractor as is necessary for the extract to reach the upper level of the siphon loop and begin to flow into the evaporator, which is then heated. The extractant vapors that are formed rise to the condenser. *5* , which is served by a coil heat exchanger, and from it — into the collector. Then the extractant falls on the raw material. When the extractor is gradually filled, when the extractant level reaches a certain value, the extract will be drained through a siphon. The saturated extract will again enter the evaporator.

The extractant is circulated many times until the raw material is completely exhausted. The resulting extract is concentrated by distilling the extractant into a receiver. A concentrated solution of extractive substances remains in the evaporator . A significant amount of thick extracts is obtained by the method of circulating extraction.

This method is characterized by a high yield of BAS and maximum depletion of the raw material, the use of a small amount of extractant, the creation of a high concentration difference at the phase separation boundary (since pure extractant is fed to the raw material each time) and the reduction of the total extraction time. The disadvantages of the method include a long temperature effect on the extractive substances and significant coolant consumption.

Intensive methods extraction

With the development of the production of extraction preparations, new methods of processing plant raw materials were introduced, with maximum dynamization of all types of diffusion. To increase the efficiency of BAS extraction, it is carried out in different ways — in a turbulent flow of extractant, with vibration, pulsation of liquid through a layer of raw materials, with the use of ultrasound, electrical treatment of the material, etc.

Vortex extraction, or **turboextraction,** is based on vortex, very intensive mixing of raw materials and extractant by high-speed multi-blade propeller or turbine mixers, which rotate at a speed of 8000-13000 rpm. The movement of the liquid occurs along spiral trajectories and has the shape of a torus. Each liquid particle moving inside the vortex also performs an oscillatory motion. During the extraction process under such conditions, the way the extractant flows around the raw material particles changes, the thickness of the laminar layer becomes minimal, and convective diffusion occurs instantly. The high mixing speed creates conditions of uneven pressure on the mixture flow, while the system produces a cavitation and pulsation effect, which affects the speed of internal diffusion. The extraction time is reduced to 10 minutes. With intensive mixing, the raw material is crushed, so the extraction process is supplemented with a process of washing out extractive substances from destroyed cells. The extracts are obtained saturated, but they contain many small particles of plant material, which significantly complicates further purification. Other disadvantages of this method include an increase in temperature during the operation of the mixers, which can affect the preservation of BAS and cause losses of the extractant.

Extraction of raw materials using a rotary pulsation apparatus (RPA). This method is based on multiple circulation of raw materials and extractant, which are fed into the extractor using a RPA. These devices have two coaxially arranged rotor-cylinders with holes. During the operation of the RPA, mechanical grinding of particles occurs, intense turbulence and pulsation of the processed mixture occur. The raw materials are loaded into the extractor and filled with extractant, the RPA is installed below the bottom of the extractor. The liquid phase enters the RPA through the fittings, and raw materials — using a screw. From the RPA, the mixture of solid material and extractant is lifted and fed through the fitting into the extractor with a mixer. The process is repeated until a concentrated extract is obtained (to equilibrium concentration). At the same time, extraction and grinding occur simultaneously. Dichloroethane, methylene chloride, mineral oils and vegetable oils are used as extractants. The use of RPA is effective for obtaining tinctures of calendula and valerian, tannin from the leaves of the scumpia, carotenoids and oxymethylenetetramines from the fruits of the rosehip, oxyanthraquinones from the bark of the thorny thorn, etc. In all cases, productivity increases and the yield of extractive substances increases. Disadvantages of the method — heating of the system and possible evaporation of the extractant, intensive grinding of the raw material and the formation of cloudy extracts.

To intensify extraction, the Laboratory of Phytochemical Production Technology of the State Scientific and Technological Research Center of Plant and Animal Health (Kharkiv) has developed a **filtration extraction method** that allows working with finely ground plant raw materials. The method is based on the processes of dissolution and washing off of substances from the highly developed surface of plant material in dynamic non-equilibrium conditions. This allows significantly reducing the extraction time, increasing the yield of BAS up to 90% and obtaining highly concentrated extracts. The proposed method and the technology developed on its basis allow replacing a battery of percolators with a single filtration extractor, mechanizing and automating the processes of loading and unloading plant material and extractant regeneration.

oscillations have been increasingly used to accelerate mass transfer in

extraction processes . One of the main reasons is that oscillations create microstructures in the flows, which affect the process much more than significant vortex motions. Hydrodynamic cavitation allows you to intensify the mass transfer process due to the destructive effect of cumulative microflows of the solvent by their high-speed penetration into particles of the solid or liquid phases. In this case, the crushed raw material is placed in an extraction apparatus in bags of filter material, and the extractant is recirculated by a pump through cavitation generators (hydrodynamic, ultrasonic, pulse-vortex, electromagnetic).

Ultrasonic (acoustic) extraction . For intensification The use of ultrasonic vibrations is effective in the extraction process. This accelerates the extraction and achieves complete extraction of active substances. The ultrasound source (US) is placed in the treated medium or attached to the extractor body in a place filled with the extractant and raw material. The greatest effect from the action of ultrasound is achieved when the cell of the extracted material is well impregnated with the extractant, which conducts ultrasound. The resulting ultrasonic waves create pressure, cavitation and "sonic wind". As a result, the impregnation of the material and the dissolution of the cell contents are accelerated, the flow velocity of the raw material particles increases, turbulent and vortex flows arise in the adjacent diffusion layer of the extractant. Molecular diffusion inside the cells of the material and in the diffusion layer changes to convective, which accelerates mass transfer. However, the occurrence of cavitation causes the destruction of the cells, so the extraction is accelerated due to the leaching of extractive substances from the destroyed cells and tissues.

For receipt Ultrasonic waves most often apply magnetostrictive and piezoelectric emitters. Optimal frequency extraction 21—22 kHz, radiation intensity — no more than $(1.5…2.2)•10^{4}$ W/m ^{2} . In this way, the extract can be obtained in a few minutes, but due to the destruction of the cells, it will contain a lot of ballast substances and suspended particles of material.

The disadvantages of ultrasonic processing also include a negative effect on the operating personnel. In addition, ultrasonic vibrations cause cavitation, ionization of molecules, and changes in the properties of the BAS, reducing or enhancing

Materials for activating higher education students during lectures: questions, situational tasks, etc.:

Question:

1. What is the physical significance of the extraction process?
2. What are the features of maceration extraction?
3. What is the purpose of the percolation method?
4. What factors affect the extraction process?
5. What is the flow-through extraction method?

General material and methodological support for the lecture:

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

Questions for self-control:

1. What is the purpose of maceration?
2. What stages of the percolation process exist in the production of extracts?
3. What are the methods of standardizing extracts?

List of sources used:

1. A textbook for independent work of students of the Faculty of Pharmacy for the licensing exam "Step 2. Pharmacy" / V.Yu. Anisimov, O.I. Belyaeva, G.G. Vidavska, V.O. Helmboldt, A.V. Zamkova, I.V. Lytvynchuk, A.V. Nikitin, B.V. Prystupa, I.B. Petkova, Ya.V. Rozhkovsky, S.B. Strechen, L.M. Unguryan, N.S. Fizor Odessa: Odessa National Medical University. 2020. - 240 p.

Access mode 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 of higher. educational. pharmaceutical institutions (pharmac. faculties) / E.V. Gladukh, O.A. Ruban, I.V. Saiko and others. - Kh.: NPhU: Original, 2016. - 632p. : Named after. - (Series "National textbook")

2. Workshop on industrial technology of medicines, specialty "Pharmacy" / Edited by Ruban O.A. - Kh .: National University of Physics and Technology, 2015. - 374 p.

3. INDUSTRIAL technology of medicines : a teaching aid for independent work of students / O. A. Ruban , V. D. Rybachuk , L. M. Khokhlova etc. – KH.: NATIONAL UNIVERSITY OF PHYSICS AND TECHNOLOGY, 2015. – 120 p.

- Excipients in the production of medicines: a manual for students of higher pharmaceutical schools / O. A. Ruban , I. M. Pertsev, S. A. Kutsenko, Yu. S. Masliy; edited by I. M. Pertsev. – Kh.: Zoloti storyny, 2016. – 720 p.
- Technology of industrial drug production: a textbook for students of higher education institutions: in 2 parts / V. I. Chuyeshov, E. V. Gladukh, I. V. Sayko and others – 2nd ed., revised and supplemented – Kh.: National University of Physics and Technology: Original, 2012. – Part 1. – 694 p.
- Technology of industrial drug production: a textbook for students of higher education: in 2 parts / V. I. Chuyeshov, E. V. Gladukh, I. V. Sayko and others – 2nd ed., revised and supplemented – Kh.: NPhA: Original, 2013. – Part 2. – 638 p.
- Modern pharmaceutical technologies: teaching aids for laboratory classes of undergraduates of full-time, evening and correspondence forms of study in the specialty 8.110201 "Pharmacy" / edited by O. A. Ruban. – Kh.: Publishing house of the National University of Physics and Technology, 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 Ukraine / State enterprise « Ukrainian scientific officinal center qualities medical " means " - 2nd ed . – Kharkiv : State enterprise « Ukrainian scientific officinal center qualities medical means ”, 2015. – T. 1. – 1128 p .
- State Pharmacopoeia Ukraine / State enterprise « Ukrainian scientific officinal center qualities medical " means " - 2nd ed . – Kharkiv : State enterprise « Ukrainian scientific officinal center qualities medical means ”, 2014. – T. 2. – 724 p .
- State Pharmacopoeia Ukraine / State enterprise « Ukrainian scientific officinal center qualities medical " means " - 2nd ed . – Kharkiv : State enterprise « Ukrainian scientific officinal center qualities medical means ”, 2015. – T. 3. – 732 p .
- On medicinal products: Law of Ukraine of 4.04.96 No. 123/96 // Bulletin of the Verkhovna Rada of Ukraine. – 1996. – .№ 123.

Lecture No. 7

Topic: Tinctures. Production of thick, dry extracts. Concentrated extracts. - 2 hours.

Relevance of the topic: Drug technology (industrial drug technology) is one of the fundamental technological sciences. It consists of several key aspects that are important for modern medicine and patients: Efficacy and safety - Modern technologies allow the production of drugs with high efficiency and safety for patients. Accurate dosing, quality control and the absence of impurities make drugs more effective and safe. Innovations in the medical field: 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 treatment. Minimization of side effects: Technologies allow the development of drug formulas that minimize side effects and negative effects on the body. This provides more comfortable and safe treatment for patients. Fast production

and delivery process: The use of modern technologies allows the acceleration of the production process of drugs, which is especially important in a rapidly changing medical environment, such as the spread of diseases or epidemics. Personalized treatment: Technologies allow for the development of medicines that take into account the individual characteristics of the patient, leading to a personalized approach to treatment and increasing its effectiveness. Cost-effectiveness and accessibility Improved manufacturing technologies can reduce production costs, making medicines more accessible to a wider range of patients, ensuring cost-effectiveness in healthcare.

Thus, the use of modern pharmaceutical manufacturing technologies is an important factor in improving the effectiveness of treatment, patient safety, and the overall state of public health.

Objective: to get acquainted with the main stages of industrial production of dosage forms and the discipline "Drug Technology", to describe the pharmaceutical development of the production of tinctures, thick and dry extracts , and extract concentrates.

Basic concepts:

***Tinctures* (*Tincturae*)** - are colored liquid alcoholic or aqueous-alcoholic extracts from medicinal plant raw materials, obtained without heating and removal of the extractant.

Molecular diffusion is the process of transferring a distributed substance (biologically active substance - BAS) due to the chaotic movement of the molecules themselves in a stationary medium.

The porosity of the raw material *is* the amount of voids inside the plant tissue. The higher it is, the more internal juice is formed during swelling.

Porosity *is* the amount of voids between pieces of crushed material.

Thick extracts are concentrated extracts from medicinal plant raw materials, which are viscous masses with a moisture content of no more than 25%.

Dry extracts are concentrated extracts from medicinal plant raw materials, which are loose masses with a moisture content of no more than 5%.

Lecture plan and organizational structure:

No. 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* Defining learning goals. Providing positive motivation. *Main stage* Presentation of lecture material. 1. Production of extraction preparations . 2. Theoretical foundations of extraction . 3. Features of extraction from plant raw materials with a cellular structure . 4. Stages of the extraction process and their quantitative characteristics . 5. Main factors affecting the completeness and speed of extraction . 6. Dissolving thick and	 I II III	 Combined lecture Slides Bibliography, questions, assignments.	 1% 2% 90%

	dry extracts . 7. Standardization . 8. Liquid extracts . 9. Thick and dry extracts *Final stage* Lecture summary, general conclusions. The lecturer's answers to possible questions.			
III 4. 5. 6.	Tasks for student self-study.			2% 3% 2%

Structural and logical diagram of the lecture content

1. Production of extraction preparations .
2. Theoretical foundations of extraction .
3. Features of extraction from plant raw materials with a cellular structure .
4. Stages of the extraction process and their quantitative characteristics .
5. Main factors affecting the completeness and speed of extraction .
6. Requirements for extractants .
7. Dissolving thick and dry extracts .
8. Standardization .
9. Concentrated extracts
10. Thick and dry extracts

TINTINGS

Tinctures (*Tincturae*) — these are liquid alcohol or water-alcohol extracts from dried or fresh plant or animal raw materials, obtained without heating and removal of the extractant. They are clear colored liquids that have the taste and smell

of the plants from which they are prepared.

Tinctures — an old medicinal form introduced into medical practice by Paracelsus (1493—1541), which has not lost its significance to this day. Tinctures have firmly entered medical practice as independent preparations for internal and external use or as a component of ointments, syrups, drops, potions, etc.

Tinctures can be *simple* , which are obtained from a single type of raw material, and *complex* , that is, mixtures of extracts from several plants, sometimes with the addition of medicinal substances. Complex tinctures are also obtained by mixing simple ones in order of increasing strength of the ethanol on which they are obtained.

Most tinctures are obtained using 70% ethanol, less often 40% (barberry tincture, St. John's wort) and extremely rarely other concentrations: 90% (mint tincture, capsicum tincture), 95% (lemongrass tincture), etc.

When making tinctures, a weight-volume ratio is adopted, when one part by weight of plant raw materials yields five parts by volume of the finished product, and from potent raw materials - 10 parts. In some cases, tinctures are prepared in other ratios (tincture of arnica, calendula, hawthorn, peony - 1:10, mint - 1:20, sophora - 1:2).

For **obtaining tincture** exist such ways:

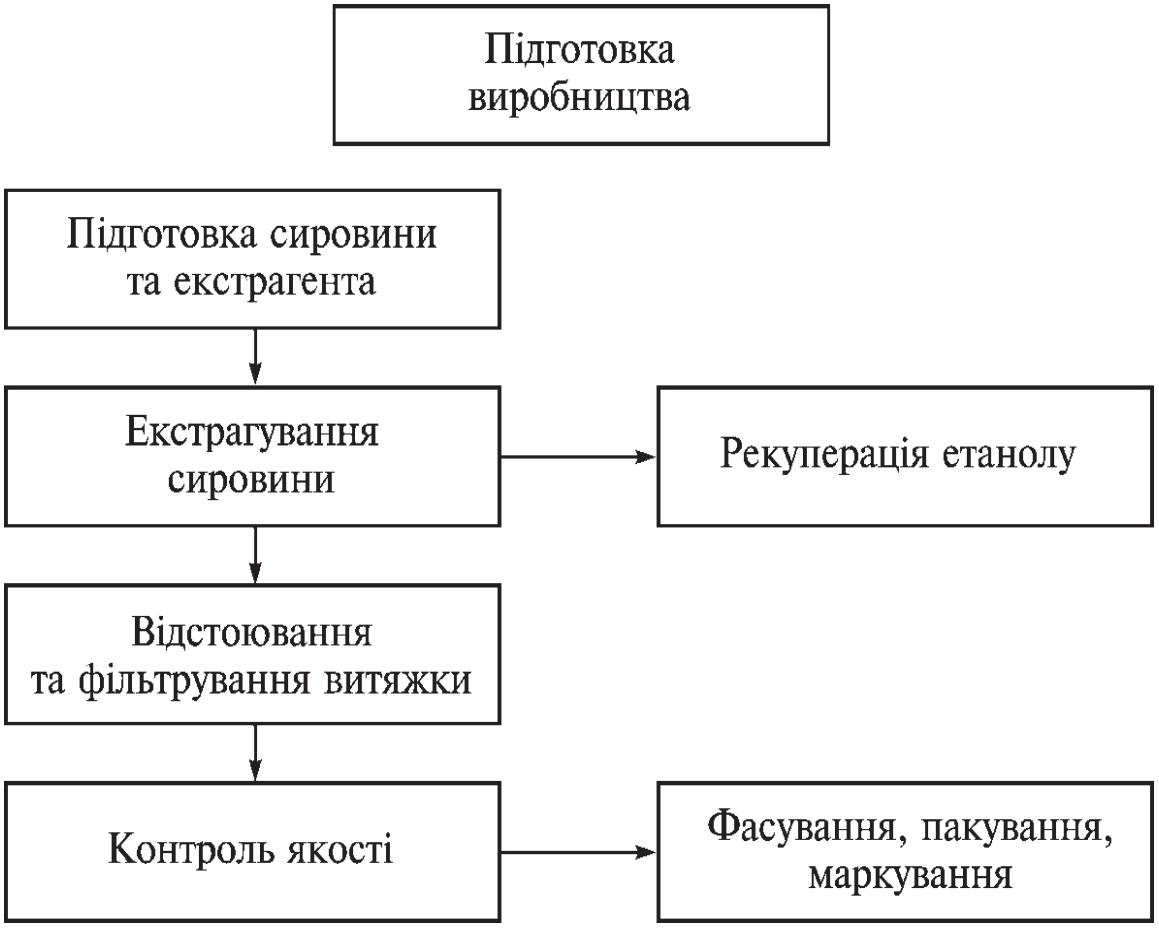
1) extraction methods (maceration and its varieties, percolation);
2) dissolution thick and dry extracts.

The second method is to prepare a small amount of tincture. Thus, using dry extract, receive tincture *of vomiting nut* , which has poisonous seeds, which are also difficult to powder due to their great hardness. From thick or dry extract *root licorice* are preparing breast elixir. The technology of obtaining tinctures by this method is reduced to simple dissolution in a reactor with a stirrer designed amount of dry or thick extract in ethanol of the required concentration. The resulting solutions are filtered. This method is characterized by a significant reduction in the time required to obtain the tincture, but may differ slightly in composition.

The majority of tinctures are obtained by extracting LRS, which is ground to

the required parameters and sieved before extraction.

Sequence of technological stages of obtaining tinctures by extraction methods.



Technological scheme obtaining tinctures

At extracted LRS in advance calculate quantity extractant

X for production desired quantity tinctures by formula

$X = V + m \bullet K$, (7.3)

where *V* is the required volume of tincture, l; *m* is the amount of LRS, kg; *K* is the coefficient of alcohol absorption by the raw material, which shows the amount of alcohol contained in 1 g of raw material.

Simple tinctures more often receive in a way percolation. At Jeanne's dress tincture in ratios 1:5 with purpose achievement completeness T h e extraction of raw materials is carried out using circulating mixing using centrifugal pumps, vibration or other methods. If the amount of active substances in the extract is higher than the established limit, it is diluted by adding pure extractant.

Purification of extracts. The obtained extracts from LRS are turbid liquids

containing a significant amount of suspended particles. Their purification is carried out by settling for at least two days at a temperature not higher than 10 °C until a clear liquid is obtained. At this temperature, the solubility of ballast substances (proteins, mucus) decreases and their precipitation occurs. Therefore, in the future, during the storage of tinctures at a temperature of 15 °C, the probability of precipitation is small.

Pharmacopoeias of different countries contain different recommendations regarding the time for standing tinctures: according to the Japanese Pharmacopoeia, it should last 2 days, according to the Romanian Pharmacopoeia, 6 days, in Italian — 12 hours, and when using vortex extraction - 3 days at low temperature.

After settling, filtration is carried out in combination with decantation (i.e. without shaking the sediment), using filter presses, centrifuges, filter presses. It is not recommended to use nutch filters due to the possible loss of extractant. The prepared tincture is filled into bottles, corked and packaged in accordance with regulatory documentation. The final stage of the process of obtaining extractive preparations is the recovery of the extractant from the meal.

Standardization of tinctures. Common methods for testing tinctures include: ***control of organoleptic characteristics ; quantitative determination of ethanol , extractives , heavy metals ; density , microbiological purity ,*** **and** ***dosage accuracy.***

Control of organoleptic characteristics . Tinctures must be transparent and retain the taste and smell of the substances contained in the starting medicinal raw material.

Contents ethanol in tinctures determined by distillation or by boiling point. *The density* of tinctures is determined using a pycnometer or hydrometer (densimeter).

Extractives determined by dry residue. *The content of active substances* in tinctures is determined by instrumental methods.

Storage tinctures. Their trace to save in good clogged vials in a place protected from sunlight, at a temperature not higher than 15 °C.

EXTRACTS

Extracts (from Latin *extractum)* — extract) — These are concentrated extracts of various consistencies from plant or animal raw materials.

They can be classified depending on from consistency on *liquid* extracts (*Extracta fluida*), *thick extracts* (*Extracta spissa*) and *dry extracts* (*Extracta sicca*); or depending on the extractant used: *aqueous* (*Aqueous extract*), *alcohol* (*Extracta spirituosa*), *ethereal* (*Extracta aetherea*), *oil* (*Extracta oleosa*) and obtained using liquefied gases. In addition, *standardized* ***extracts*** **(** ***Extracta standartisata*** **), or** ***extract concentrates, are distinguished*** **. Liquid extracts**

Liquid extracts **—** These are liquid concentrated aqueous-alcoholic extracts from LRS, which are obtained in a ratio of 1:1. At pharmaceutical enterprises, liquid extracts are prepared by mass (1 kg of liquid extract is obtained from 1 kg of raw material). Liquid extracts are only alcoholic.

Liquid extracts have found wide application in the pharmaceutical industry, since they have certain advantages: 1) the same ratios between active substances in medical raw materials and in ready drugs;

2) ease of measurement in pharmacies; 3) the possibility of production without evaporation allows obtaining liquid extracts containing volatile substances (*essential oils*).

The disadvantages of liquid extracts include: 1) their saturation with accompanying substances extracted from plant raw materials; 2) the appearance of precipitates with a slight decrease in temperature or partial loss of alcohol; 3) the need for hermetic sealing and storage at a temperature of 15-20 °C; 4) to obtain liquid extracts, large volumes of extractants are used, which are then evaporated.

Since the extracts are concentrated extracts, for maximum extraction of BAS, a deliberately excessive amount of extractant is used, which must then be evaporated to a ratio of 1:1 relative to the mass of the raw material. The amount of extractant X is calculated using the formula

$$X = n \bullet V + m \bullet K ,$$

where n is the number of volumes of extractant required for complete depletion of the raw material (usually 3 to 10 volumes of extractant are required and depend on the properties and extractability of the raw material); V — required amount of extract, kg; m — quantity of LRS, kg; K — the coefficient of alcohol absorption by the raw

material, which shows the amount of alcohol contained in 1 g of raw material.

If the extraction method does not involve concentration of extracts, then $n = 1$ is assumed.

As an extractant in the production of liquid extracts, 50–70% ethanol is usually used, less often other concentrations.

Methods of production. Liquid extracts are obtained by extraction methods of percolation, repercolation (in various versions), remaceration in various modifications, countercurrent extraction. Liquid extracts are also obtained by dissolving dry or thick extracts. The method is used relatively rarely, although it deserves greater implementation in practice due to the reduction in the duration of the technological process. The preparation technology is reduced to dissolving a thick or dry extract in a suitable extractant with subsequent purification and standardization. The best quality liquid extracts are obtained by methods that exclude concentration (evaporation) of extracts. **Concentration.** Extracts that require concentration of the infusions after extraction are concentrated using vacuum evaporation units.

Purification of extracts. Extracts obtained by any of the above methods in the production of liquid extracts are settled for at least 2 days at a temperature not exceeding 10 °C until a clear liquid is obtained. Settling is sometimes allowed to be carried out in the presence of adsorbents, which contributes to better purification and greater stability of the extracts during storage and transportation. The clear part of the settled extracts is filtered through filter presses, XNDXFI filter, filter presses or centrifuged. Finally, the remainder of the extract with the precipitate is filtered. The filtered extracts are thoroughly mixed and standardized .

Standardization. In liquid extracts, the content of active substances is determined by instrumental methods, the quantitative indicators of some liquid extracts are established by the sum of extractive substances. Organoleptic characteristics are checked, the content of alcohol, heavy metals is determined, as well as the accuracy of dosage, microbiological purity and density of the extract .

Storage. Liquid extracts are stored in well-sealed bottles at a temperature of 12–15 °C, in a place protected from light.

mouth and dry extracts

Thick extracts — These are concentrated extracts from medicinal raw materials, which are viscous masses with a moisture content of no more than 30% (according to European requirements) and 25% (according to the national section of the State Federal University), obtained by partial evaporation applied extractant. They are usually not poured out of the vessel, but are stretched into threads, which are then poured into a solid mass. Most thick extracts are used as intermediates for obtaining various dosage forms (tablets, suppositories, ointments, syrups, etc.) and combined preparations.

The disadvantages of thick extracts include their inconvenience in use, which requires certain weighing techniques. In addition, in dry air they dry out and become solid; in humid air they They get damp and moldy. Therefore, they need airtight packaging.

Dry extracts — it concentrated hoods with medical raw materials,

What there are loose by the masses with content moisture not more 5 %, received by

removal of the used extractant. They are considered the most rational type of extracts. They are convenient to use, have the minimum possible mass. The disadvantages of dry extracts include high hygroscopicity, as a result of which they turn into lumpy masses that lose their flowability

Dry extracts share:

1) on extracts with limited upper border active substances;
2) extracts with unlimited upper border 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 specified amount. This is achieved by adding fillers or mixing extracts containing active substances more and less than the norm in certain ratios. Milk sugar, glucose, dextrin, potato starch, etc. are used as fillers. Fillers are preferably added to the dried product at the grinding stage.

Extracts with an unlimited upper limit of active ingredients are obtained without adding fillers from medicinal raw materials that do not contain potent substances.

Methods of obtaining.

The process of producing *thick extracts* includes three main stages:

1) obtaining the extract; 2) its purification; 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 the extract; 2) purification of the extract; 3) thickening of the extract; 4) drying of the thickened extract. According to the second scheme, the process of producing dry extracts is carried out without a condensation stage, and then it includes three stages: 1) obtaining the extract; 2) purification of the extract; 3) drying of the liquid or slightly condensed extract. Drying of the liquid extract can be carried out in spray, sublimation (lyophilic, molecular) or other dryers. The extract, which is slightly condensed, is dried in vacuum roller dryers.

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

To obtain thick and dry extracts, a wide range of assortment solvents with taking into account specific properties of the active substances, since the extractant is partially or completely removed. As extractants 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 oils and mineral oils are used.

Extraction purification. Depending on the nature of the ballast substances and the extractant used in the manufacture of thick and dry extracts, various methods of

removing ballast substances are used.

Purification of aqueous extracts. When extracting plant material with water or weak aqueous-alcoholic solutions (20-40 %-vimi), In addition to the active substances, ballast substances (such as mucus, starch, sugars, pectin and protein substances, polysaccharides) are also extracted, which must be removed before evaporation. Decomposing during storage, these impurities give the extracts an uncharacteristic odor and can have an undesirable effect on the BAS. The following methods are used to remove ballast substances from aqueous extracts:

1. The simplest of them is *settling* at 8-10 °C for two to three days with subsequent filtration.

2. Thermal denaturation. To remove proteins, aqueous extracts are boiled at 100 °C for 0.5—3 h, if the active ingredients allow it. In this case, most of the protein substances coagulate and exfoliate, the liquid is then settled, filtered. For their more complete precipitation, the primary extract is evaporated to 1/2-1/4 volume, settled for one day and filtered or centrifuged, after which it is evaporated to readiness. Boiling, in addition, leads to hydrolysis of polysaccharides, which clarifies the solution.

3. Adsorption. For intensification process advocacy use illuminators, such as suspension talc (2%), kaolin (5%), bentonite, cellulose powder and others that adsorb suspended particles, pigments, resins on their surface. The lumps enlarged in this way are faster settle.

WITH this purpose also use activated coal, but enough limited — It adsorbs alkaloids, glycosides, pigments and other active substances .

4. Dehydration. Slimes, pectin substances, squirrels and others Navy can be precipitated from the solution using alcohol, i.e., to carry out the actual alcohol purification. When adding a strong (95—96 %) alcohol, dehydration of the VMS molecules or colloid micelles and their precipitation occurs. Alcohol is added: a) directly to the primary extract, two to three times the volume of 96% alcohol (this depends on the amount of extract, the concentration of ballast substances and their properties); b) the extract is evaporated to 1/2 the volume in relation to the mass of the starting raw material, and then a double volume is added volume alcohol on in

relation to to extract, leave on 5—6 days at a temperature of 10 ° C. After settling, the extract is filtered and evaporated.

Ethanol, methanol, acetone cause the destruction of the hydration shell around the protein molecule, which contributes to the stability of the protein and prevents its precipitation. If water molecules are removed from protein molecules, they will begin to stick together, forming larger particles that settle in the form of a precipitate.

1. ***Salting out*** — precipitation of proteins and carbohydrates from extracts due to dehydration when salts are added.

2. ***Precipitation with heavy metal salts .*** To remove heavy metal salts from exhausts, solutions heavy metals (lead acetate, cuprum hydroxide, etc.), which form insoluble compounds with proteins.

3. ***Creation of an isoelectric point*** . Amino acids that make up proteins, due to the presence of carboxyl and amine groups, have amphoteric properties. Isoelectric point — The pH value of the medium at which an amino acid is neutral. At the isoelectric point, protein molecules are generally least soluble and prone to association.

4. ***Fermentation.*** To remove polysaccharides, enzymes are sometimes added to the extract, which catalyze the process of hydrolysis along acetal bonds to mono- and oligosaccharides, the content of which is permissible in extracts.

5. ***Dialysis and electrodialysis .*** To separate BAS from ballast VMS, the difference in their sizes is used. Proteins and other VMS do not penetrate through the pores of a semipermeable membrane, which is what the method is based on. dialysis and electrodialysis.

Purification of alcohol extracts. Alcohol extracts from plant material, as a rule, contain resinous substances, pigments - anthocyanins, carotenes, chlorophyll, flavones and other ballast substances (wax, sterols, cerine, fats, etc.). To remove them, one extractant is replaced by another. To do this, first the alcohol is distilled off at normal pressure, and then an equal volume of hot water or aqueous suspensions of talc are added to the residue. (2 %), kaolin (3 %) or another illuminator. Thoroughly stir and after settling, filtration or centrifugation, the solvent is distilled off. Distillation is carried out at a reduced temperature in a vacuum. Water in this case is

added in order to further reduce the alcohol concentration, and thus reduce the solubility of resins, fats, etc. Talc, kaolin, bentonite well adsorb droplets of resin that have separated from the solution, make them heavier and thereby contribute to faster clarification of the solution . Suspended particles are removed by filtration and centrifugation in settling or filtering centrifuges.

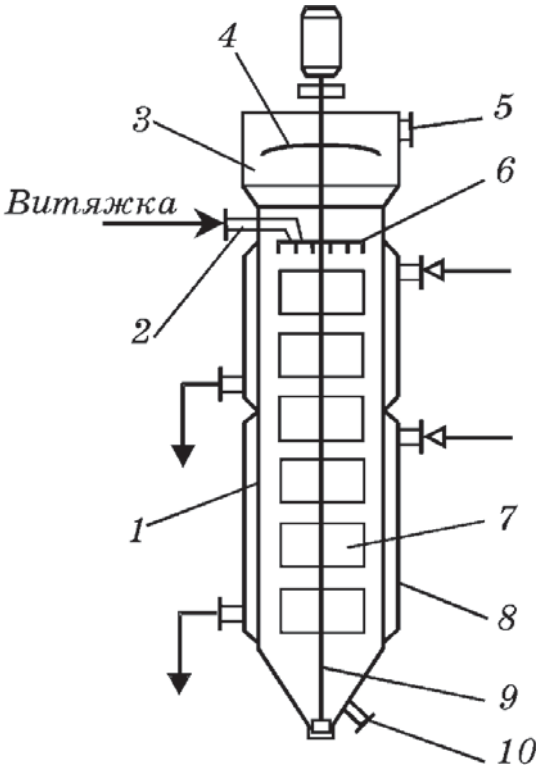
Purification of chloroform extracts. For such extracts (extractant chloroform, tetrachloromethane), the extractant replacement method is also used, for example non-polar on polar. At this to steamed To the extract (to half the volume relative to the mass of the starting material), water is added in an amount equal to the mass of the raw material. Chlorophyll and resinous substances soluble in chloroform (tetrachloromethane) precipitate, since they do not dissolve in water. The extract is settled, filtered and subjected to further processing.

To remove resins and fatty impurities from the extract, the organic extractant is completely distilled off and replaced with water. The ABA that needs to be isolated (alkaloids, glycosides) is transferred to the water, and the resins as a by-product are separated by filtration.

Condensation of extracts. The purified extracts are evaporated under vacuum at a temperature of 50-60 °C and a vacuum of 80-87 kPa (600-650 mm Hg) to the required consistency. When condensing alcohol extracts or extracts after alcohol purification, alcohol is first distilled off without turning on the vacuum. The equipment used for evaporation of extracts in pharmaceutical production has its own characteristics. This is explained by the fact that the extracts contain BAS, which during evaporation can precipitate on the walls of steam-heated evaporators and lose their activity due to the high temperature of the walls. Therefore, devices in which there is no circulation of the extract or it is weak (as in an evaporation cube) are used extremely rarely in pharmaceutical production.

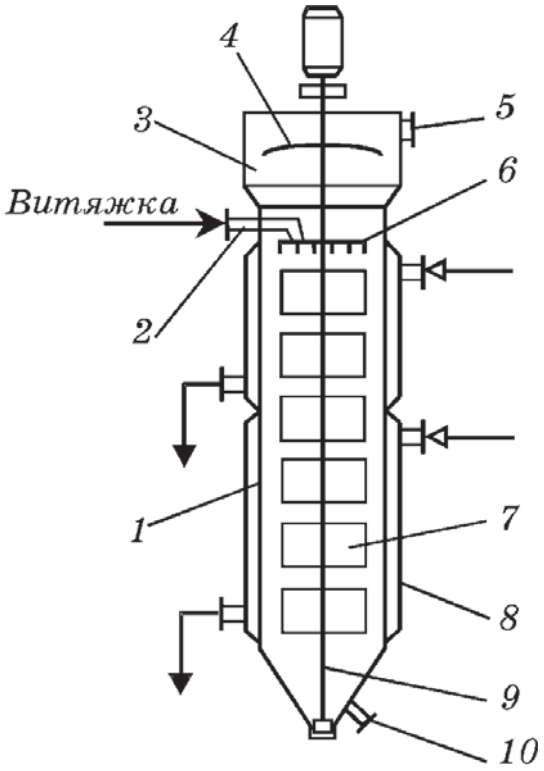
Various evaporation schemes are used to concentrate extracts from LRS. installations periodic and continuous actions. Choice type The installation is determined by the scale of production and the intended purpose. The most widely used at this stage (as reliable in operation, highly efficient, easy to maintain and low energy consumption) are such designs as direct-flow rotary, circulating vacuum

evaporators and foam evaporators.



Rotary straight-flow apparatus.

Has a vertical body *1* with steam jacket *8.* Along the center of the housing is a rotor in the form of a vertical rotating shaft *9* with scrapers hinged to it. *7.* The extract to be evaporated is fed into the upper part of the rotary evaporator housing through a fitting *2* into the cavity of the distribution ring *6* , from which it flows in the form of numerous streams that wet the rotating scrapers. From the scrapers, the exhaust is sprayed onto the cylindrical surface of the heated housing in the form of a thin film from which the solvent evaporates. The exhaust, which thickens, is removed by the scrapers and, under the action of gravity, flows into the lower conical chamber, from where it is continuously discharged through the fitting *10* . In the separation chamber *3* , liquid droplets are separated from the secondary vapor by means of a drop deflector *4* . The secondary vapor formed, without droplets of the captured liquid, enters the upper part of the separation chamber *3* and through the pipe *5* is taken to the condenser. The rotary evaporator can operate both under atmospheric pressure and under vacuum.



Scheme rotary straight-flow apparatus

The circulating vacuum evaporator of the company "Simax" (Fig. 7.15) can operate both under vacuum and under atmospheric pressure. Usually the apparatus is made of heat-resistant borosilicate glass, which allows you to control the process, including the circulation of the evaporated extract, the condensation of the extractant vapor, the amount of evaporated extract and the volume of condensed extractant.

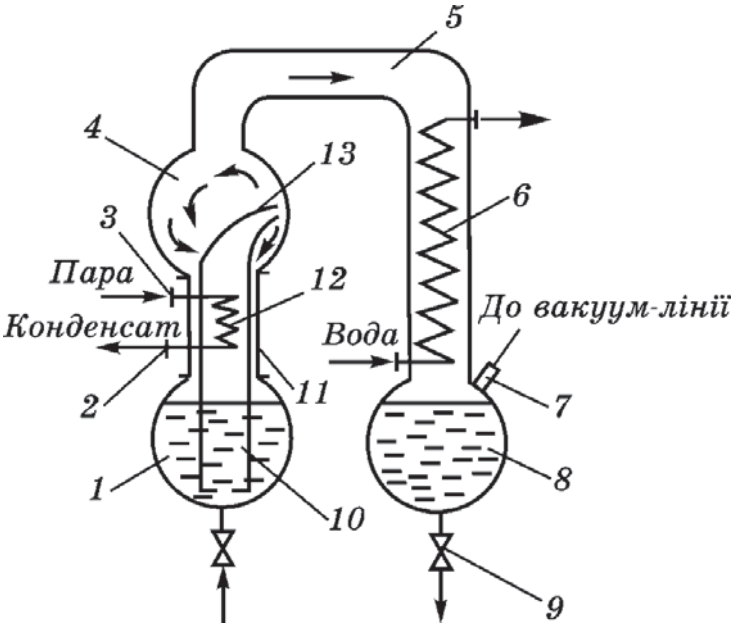


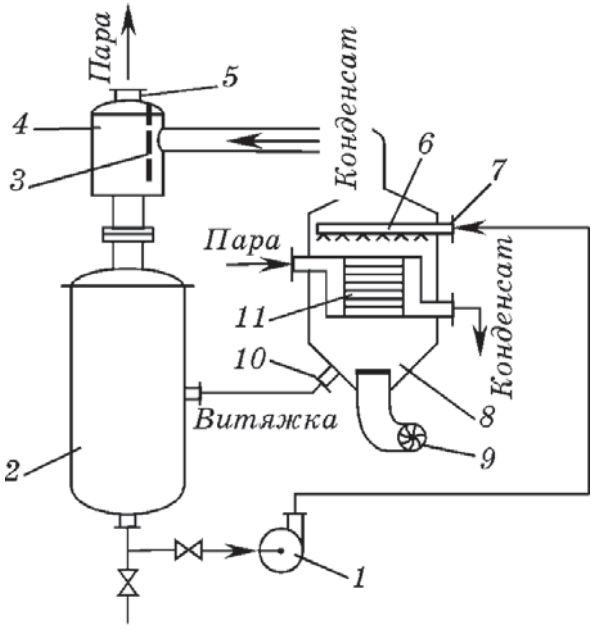
Рис. 7.15. Scheme vacuum evaporator apparatus of the company "Simax"

Into the receiving flask *1* using the vacuum created through the fitting *7* , tighten the extract to be evaporated. The extract level in the flask *1* should reach the upper edge of the heater coils *12* . Heating steam is supplied to the heater through the pipe *3* and the condensate formed is drained through the pipe *2*. In the heater zone, the hood boils quickly and in in the form of a vapor-liquid mixture is discharged through the trunk *13* into the expansion flask *4* , where it circulates intensively, forming a large evaporation surface. The vapors that are formed rise up and are discharged through a wide pipe *5* in the refrigerator-condenser *6* , where they are cooled with cold water. The condensed extractant vapors are collected in the receiving flask *8* and are discharged through the fitting *9* after removing the vacuum in the unit. The extract that did not evaporate from the flask *4* flows through the gap between the circulation pipe *10* with a trunk *13* and the king *11* in a flask *1* , from which it rises again through pipe *10* , boils from the heater *12* and is thrown into flask *4* .

This circulation of the evaporated extract continues until a given final volume of extract is obtained, after which the concentrated extract and pure extractant are drained, and a new portion of extract is loaded into the installation.

The foam evaporator is used for evaporation of water extracts, since it does not provide for condensation of secondary steam. The installation consists of a

working tank *2* , into which the output exhaust is loaded. Exhaust by pump *1* through the pipe *7* is fed to the distribution device *6* , from which it flows in the form of numerous jets onto horizontal tubes *11* evaporation chambers *8* , heated from the inside by steam. The extract boils, foams strongly, creating a large evaporation surface. To accelerate the evaporation process through the boiling extract from below using a fan *9,* air is pumped in, which, taking moisture from the foaming exhaust, enters the separator *4* .



Scheme foam evaporator

Here, hitting the partition *3* , the air is freed from the exhaust droplets and, already enriched with moisture, is released into the atmosphere through the pipe *5.* The exhaust droplets that have separated from the separator *4* merge into the working vessel. *2.* The exhaust is circulated in the installation to the required final concentration. The exhaust drops that have passed between the tubes are directed from the evaporation chamber 8 through the pipe *10* into the working tank. *2.* The device is highly efficient, low energy consumption, easy to operate. It is widely used for evaporation of water extracts in the production of plantaglucid.

When condensing water extracts, it is also advisable to use multi-casing vacuum evaporation units with multiple use of the heat of the heating steam, since this stage is the most energy-intensive and requires a large amount of heat.

An alternative and economical method of concentrating solutions is membrane technology. The process is carried out through filtering osmotic membranes under pressure, without the action of high temperatures and mechanical mixing devices, maximally preserving the BAS from destruction. By using polymer membranes with different hole diameters, it is possible to achieve separation of extractive substances into fractions according to particle size.

Extraction of extracts. Various types of drying devices are used to dry plant extracts, which are classified by *design features, operating mode, volume in the drying chamber, nature of the drying agent, direction of flows, etc.*

Drying in phytochemical production *by the method of drying the material* is carried out:

- when heating the materials to be dried with a heat carrier through an impermeable wall that conducts heat (*contact drying*);
- by direct contact of the materials to be dried with a hot gaseous coolant, such as air (*convective or air drying);*
- by summary or creation heat infrared rays, high-frequency currents, from a frozen state, in a microwave field, etc. (*special methods).*

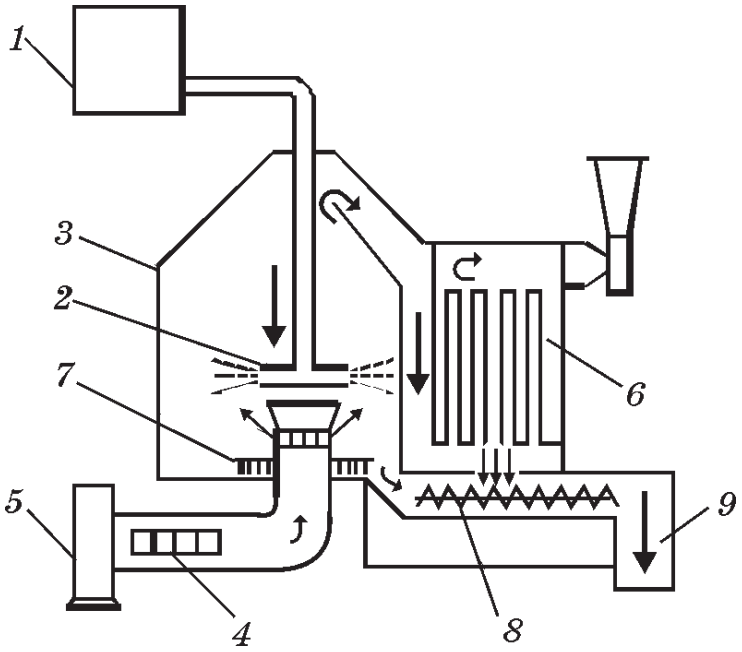
To summarize, for drying wet materials, various methods can now be used, differing in the nature of the heat agents, the principles of their supply and the structural details of the dryers. The choice of the type of drying unit is determined by the properties of the dried material, the scale of production and the intended purpose.

Drying cleaned hoods maybe to be held by two schemes:

1) without compression liquid hoods;
2) through stage compression with further drying.

In the first case, the drying of the extracts can be carried out in ***spray dryers*** . The liquid extract from the tank *1 is drawn* by means of a disk rotating at a frequency of (5-10)•10 ^{3} rpm, or a mechanical nozzle. *2* is sprayed in the form of the smallest droplets with a diameter of 10-50 microns in a drying chamber *3.* From below, opposite the settling droplets, by with help fan *5* heat up air with temperature 150-

200 °C. The air is heated in the radiator *4.* The smallest drops of liquid, blown from all sides by hot air, are drawn from 0.01 to 0.04 with absorb moisture and settle in the form of powder particles at the bottom of the chamber. At the same time, significant heating of the material does not occur due to the large specific evaporation surface, i.e. all the heat of the air goes to changing the aggregate state of moisture from the droplets of the extract. The temperature of the dried material does not exceed 50-60 ° C. Dry powder is removed from the chamber using



Scheme spraying dryers uninterrupted actions

special devices *7* , fed to the screw *8* and dumps it in the bin *9.* The exhausted air with a significant amount (almost 20%) of dried material in the form of dust enters the bag filter system *6* , is cleaned and removed. Fabric bag filters periodically shake the powder onto the screw. The obtained material does not require further grinding and has good solubility. Since the drying process is carried out in a fraction of a second and the material does not overheat, it is recommended for thermolabile BAS.

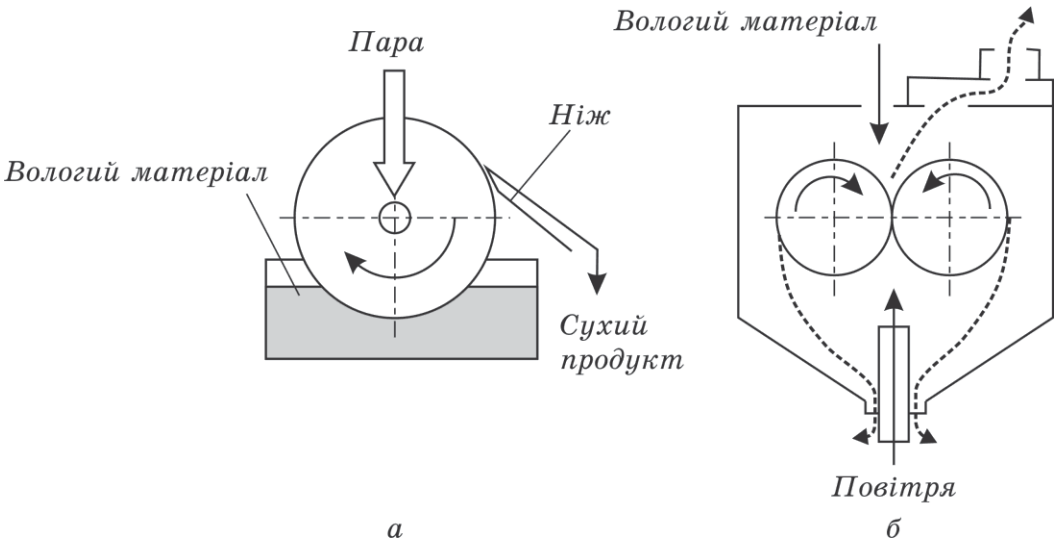
In recent years, more advanced designs of spray dryers have been developed, which are distinguished by a conical bottom of the drying chamber, where the dried material is collected. Disc spray nozzles with a diameter of 100-400 mm have special relief and are turning around with frequency up to 40 000 rpm It contributes formation microdroplets, which are drying out even faster. For dispersion liquids

are used also injectors, which are powered by compressed air. The use of such nozzles simplifies the spraying of the material, but requires the absence of any mechanical impurities in the exhaust. The coolant (air or nitrogen) can also be supplied from above the spraying device using a direct-flow type. This method is less intensive compared to the counter-flow type, but contributes to a milder drying regime.

Spray dryers are quite complex and dangerous to use, as they can create an explosive situation during operation. Therefore, efforts are being made to automate their operation and use inert gases as drying agents.

According to the first scheme, drying can also be carried out in ***drum (roller) vacuum dryers.*** In this case, the extract is slightly evaporated (so that a sufficient layer of dry extract forms on the rollers after drying) and fed onto rollers that are heated from the middle and rotate towards each other. The crust of dry extract removed from the rollers is then ground in a mill.

Roller dryers consist of one or two drums (rollers) that rotate slowly in a trough-shaped vessel filled with the material to be dried. Inside, these drums are hollow and heated by steam, and the rollers are only partially immersed in the material. During rotation, the evaporated extract adheres to the hot polished surface of the rollers, is leveled in a thin layer and dried during its rotation. Dry material 0.1-1.0 mm thick is cut with a knife and removed from the dryer by means of a screw conveyor (or other means). The evaporation capacity in vacuum roller dryers is significantly higher than in shelf dryers. The industry produces dryers in hermetic cases in which it is possible to create a vacuum and dry thermolabile products at low temperatures.



Scheme single-cylinder (*a*) and two-roller (*b*) dryers

Drying from the liquid state can also be carried out in ***sublimation (lyophilic, molecular) dryers.*** The extract is frozen, placed in a sublimation chamber, which creates a deep vacuum. Under such conditions, moisture from the frozen material is sublimated, 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 BAS in an unchanged form. When drying by sublimation during the cooling and freezing period (the first period), 5-20 % moisture, during direct drying (second period) — 75—80 % and during thermal (vacuum drying) 5-15 is removed % moisture. The duration of freeze-drying varies from 8 to 20 hours depending on the selected mode. Leading manufacturers of Germany, Italy, Japan, the USA, China and other countries have created the latest designs of freeze-dryers, which are equipped with automatic product loading and unloading systems, a liquid nitrogen cooling system, a CIP system, a device for determining the eutectic point, an automatic system for controlling technological parameters, etc.

According to the second technology, drying is carried out in ***vacuum drying cabinets*** . Condensed hood in in the form of thin layer (0.5-0.8 cm) is placed on letters and spend drying at temperature 50—60 °C and pressure 80— 87 kPa (600-650 mm. mercury art.), that is, under vacuum. The result is a very loose, light mass in the

form of cakes, which are ground in a mill. In shelf dryers, heat exchange is carried out through the extract layer, so the dried material is exposed to high temperature for a long time and is prone to overheating in the lower layers, which affects the quality of dry extracts. The disadvantages of such dryers also include the need for sealing the structure and low productivity.

vibration multifunctional devices is promising , allowing the following technological processes to be carried out in a single working volume: dissolution, crystallization, evaporation, filtration, purification of extracts from solvent residues, conductive drying and grinding in a vibrating fluidized bed. The main advantages of these devices are: the absence of a gas coolant and mixing devices in the working volume, minimal product losses due to the complete tightness of the working volume, reduction of the duration of the technological process, environmental friendliness, low energy consumption.

Standardization. Standardization of thick and dry extracts is carried out according to organoleptic indicators, quantitative content of active substances, heavy metals, dry residue and microbiological purity are determined. Mass loss during drying is also determined, in thick extracts this indicator must draw up no more 25—30 %; in dry — no more 5 %. If specified in individual articles, the residual content of the extractant used to prepare the extract is determined . If the extract is used as a finished product, the dosage accuracy is additionally determined.

Storage. Thick extracts are stored in a hermetically sealed container that does not allow drying out, in a place protected from light. Dry extracts, which are characterized by high hygroscopicity, should be stored in shallow, wide-mouthed jars, hermetically sealed, with a capacity of no more than 100 g, in a place protected from light.

Extracts-concentrates

Concentrated extracts , or ***extracts for the preparation of infusions and decoctions,*** are standardized liquid and dry extracts from LRS, which are used for the rapid preparation of aqueous extracts in pharmacy practice. **Liquid concentrates are distinguished** , which are prepared in a ratio of 1:2, and **dry** concentrates in a ratio

of 1:1. This means that from one part by mass of plant material, two parts by volume of liquid concentrate or one part by mass of dry concentrate are obtained. To obtain extracts, low-concentration ethanol (from 20 to 40%) is used as an extractant. This is explained by the desire to bring the concentrates closer in terms of the composition of active substances to pharmacy water extracts. The upper limit of ethanol concentration is used for preserving the extracts.

The technology for obtaining liquid concentrates provides for the following: The most basic stages, as for the production of liquid extracts, are *obtaining an extract from a medicinal plant extract, its purification* . To obtain thicker extracts, methods are used in which evaporation does not occur (the amount of the final product will be higher in this case). Purification of extracts is reduced to settling and filtering the settled extract. Liquid concentrates are standardized according to the same indicators as liquid extracts (content of active substances, content of extractive substances (dry residue), alcohol content or density, content of heavy metals).

The industry produces liquid extract concentrates (1: 2) mountain ash, thermopsis, valerian, marshmallow, dog nettle, etc.

Dry concentrates differ from ordinary dry extracts in that the content of active substances in them is equal to that in the starting raw material, i.e. 1: 1 (only for dry lily of the valley concentrate it equals half the amount — 1 : 2). Therefore, for the preparation of infusions and decoctions from dry concentrates, instead of the amount of medicinal raw material specified in the recipe, an equal amount of dry concentrate is taken by weight and dissolved in the calculated volume of water. Dry concentrates (or "concentrated dry infusions and decoctions") are better known in foreign pharmaceutical literature under the name "abstracts". One part of the abstract may correspond to one (1:1) or 0.5 (1:2) part of the initial medicinal plant raw material.

Dry concentrates are obtained in the same way as dry extracts. Extraction of extracts leads to complete depletion of the raw material, using most often highly efficient methods (for root Althea — maceration). For The purification of the extracts involves settling and subsequent filtration. Drying can be carried out through a thickening stage. In this case, all types of apparatus are used, designed for evaporation of extracts. The subsequent drying process takes place in vacuum roller dryers or

vacuum drying cabinets at 50-60 °C. If drying is carried out without a thickening stage, spray and freeze dryers are used.

Fillers (dextrin, lactose or mixtures thereof) are introduced during grinding of the dried extract. Standardization of dry concentrates is carried out by moisture and heavy metal content.

Dry concentrates are produced (1 : 1) thermopsis, adenium, foxglove, root marshmallows and some others, which are included to warehouse different drugs.

Combined herbal remedies

Modern ***multicomponent herbal preparations*** — These are various combinations of extracts from LRS and other medicinal substances. According to some researchers, such preparations already make up almost 20% of the total nomenclature of extraction agents. For example, liquid extracts (1 : 1) from chamomile flowers, flowers marigolds, herbs yarrow in proportional 2 : 1 : 1 at 40 % alcohol under the name "Rotokan". The drug "Cardiovalen" contains liquid extract of yarrow, concentrated adonizide, tincture of valerian from fresh roots and rhizomes, liquid extract of hawthorn, camphor, sodium bromide, ethyl alcohol 95%, chlorobutanol hydrate. The technology of combined herbal preparations is reduced to mixing extracts and dissolving the components of the composition, and the methods and equipment for obtaining the extraction components do not differ from those already considered. Due to the multicomponent nature of such herbal preparations, the range of their use is much wider compared to "classical" extraction preparations.

Oil extracts

Oil extracts , or ***medicinal oils*** (*Olea medicata*), are extracts from LRS obtained using vegetable oils or mineral oils, therefore the complex of substances extracted is of a lipophilic nature. They have been widely used for centuries (oil of yarrow, oil of dope, etc.). etc.). Currently, medical practice uses oil extracts from St. John's wort, eucalyptus leaves (chlorophyllipt), rosehip fruit pulp oil (*Extractum Rosae oleosum*), carotolin (*Carotolinum*), rosehip seed oil (*Oleum Rosae*), sea buckthorn oil (*Oleum Hippophae*), chokeberry oil (from chokeberry fruits), etc.

obtained according to two main schemes :

Refined, deodorized and heated to 60-70°C is used as an extractant. °C vegetable oil (sunflower, olive, sesame), which finely ground raw materials are infused (macerated), obtaining an oil extract.

2. Volatile organic solvents (methylene chloride, dichloroethane, chloroform, ethyl ether, 70% ethanol or liquefied gases) are used as extractants. — carbon dioxide, chlorofluorocarbons) and obtain a concentrate of lipophilic complexes, which is blended (adjusted to standard parameters) with vegetable oil.

When extracting with oils, the technological process consists of obtaining extracts (by maceration or countercurrent method in a battery of percolators), their purification (mainly by filtration through filter presses), packaging, labeling, and packaging of the finished product.

Extraction with volatile solvents involves extraction of raw materials (by circulation, countercurrent method, or extraction with liquefied gases), removal of the extractant (obtaining a concentrate), blending, filling, labeling, and packaging of the product.

In circulating extraction, the extractant is distilled from the concentrate under vacuum, sometimes water is added to remove the extractant residues and reduce the distillation temperature. During extraction with liquefied gases, they are removed from the concentrate by reducing the pressure in the evaporator, as a result, a concentrate is obtained in the evaporator, which is subjected to blending with oil. In the production of rosehip oil, blending is not carried out.

Standardization of oil extracts is carried out by the content of active substances, acid number (content of free acids), dosage accuracy. If specified in individual articles, the residual content of the extractant used to prepare the extract is determined.

Storage. Oily extracts keep in hermetically clogged dark glass containers, in a cool, dark place.

Materials for activating higher education students during lectures: questions, situational tasks, etc.:

Question:

1. What is the physical significance of the extraction process?

2. What are the features of the extraction of dried and fresh medicinal plant materials?

3. What factors affect the extraction process?

General material and methodological support for the lecture:

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

Questions for self-control:

1. What equipment is used to prepare tinctures and extracts?

2. What are the methods for standardizing tinctures and liquid extracts?

3. What are the methods of purifying liquid and thick extracts?

4. What are the stages in the process of making oil extracts?

List of sources used:

1. A textbook for independent work of students of the Faculty of Pharmacy for the licensing exam "Step 2. Pharmacy" / V.Yu. Anisimov, O.I. Belyaeva, G.G. Vidavska, V.O. Helmboldt, A.V. Zamkova, I.V. Lytvynchuk, A.V. Nikitin, B.V. Prystupa, I.B. Petkova, Ya.V. Rozhkovsky, S.B. Strechen, L.M. Unguryan, N.S. Fizor Odessa: Odessa National Medical University. 2020. - 240 p.

Access mode 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 of higher. educational. pharmaceutical institutions (pharmac. faculties) / E.V. Gladukh, O.A. Ruban, I.V. Saiko and others. - Kh.: NPhU: Original, 2016. - 632p. : Named after. - (Series "National textbook")

2. Workshop on industrial technology of medicines, specialty "Pharmacy" / Edited by Ruban O.A. - Kh .: National University of Physics and Technology, 2015. - 374 p.

3. INDUSTRIAL technology of medicines : a teaching aid for independent work of students / O. A. Ruban , V. D. Rybachuk , L. M. Khokhlova etc. – KH.: NATIONAL UNIVERSITY OF PHYSICS AND TECHNOLOGY, 2015. – 120 p.

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- State Pharmacopoeia Ukraine / State enterprise « Ukrainian scientific officinal center qualities medical " means " - 2nd ed . – Kharkiv : State enterprise « Ukrainian scientific officinal center qualities medical means ”, 2015. – T. 1. – 1128 p .

- State Pharmacopoeia Ukraine / State enterprise « Ukrainian scientific officinal center qualities medical " means " - 2nd ed . – Kharkiv : State enterprise « Ukrainian scientific officinal center qualities medical means ", 2014. – T. 2. – 724 p .
- State Pharmacopoeia Ukraine / State enterprise « Ukrainian scientific officinal center qualities medical " means " - 2nd ed . – Kharkiv : State enterprise « Ukrainian scientific officinal center qualities medical means ", 2015. – T. 3. – 732 p .
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Lecture No. 8

Topic: Production drugs under pressure. Characteristics, structure of aerosol packaging. Propellants.

Relevance of the topic: Drug technology (industrial drug technology) is one of the fundamental technological sciences. It consists of several key aspects that are important for modern medicine and patients: Efficacy and safety - Modern technologies allow the production of drugs with high efficiency and safety for patients. Accurate dosing, quality control and the absence of impurities make drugs more effective and safe. Innovations in the medical field: 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 treatment. Minimization of side effects: Technologies allow the development of drug formulas that minimize side effects and negative effects on the body. This provides more comfortable and safe treatment for patients. Fast production and delivery process: The use of modern technologies allows the acceleration of the production process of drugs, which is especially important in a rapidly changing medical environment, such as the spread of diseases or epidemics. Personalized

treatment: Technologies allow for the development of medicines that take into account the individual characteristics of the patient, leading to a personalized approach to treatment and increasing its effectiveness. Cost-effectiveness and accessibility Improved manufacturing technologies can reduce production costs, making medicines more accessible to a wider range of patients, ensuring cost-effectiveness in healthcare.

Thus, the use of modern pharmaceutical manufacturing technologies is an important factor in improving the effectiveness of treatment, patient safety, and the overall state of public health.

Objective: to get acquainted with the main stages of industrial manufacturing of dosage forms and the discipline "Drug Technology", to characterize and classify aerosols.

Basic concepts:

Aerosols (Greek: *aer* — air + Latin *solution* — solution) — dispersed systems consisting of a gaseous medium in which solid or liquid particles are suspended.

Pharmaceutical aerosols — This is a dosage form consisting of a cylinder, a valve-spray system, and contents of various consistencies, capable of being expelled from the cylinder using a propellant.

Medical aerosols — These are aerosols of one or more medicinal products in the form of solid or liquid particles, obtained using special stationary installations and intended mainly for inhalation administration.

Metal containers are most often made of aluminum, the inner surface of which is coated with protective varnishes. For this purpose, various polymeric materials, anti-corrosion varnishes or copolymers are used.

Glass containers are made of neutral glass of the NS-1 and NS-2 grades. When manufacturing glass cylinders, two main conditions must be taken into account: the containers must withstand excessive internal pressure created by the propellant (not less than 2 MPa) and be resistant to impact.

Lecture plan and organizational structure:

	The main stages of the lecture and their content.	**Goals in levels of abstraction.**	**Type of lecture, lecture equipment.**	**Time allocation.**
	2	**3**	**4**	**5**
	Preparatory stage Defining learning goals. Providing positive motivation. *Main stage* Presentation of lecture material. Plan: 1. Characteristics and classification of aerosols. 2. Structure of aerosol packaging. 3. Valve-spray devices. 4. Propellants used in aerosol packaging. 5. Types of aerosol systems.	I I AND	Combined lecture Slides	1% 2%

	Final stage Lecture summary, general conclusions. The lecturer's answers to possible questions. Tasks for student self-study.		Bibliography, questions, assignments.	90% 2% 3% 2%

Structural and logical diagram of the lecture content

1. Characteristics and classification of aerosols.
2. Characteristics of pharmaceutical aerosols.
3. Medical aerosols.
4. Structure of aerosol packaging.

4.1 Metal containers

4.2 Three-piece cylinders

4.3 Two-piece cylinders

4.4 Monoblock aluminum cylinders

4.5 Glass containers

5. Valve-spray devices.

5.1 Principle of operation of the aerosol valve.

6. Propellants used in aerosol packaging.

6.1 Main groups of propellants.

6.2 Liquefied gas.

6.3 The oppressed (difficult to liquefy) gas.

6.4 Volatile organic solvents.

7. Types of aerosol systems.

7.1 Aerosol suspensions.

Content of the lecture material (lecture text)

GENERAL CHARACTERISTICS OF TEAK I CLASSIFICATION

AER O Z O L IB

Aerosols (Greek: *aer* — air + Latin *solution* — solution) — dispersed systems consisting of a gaseous medium in which solid or liquid particles are suspended. They are widely distributed in nature (fogs, clouds, soil and volcanic smoke, plant dust, etc.), and are also formed in the process of human production activities when obtaining, processing and using various materials.

The term " *aerosol* " refers to all aerodispersed systems, if we consider them from the point of view of physical chemistry. From a medical point of view, this is a method of applying drugs, the effect of which is manifested in sprayed disperse systems. And in pharmacy, an aerosol is a drug contained in a sealed cylinder under pressure.

The first patents for aerosol devices were issued in Norway and the United States in the 1930s. However, the real development of aerosol production dates back to 1941, when, during World War II, the United States patented pressurized containers, the so-called "god bombs", containing mixtures of hydrogen fluoride, hydrogen chloride and insecticides. From that time on, the rapid growth of industrial aerosol production began.

Nowadays, the principle of aerosol packaging is used in many industries to spray liquids, powders, foams, pastes, and creams. A significant share of these products is occupied by sanitary and hygienic preparations, deodorants, cosmetics,

repellents, and veterinary preparations.

Industrial production of pharmaceutical aerosols was first organized in Ukraine at the experimental plant of the National Center for the Study of Medical Aerosols (Kharkiv), when in 1969 the first industrial batch of the drug "Ingalipt" was released. Then in Ukraine the production of aerosols was mastered at various plants. The main developer of drugs of this group was the laboratory of medical aerosols of the National Center for the Study of Medical Aerosols (founder - Professor G. WITH. Bashura), in which almost 20 aerosol preparations were developed ("Livian", "Kameton", "Camphomen", "Gipozol", etc.) and the foundations for the further development of this direction were laid.

The widespread popularity of the use of pressurized drugs in medical practice is determined by the following advantages:

- the use of aerosols ensures convenience, aesthetics, hygiene, speed and effectiveness of treatment;
- Aerosols are characterized by high efficiency of action with relatively low consumption of medicinal substances, sometimes the effect occurs as quickly as with intravenous administration;
- the small size of the particles determines their high degree of penetration into folds, pockets, cavities and other hard-to-reach places on the skin, mucous membranes and in the respiratory tract;
- software accurate dosage medicines by with help dosing devices;
- The aerosol can is hermetically sealed, which prevents contamination of the medicine. drug from the outside, he protects preparation from drying out, actions light and moisture;
- Pressurized medicines are sterile throughout their shelf life.

Aerosols have some disadvantages: the possibility of the cylinder exploding upon impact or exposure to high temperature; contamination of the room air with drugs and propellant during manipulation; relatively high cost. However, despite the disadvantages, the use of aerosols is considered a progressive phenomenon in medical practice.

According to the State Federal Agency for the Protection of the Environment, ***aerosol preparations*** — These are medicines that are in special containers under gas pressure and contain one or more active substances and are solutions, emulsions or suspensions intended for topical application to the skin, mucous membranes or inhalation. These medicines, when leaving the container after pressing the valve-spraying system, are *an aerosol* (dispersion of solid or liquid particles in a gas, the size of which depends on the purpose of the medicine), *liquids, soft foams or films* . The pressure required for the medicine to exit the aerosol container is provided by the appropriate propellants.

The starting materials for the preparation of this group of drugs are various active and auxiliary substances, which allow them to be dispensed from the container in various forms according to their intended use (on the skin, inside, rectally, vaginally, etc.).

Medical aerosols are divided on *pharmaceutical* and *medical* .

Pharmaceutical aerosols — This is a dosage form consisting of a cylinder, a valve-spraying system and contents of various consistencies, capable of being expelled from the cylinder with the help of a propellant. The composition of the aerosol includes medicinal substances, excipients and one or more propellants. Aerosol preparations are *metered* and *non-metered* .

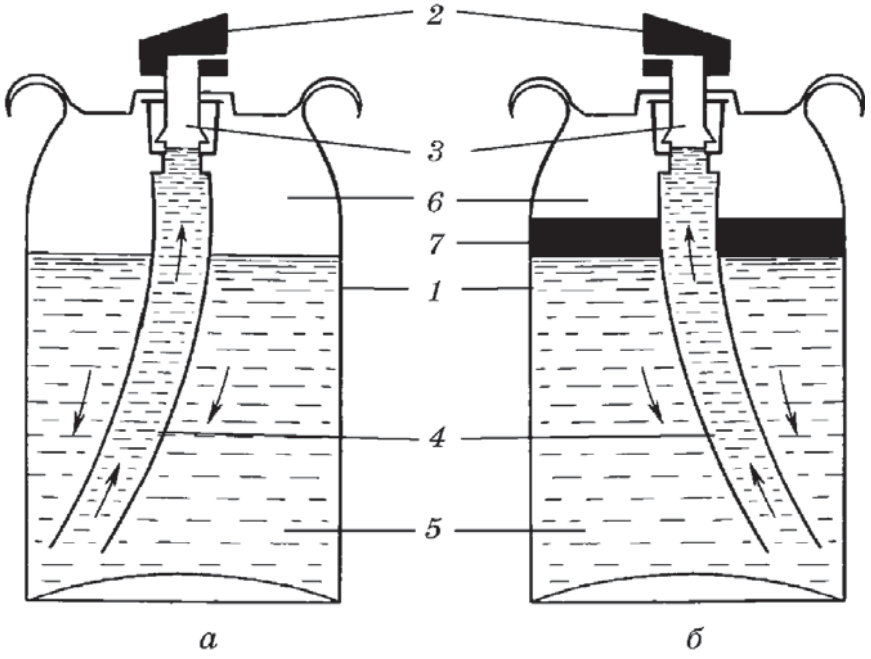
By by appointment pharmaceutical aerosols distribute on *inga-*

lation , *otolaryngological* (nasal and ear), *dermatological* , *dental* , *proctological* , *gynecological* , *ophthalmological* , *special purpose* (diagnostic, dressing, hemostatic, etc.).

Medical aerosols — These are aerosols of one or more medicinal products in the form of solid or liquid particles, obtained using special stationary installations and intended mainly for inhalation administration.

BUILDING AEROSOL PACKAGING

To convert medicinal substances into an aerosol state, devices operating under pressure and mounted in containers are used. The structure of aerosol packaging is shown in Fig. 13.1.



Puc. 13.1. Ingredients aerosol packaging:

a — two-phase system; *b* — three-phase system; *1* — cylinder; *2* — sprayer; *3* — valve; *4* — siphon tube; *5* — solution medical substances; *6*

— couples propellant; *7* — propellant

Aerosol packaging is hermetically sealed and consists of a cylinder (container), a valve-spray system, a medicinal product (concentrate) and a propellant. The contents of the cylinder are released through a siphon tube to the valve stem opening using a propellant.

Aerosol cylinders

Depending on the material from which the containers are made, they are divided into several groups: *metal, glass, plastic* and *combined* . Each type of cylinders has its own disadvantages and advantages. When using them, the indifference of the material, cost, availability of materials are mainly taken into account. for their manufacture, as well as the possibility of packaging certain products in them. The capacity of containers can vary: from 3 ml to 3 liters (except glass ones, the capacity of which is limited to 300 ml).

Metal containers are most often made of aluminum, the inner surface of which is covered with protective varnishes. For this purpose, various polymeric materials,

anti-corrosion varnishes or copolymers are used.

By design, metal cylinders are distinguished as monoblock, two-piece, and three-piece.

Three-piece cylinders appeared among the first and are now widely used. They consist of a tin body with a longitudinal belt or weld, a bottom and a lid made of tin, rolled to the body with a double seam with the use of a sealing compound for sealing. Cylinders with a weld are slightly more expensive, but have some advantages: high strength, possibility of manufacturing from black tin. Maximum capacity — 650 ml.

Two-piece cylinders stronger and more airtight than three-piece ones. The seamless body of such cylinders is made either from sheet metal by deep drawing or from a flat aluminum billet by impact extrusion. The maximum capacity of such cylinders is 900 ml.

Monoblock aluminum cylinders most suitable for aerosol packaging. The maximum capacity of such cylinders is 1360 ml, although there are cylinders with a capacity of 2040 ml. Aluminum has a number of positive properties: it has no smell, taste, is non-toxic, practically sterile, and resists corrosion. This allows it to be used as a material for packaging food products, chemicals, and pharmaceuticals . Advantages of a monoblock cylinder over two- and three-piece ones: seamless construction; high strength; high corrosion resistance; high weather resistance; ease of packaging; the possibility of manufacturing cylinders with a large capacity; great possibilities for obtaining an aesthetic appearance. Monoblock aerosol cylinders are made of aluminum blanks (rondoles) from with an aluminum content of 99.5 % by cold pressing on special equipment.

Next stage — applying a layer of protective varnish (golden Epoxyphenol, pigmented Epoxyphenol and Mikoflex) to the inner surface of the cylinders, which is selected depending on the product that will be placed in the cylinders. A white primer is applied to the outer surface of the cylinders, after which They are ground and polished. Printing on the outer surface of the cylinders is carried out using the color lithography method, after which the outer surface of the cylinder is covered with a protective varnish, which can be glossy, matte or mixed. Neck formation — the final stage in the production of cylinders, which is carried out on special multi-spindle cone-forming machines. By combining various variants of the shoulder and neck, up

to 30 variants of the final appearance of the cylinders can be achieved. The design of the edge of the cylinder neck is possible in two variants - a shell or a shell with a chamfer. Most medicinal substances and many perfumery and cosmetic products cannot be placed in metal cylinders. More inert materials should be used for packaging these substances.

Glass containers are made of neutral glass of the NS-1 and NS-2 grades. When manufacturing glass cylinders, two main conditions must be taken into account: the containers must withstand excessive internal pressure created by the propellant (not less than 2 MPa) and be resistant to impact. Glass containers are covered on top with a protective polymer shell, the shells must be chemically and thermally resistant, have no internal glass stress, have a uniform thickness of the walls, bottom and a minimum of flat surfaces.

Glass cylinders are manufactured on automatic high-performance glass-forming machines. The process of their production involves double annealing in horizontal furnaces with a maximum temperature. 640-650 °C to eliminate or weaken residual internal glass stresses.

After molding, the glass cylinders are externally coated with a polyethylene or polyvinyl chloride protective coating.

Rice. 13.2. Varieties aerosol packaging

of plastic containers made of polypropylene, nylon, polyethylene, polyformaldehyde, delrin, and celcon are currently in use. and other substances. But, despite on whole a number of advantages, Plastics are permeable to some substances and propellants and do not retain their shape well under high internal pressure. Plastic aerosol cans are manufactured by vacuum forming (monoblock) or injection molding (two-piece) on molding or casting machines.

Valve-spray devices

The purpose of the aerosol, the condition of the container contents, its consistency, composition and route of administration require the use of different, in each case precisely defined types of valve-spray systems, which consist of a closing part (valve) and a sprayer or spray nozzle. Valve aerosol packaging has provide its tightness at a pressure in the cylinder of up to 2 MPa and evacuation of the drug from the container.

There are many designs of valve devices. They are classified *by the design of the locking mechanism, the principle of operation, the method of attachment to the cylinder, the method of evacuation of the contents, and the purpose* .

By ***principle actions*** their share on groups:

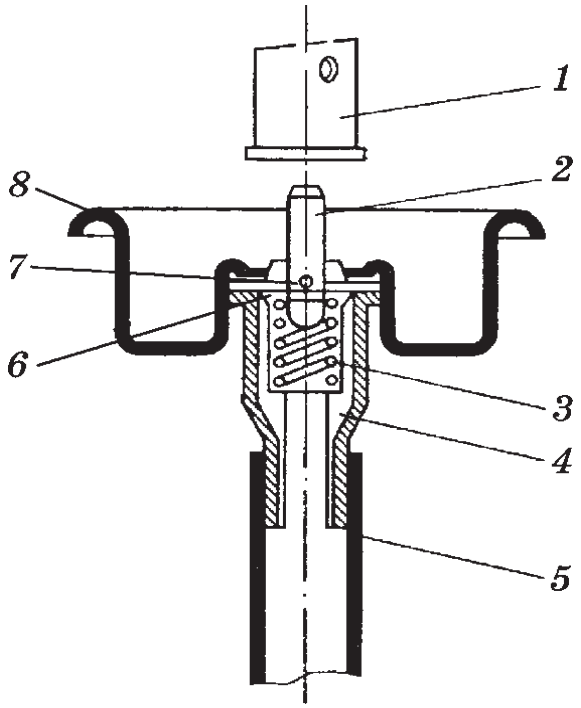
— spring-loaded, which operate when the spray head is pressed vertically downwards (spring-loaded, in turn, are divided into single-use and reusable; continuous and dosing);

— springless rockers that operate when you press on the spray head from the side;

— valves with screw valve.

By ***purpose,*** valves are classified as: standard for liquid products; for foams; viscous products; powders and suspensions; special purpose; dosing.

A standard valve-spray system for liquid products is shown



. Components of a spring valve:

1 — spray head (nozzle); *2* — stem; *3* — spring;

4 — valve body; *5* — intake siphon tube; *6* — outer gasket;

7 — hole in stock, What closing internal gasket;

8 — capsule (cup)

The principle of operation of the aerosol valve. The valve is actuated by pressing the spray head vertically downwards, with which the stem moves downwards, compressing the spring. The hole in the stem exits from under the rubber inner gasket into the cavity of the housing pocket, filled with product. The product is directed into this hole and through the cavity of the stem is directed into the sprayer. When the pressure on the sprayer is released, the spring lifts the stem up and the valve action stops.

valve capsule **(** ***cup*** **)** is used for assembly and subsequent fastening to the cylinder. Valve capsules are made of stainless steel. steel, aluminum stamping in 5—6 operations. To avoid corrosion and for decorative purposes, they are coated with a protective varnish or electroplating (chrome or nickel plating).

The valve body in spring-loaded aerosol valves serves as a seat for the spring and holds the valve parts together, except for the spray head. The siphon tube may be inserted into or slipped over the body. This part is usually made of nylon, nylon, or low-density polyethylene.

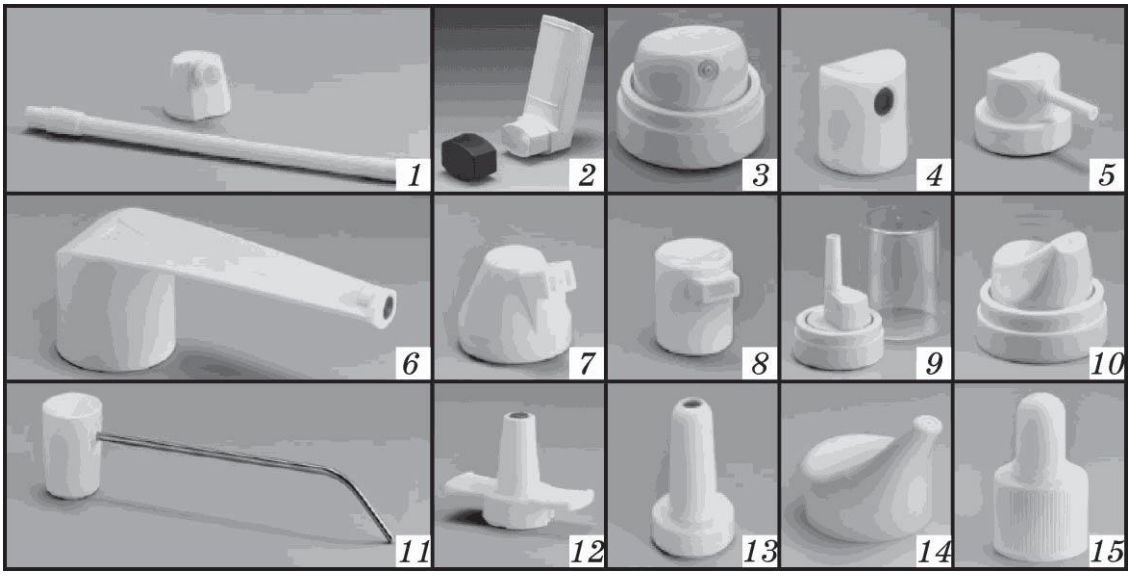
Stock **(** ***constipation*** **)** maybe have the most diverse construction, which

depends on the valve as a whole and the spray head in particular. The internal cavity of the stem serves to feed the product into the spray head. The stem is made of plastic (nylon, polyethylene) or metal.

Spring returns stock with sprayer in initial position, i.e. closes the valve. It is made of spring stainless steel wire.

Rubber gaskets (inner and outer): the inner one is intended for to seal the connection point of the stem with the hole in the valve body and at the same time serves as a cuff that closes or opens the valve. When the hole in the stem is above the cuff, the valve is closed; if the hole is moved lower by pressing on the spray head: the product enters the stem cavity and then into the spray head. The rubber gasket, with which the valve stem is closed, is of decisive importance in the valve, therefore the requirements for the accuracy of manufacturing of cuffs on all factories very tough. Friend (outer) rubber The gasket is placed where the valve body edge meets the neck of the canister. These gaskets are made of various polymer materials (neoprene, butyl, Viton) depending on the nature of the chemicals with which this part will come into contact during operation of the aerosol canister.

An integral part of the valve-spraying system are ***sprayers*** **(** ***nozzles*** **)** , designed to actuate the valve and spray the medication. They can be of different designs depending on the state of aggregation of the drug and the route of its administration. Sprayers must ensure: complete connection of the valve with the stem to avoid leakage of the medication when the stem is pressed; formation of an aerosol of the required dispersion; necessary routes of administration of the medication .



Types aerosol sprayers:

1 — gynecological appointment; *2* — for anti-asthmatic drugs;

3—5 —for liquid preparations; *6* — for oral use;

7—9 -for foamy drugs; *10* — for gels; *11* — dental purposes; *12-15* - for nasal preparations

To obtain aerosols with sufficiently large or small particle sizes, additional metal or plastic nozzles are inserted into the nebulizer for mechanical crushing of the drugs coming out of the packaging. By adjusting the calibrated holes within certain limits, it is possible to obtain high-quality atomization of the drugs.

PROPELLENTS, WHAT APPLY IN AEROSOL PACKAGING

Dispersing or evacuation gases are important for the delivery of an aerosol product, which create pressure inside the containers. Such gases are called ***propellants*** .

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

Depending on ***the saturated steam pressure,*** they are divided into two groups: *main* , capable of independently creating a pressure of at least 0.2 MPa, and *auxiliary* — create a pressure of less than 0.1 MPa **.**

By ***aggregate by state*** they are divided on three groups:

1) ***liquefied gas* :**

— organofluorine compounds (chladons, or freons);

— hydrocarbons propane row (propane, butane, isobutane);

— chlorinated hydrocarbons (vinyl- and methyl chloride etc);

2) ***confined*** (difficult to liquefy) *gas* (nitrogen, nitrogen oxides, carbon dioxide);

1) ***volatile organic solvents*** (methylene chloride, ethylene chloride , etc.).

***Xaldons* (*freons*)** — saturated fluorocarbons or polyfluorocarbons (often also contain Cl atoms, less often Br). Their trade names consist of the brand name (in Ukraine - chladone, in the USA — Freon, according to international standard — letter R) and digital designation. In pressurized medicines, liquefied gases are most often used - haldons 11 (CCl_3F) and 12 (CCl_2F_2).

Due to their impact on stratospheric ozone, their use is decreasing. In view of this, new, environmentally friendly refrigerants are being developed. (like 123, 134 and etc.), What have necessary operational properties and light are collapsing in atmosphere with formation inactive substances. For physicochemical properties refrigerants - gaseous or liquid substances, what dissolve in organic solvents, badly or poorly soluble in water; some with them form crystal hydrates.

Saturated paraffin hydrocarbons are stable in aqueous media and lighter than chlorofluorocarbons, making them suitable for spraying water-based products. Due to the low density of propane and butane, they require significantly less than chlorofluorocarbons to fill an aerosol can. However, the flammability of these liquefied gases does not allow them to compete with organic solvent-based products.

Compressed gases differ from liquefied gases not only in their physical state, but also in their properties. The pressure of compressed gases is much less dependent on temperature. However, the pressure in the cylinder decreases as the products are consumed, which can lead to incomplete consumption of the contents. Compressed gases are usually practically insoluble or have a rather limited solubility. Therefore, in recent years, research has been carried out in the field of increasing the solubility of compressed gases.

The amount of compressed gas required to dispense the contents of the package

is small. Therefore, such packages are very sensitive to gas leakage caused either by insufficient tightness or by careless handling. To eliminate this defect, aerosol packages with branched or inverted siphon tubes have been developed, which prevent the drug from being dispensed in an inverted position. Propellants of this group are non-flammable, cheap, and do not aggressively affect metal and polymer materials.

TYPES OF AEROSOLS SYSTEM

Materials for activating higher education students during lectures: questions, situational tasks, etc.:

Question:

1. Classification of aerosols.
2. Characteristics of pharmaceutical aerosols.
3. Medical aerosols.
4. Structure of aerosol packaging.

4.1 Metal containers

4.2 Three-piece cylinders

4.3 Two-piece cylinders

4.4 Monoblock aluminum cylinders

4.5 Glass containers

5. Valve-spray devices.

5.1 Principle of operation of the aerosol valve.

6. Propellants used in aerosol packaging.

6.5 Main groups of propellants.

6.6 Liquefied gas.

6.7 The oppressed (difficult to liquefy) gas.

6.8 Volatile organic solvents.

7. Types of aerosol systems.

7.1 Aerosol suspensions.

General material and methodological support for the lecture:

- educational premises – the department's auditorium;

- equipment - computer, tables;
- equipment – multimedia projector;
- illustrative materials – presentation, slides.

Questions for self-control:

1. What does the aerosol environment consist of?
2. How to characterize aerosol preparations?
3. How to characterize pharmaceutical aerosols?
4. What groups are aerosol cans divided into?
5. What is the principle of operation of valve-spray systems?
6. What propellants are used in aerosol cans?
7. What types of aerosol systems are there?
8. What are the characteristics of aerosol suspensions?

List of sources used:

1. A textbook for independent work of students of the Faculty of Pharmacy for the licensing exam "Step 2. Pharmacy" / V.Yu. Anisimov, O.I. Belyaeva, G.G. Vidavska, V.O. Helmboldt, A.V. Zamkova, I.V. Lytvynchuk, A.V. Nikitin, B.V. Prystupa, I.B. Petkova, Ya.V. Rozhkovsky, S.B. Strechen, L.M. Unguryan, N.S. Fizor Odessa: Odessa National Medical University. 2020. - 240 p.

Access mode 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 of higher. educational. pharmaceutical institutions (pharmac. faculties) / E.V. Gladukh, O.A. Ruban, I.V. Saiko and others. - Kh.: NPhU: Original, 2016. - 632p. : Named after. - (Series "National textbook")

2. Workshop on industrial technology of medicines, specialty "Pharmacy" / Edited by Ruban O.A. - Kh .: National University of Physics and Technology, 2015. - 374 p.

3. INDUSTRIAL technology of medicines : a teaching aid for independent work of students / O. A. Ruban , V. D. Rybachuk , L. M. Khokhlova etc. – KH.: NATIONAL UNIVERSITY OF PHYSICS AND TECHNOLOGY, 2015. – 120 p.

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- Handbook of Pharmaceutical Excipients, 6th edition / RC Rowe, PJ Sheskey, ME Quinn. - Pharmaceutical Press and American Pharmacists Association, 2009. - 521 p.
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- State Pharmacopoeia Ukraine / State enterprise « Ukrainian scientific officinal center qualities medical " means " - 2nd ed . – Kharkiv : State enterprise «

Ukrainian scientific officinal center qualities medical means ", 2014. – T. 2. – 724 p .

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Lecture No. 9

Topic: Medical sprays. Aerosol system technology. Standardization of pressurized drug storage.

Relevance of the topic: Drug technology (industrial drug technology) is one of the fundamental technological sciences. It consists of several key aspects that are important for modern medicine and patients: Efficacy and safety - Modern technologies allow the production of drugs with high efficiency and safety for patients. Accurate dosing, quality control and the absence of impurities make drugs more effective and safe. Innovations in the medical field: 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 treatment. Minimization of side effects: Technologies allow the development of drug formulas that minimize side effects and negative effects on the body. This provides more comfortable and safe treatment for patients. Fast production and delivery process: The use of modern technologies allows the acceleration of the production process of drugs, which is especially important in a rapidly changing medical environment, such as the spread of diseases or epidemics. Personalized treatment: Technologies allow for the development of 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 accessibility Improved manufacturing technologies can reduce production costs, making medicines more accessible to a wider range of patients, ensuring cost-effectiveness in the healthcare sector. Thus, the use of modern technologies for the manufacture of medicines is an important factor in improving the effectiveness of treatment, patient safety and the overall state of public health.

Purpose: The discipline provides, on the basis of general knowledge and principles, regularities of the technology of factory production, to form in students knowledge about: theoretical foundations, acquisition of professional skills and abilities in the preparation of dosage forms, phased 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 facilities and personnel. To get acquainted with the main stages of industrial production of dosage forms and the discipline "Technology of Medicines", to characterize the production of GUS preparations under pressure and describe the current state of the pharmaceutical industry of pressurized preparations. To get acquainted with the main stages of industrial manufacturing of dosage forms and the discipline "Drug Technology", to characterize medical sprays. Know the technology of aerosol systems and storage of drugs under pressure.

Basic concepts:

Medical sprays **are** pressurized preparations.

Aerosols – ***solutions*** **-** in aerosol solutions, the active substance is dissolved either in the propellant or in a co-solvent that mixes well with the propellant.

Aqueous foams consist primarily of an aqueous phase containing surfactants and an emulsified propellant.

Water-alcohol foams are a system consisting of water, ethyl alcohol, a foaming agent, and a propellant in such ratios that they are mutually soluble.

Non-aqueous foams allow the incorporation of moisture-sensitive ingredients into their composition.

Aerosol suspensions. These are heterogeneous disperse systems characterized

by the presence of a solid phase insoluble in a liquid aerosol concentrate. In aerosol suspensions, the propellant can be included in the disperse phase or in the dispersion medium.

Filling with compressed propellants **:** when using compressed gases as a propellant, the cylinders are filled under pressure through a valve.

Lecture plan and organizational structure:

	The main stages of the lecture and their content.	**Goals in levels of abstraction.**	**Type of lecture, lecture equipment.**	**Time allocation.**
	2	**3**	**4**	**5**

	Preparatory stage Defining learning goals. Providing positive motivation. *Main stage* Presentation of lecture material. Plan: 1. reating medical sprays. 2. echnology of various aerosol systems. 3. Preparation of concentrate. 4. Aerosol solutions. 5. Characteristics of aqueous, aqueous-alcoholic foams, non-aqueous foams. 6. Aerosol suspensions. 7. Pressure filling methods . 8. Standardization and storage of drugs under pressure. 9. Ways to improve aerosol packaging. 10. Modern aerosol drug delivery systems.	 I II	Combined lecture Slides Bibliography, questions, assignments.	 1% 2% 90%

	10.1 Spencers. 10.2 Nebulizers *Final stage* Lecture summary, general conclusions. Lecturer's answers to possible questions. Tasks for student self-study.	III		2% 3% 2%

1. Creating medical sprays.
2. Technology of various aerosol systems.
3. Preparation of concentrate.
4. Aerosol solutions.
5. Characteristics of aqueous, aqueous-alcoholic foams, non-aqueous foams.
6. Aerosol suspensions.
7. Pressure filling methods.
8. Standardization and storage of drugs under pressure.
9. Ways to improve aerosol packaging.
10. Modern aerosol drug delivery systems.

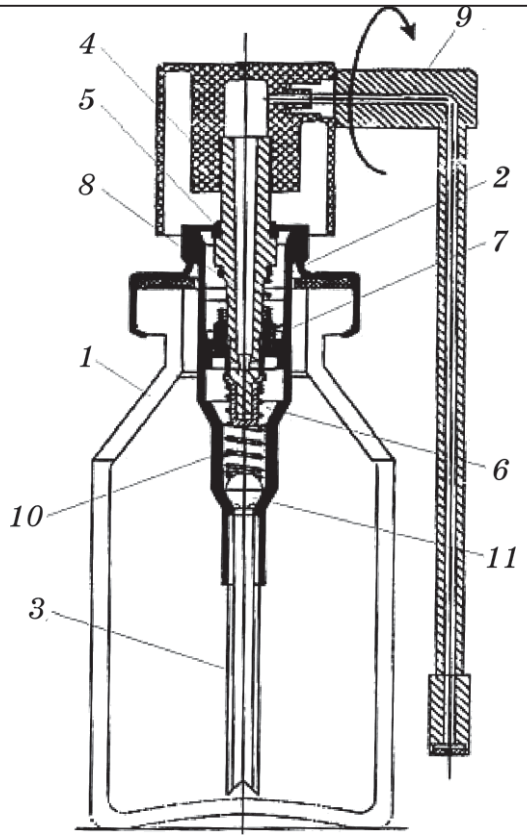
Content of the lecture material (lecture text)

CHARACTERISTICS OF MEDICAL INTERVENTIONS

Sprays are also pressurized preparations. Unlike aerosols, they do not contain

propellants, and the pressure required to release the contents in the form of a dispersed jet is achieved by means of a mechanical atomizer. — pump-type valve (micropump) or by the physical force of squeezing a polymer cylinder (the so-called "sprayer"). A comparative analysis of the characteristics shows that the aerosol and spray are quite close and differ in the size of the sprayed particles, while the "sprayer" has fundamental disadvantages: lack of tightness, inability to dose, likelihood of contamination during use, and the appearance of a jet (lack of dispersed spray) when deviated from the vertical position.

Unlike aerosol packaging, the pressure inside the spray can is equal to atmospheric pressure, which significantly simplifies the requirements for the container material and its mechanical properties. Glass and polymeric materials are most often used as packaging materials. Issuance content spray is happening by with help ***micropump*** (pumps, mechanical sprayer), which is attached to the neck of the cylinder. Micropumps consist of a larger number of parts than valves, so the technological process of their production is more complicated and requires a larger number of operations. Unlike aerosol valves, which are attached to the necks of cylinders by rolling (compression), pumps can be manufactured not only for attachment to the neck by rolling, but also for screwing or pinching. In this case, the containers There can be various plastic, glass or aluminum bottles for the product . Spray packaging (Fig. 13.5) consists of a container hermetically sealed with a micropump, a siphon tube and a nozzle with a sprayer.



Ingredients packaging spray with micropump:

1 — container; *2* — aluminum capsule; *3* — siphon tube;

4 — nozzle with sprayer; *5* — stock; *6* — pocket (cavity) pump housing; *7* — rubber gasket with a hole; *8* — gate channel;

9 — channel sprayer; *10* — spring; *11* — locking bead

The most complex element of the packaging is the micropump, which consists of a dispenser and a spray nozzle. For different drugs, depending on the method of application, nozzles that differ in configuration can be used:

—…… nozzle for external application;

—…… nozzle for local application in cavity mouth;

—…… nozzle for intranasal introduction.

The principle of operation of the micropump is as follows: when you press the nozzle *4* rod *5* moves downwards and squeezes part of the drug from the cavity of the pump housing *6* through the hole *7* into the channel *8* connected to the sprayer channel *9*. Return of the stock *5* to the initial position is carried out by a spring *10*. When the

rod returns to its original position in the body cavity *6,* a vacuum is created, the pressure on the shut-off ball *11* weakens and the liquid from the bottle through the siphon tube *3* again fills this cavity. Then the cycle repeats.

The use of such packaging is not effective for all preparations. Such pumps are not suitable for spraying suspensions with a high solids content, film-forming preparations, foams, etc.

Compared to aerosols, sprays are coarser systems, the size of the particles sprayed mainly depends on the design of the spray nozzles and the viscosity of the medicinal compositions.

To obtain a finely dispersed jet in such cases, high hydraulic pressure created by a micropump is combined with a small cross-sectional passage of the valve opening (laser technologies are used for this).

TECHNOLOGY VARIOUS AEROSOL SYSTEMS

The general scheme of the technological process for the production of pressurized preparations is shown in Fig. 13.6.

Рис. 13.6. Scheme technological process receiving drugs, that are under pressure.

Preparation of concentrate. During the preparation of aerosol concentrates, a wide variety of chemical compounds and their mixtures can be used. Most often, the concentrate consists of several individual substances that must have a certain viscosity, be compatible with the propellant, be resistant to low and high temperatures, and must not interact with the container parts. It is better to use non-polar substances as co-solvents, since even small amounts of water can cause hydrolysis of some propellants, which will lead to the release of hydrogen chloride, decomposition of active substances, and corrosion of metal parts of containers.

Depending on the degree of miscibility of the components of the main formulation with the propellant, pressurized medicinal products are divided **into *aerosol solutions, foams in aerosol packaging, aerosol suspensions, and combined systems* .**

Solution aerosols. In solution aerosols, the active ingredient is dissolved either in a propellant or in a co-solvent that is well mixed with the propellant. After issuance content with propellant cylinder evaporates, and medicinal substance remains in in the form of fog in clean in the form of or dissolved in a co-solvent.

Concentrates-solutions are preparing, as and ordinary solutions medical substances , in reactors equipped with a heat-exchange shell and a stirrer. Solutions are freed from impurities by settling, filtration or centrifugation. If solution concentrates are obtained using viscous solvents (fatty oils), then dissolution is carried out by heating, purification - under pressure. In the case of using volatile solvents (ethyl alcohol), the dissolution of substances is carried out in closed reactors, and filtration — under pressure. Aerosol systems may contain stabilizers and preservatives. After checking the intermediate product, the solution is packed into prepared cylinders.

The decisive factor in the technology of aerosol solutions is the pressure inside the canister, the control of which can serve as a quantitative characteristic of some physicochemical properties: the completeness of the release of the contents from the canister, its dispersion, as well as the solubility of the propellant in the concentrate. The greater the ability of the aerosol concentrate to dissolve the propellant, the lower

the pressure in the aerosol canister.

In case of application as propellant not compressed, and liquefied gas, the pressure in the cylinder remains constant as long as there is at least one drop of liquid propellant in it.

The solubility of propellants in aqueous media can be increased not only by introducing cosolvents that are well compatible with them, but also by using surfactants that can solubilize them during the mixing process. The greater the ability of the surfactant solution to solubilize the refrigerant, the lower the pressure inside packaging has mixture their steamed. Degree solubilization, The stability of the resulting systems and their main physicochemical properties are determined by the type of propellant and the type of surfactant.

Formulations dispensed from packaging in the form of foams. A significant number of aerosol formulations are emulsion systems dispensed in the form of foams. They are divided into three classes: ***aqueous, water-dispersible*** **and** ***non-aqueous foams.*** To obtain foaming aerosols, effective foaming agents are used, which in low concentrations ensure the production of large foam, the stability of which depends on many factors, the main of which are: the concentration of the foaming agent, the presence of electrolyte, the pH of the medium, the viscosity of the solution, the concentration and type of propellant, and the presence of additives.

Aqueous foams constitute the largest group of preparations in aerosol packages. They consist mainly of an aqueous phase containing surfactants and an emulsified propellant. When dispensed, the liquid propellant boils violently and forms a foam. The concentration of propellant in aqueous foams can be from 3.5 to 89% and depends on its type. Most often used 114 chlorofluorocarbon, chladone 12, their mixtures (40:60), less often refrigerants 142, 152. Cold 11 in aquatic aerosol systems do not It is used due to its easy hydrolysis in the presence of water.

Water-alcohol foams are a system consisting of water, ethyl alcohol, foaming agent and propellant in such proportions that they are mutually soluble. During the preparation of water-alcohol foams, the foaming agent must be partially soluble in the

“water-alcohol” system and completely in the “water-alcohol-propellant” system.

Non-aqueous foams allow the introduction of moisture-sensitive ingredients into their composition. Their properties can be varied depending on the type and concentration of the surfactant, propellant, and non-aqueous phase. In non-aqueous foams, the continuous phase is mineral oils or vegetable oils, glycols, etc. Such foams are finely porous, dense, more uniform in the size of gas bubbles, in some cases approaching creams. The mixture of propellant and oil significantly affects the pressure inside the cylinder, reducing it, therefore, to ensure complete evacuation of the contents from the cylinder, the choice of propellant plays a decisive role.

After checking the semi-finished product, the solution is packed into prepared cylinders. Foam, received with aerosol packaging, evaluate by such indicators : *external appearance* ; *the degree of its release from the packaging* (smooth, intermittent, noisy); *stability and shelf life* ; *elastic properties* ; *drying* (in percent over time); *wetting properties* ; *thickness* , *viscosity* and *elasticity* .

Aerosol suspensions. These are heterogeneous dispersion systems characterized by the presence of a solid phase insoluble in a liquid aerosol concentrate. In aerosol suspensions, the propellant can be included in the dispersed phase or in the dispersion medium. In any case, the active substance is dispersed in a non-volatile solvent.

The main factors affecting the quality of aerosol suspensions: physicochemical properties substances, What are included to warehouse aerosols; The ratio between the filler components; design features of the aerosol packaging; temperature conditions of operation of the cylinders. The stability of suspensions is also affected by the specific gravity and viscosity of the liquid phase .

In aerosol suspensions, chemically inert substances are introduced, which minimizes interaction processes and increases storage stability. Some aerosol suspensions can be stored for a long time and are not inferior in terms of storage time to the active substance in dry form.

The following advantages of preparations in the form of aerosol suspensions can be distinguished: the possibility of using substances both soluble and insoluble in

this medium; a pronounced prolonged effect; regulation of the action by changing the particle size.

The main disadvantage of suspension aerosols — thermodynamic instability, which is their natural state. Over time, all suspensions stratify, therefore the main characteristics of these systems are dispersion and the presence of aggregative and kinetic (sedimentation) stability. In order to increase the aggregative and kinetic stability of suspensions, various technological techniques and methods are used. The most effective way to stabilize aerosol suspensions — reducing the surface tension at the interface of the phases forming the suspension by adding surfactants. Such substances include fatty alcohols and some esters, which prevent particles from sticking together and simultaneously lubricate the valve-spraying system. They are used sometimes and cosolvents for propellant (mineral oils, non-ionic surfactants, glycols and other substances).

IN aerosol suspensions enter mostly polar substances; suspended in cold, they can form aggregates. For aggregation The packaging material affects particle aggregation. The least aggregation of particles occurs in metal packaging, the most in glass aerosol cans.

For aerosol suspensions, the particle size should not exceed 40-50 microns, and for inhalation aerosols the best effect was obtained with a particle size of 5-10 microns. In this case, the powder content should not exceed 10%. The powder should not be hydrophobic, since over time its particles will increase in size. After controlling the intermediate product, the suspensions are packed into prepared cylinders.

Filling cylinders with propellant. After dosing the prepared concentrate into the cylinders, they are filled with propellant. Refrigerants (propellants) are supplied to pharmaceutical production in special containers, and their supply to the filling line is These are specific operations that require special conditions and equipment operating under pressure.

Now exists two methods filling aerosol cylinders propellant:

- low-temperature way, or "cold" filling";
- filling under pressure.

At low-temperature way chilled balloon is filled with pre-cooled concentrate and liquid propellant, sealed with a valve and heated to room temperature. To prevent large losses, the propellant is usually cooled to a temperature that is 5 °C below its boiling point, and is injected into the cylinder in one go. If the amount of propellant is 5-15 %, it is mixed with the concentrate and cooled, and then the mixture is fed to the cylinder filling and sealing line.

The main disadvantage of this method is the formation of ice on the filling head, which requires periodic cleaning. This method cannot be used for highly viscous concentrates and solutions containing water. In addition, the method involves the use of deep-freezing technology, so glass cylinders cannot be used with this method.

The main method of aerosol production is ***the pressure filling method*** . Its principle is that liquefied or compressed propellant is pumped under pressure into cylinders filled with the product and sealed with a valve .

Filling with compressed propellants : when using compressed gases as a propellant, the cylinders are filled with them under pressure through a valve. In this method, the compressed gas is not dosed, but is introduced into the cylinder in such a quantity that it provides the necessary pressure in the package. Air from the cylinder can be removed either by introducing an inert gas before sealing, or by introducing a drop of refrigerant, or by vacuuming.

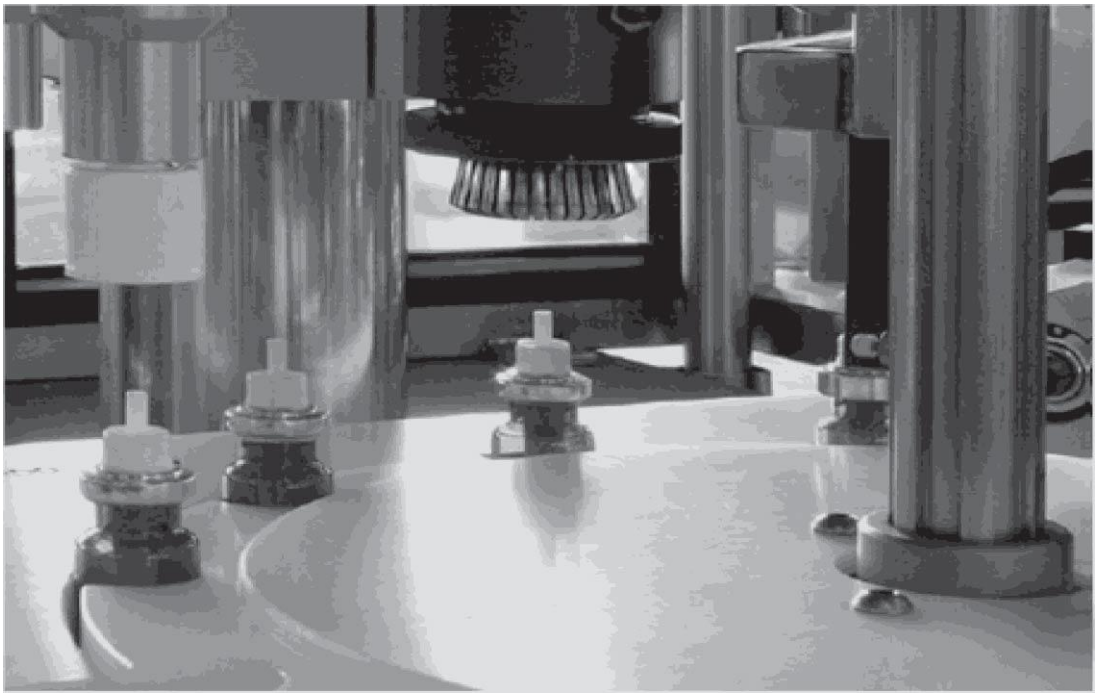
Filling with soluble propellants : if the compressed gaseous propellant is soluble in the concentrate (for example, nitrous oxide), then the cylinder is also filled with propellant through the valve, but the process must be accompanied by vigorous shaking for better absorption of the propellant by the concentrate. The introduction of gas and shaking continue until the concentrate is completely saturated and the system is in equilibrium. This usually takes up to 20 This method is used mainly for aerosol packaging of food products.

For filling aerosol cans, there are a large number of various automatic installations and lines, the productivity of which can be from 2 to 20 million aerosols per year. Among them, it is necessary to highlight automatic lines for filling aerosols and sprays of the NQDG, BQGF, GFF families of the company LUXUN (China). The

lines can be equipped with an automatic device for checking the tightness of the cans and packaging machines. Among the world leaders in the production of equipment for obtaining aerosols are the companies Terco (USA), Pamasol (Switzerland), Coster (Italy), which offer lines with a productivity of 500 cans per minute and more.

The general scheme of the aerosol can filling line consists of the following operations: the cans are loaded onto the conveyor track and fed into the washing machine, where they undergo the washing stage, are rinsed, steamed and dried. After that, the cans are fed onto the filling line's storage table, and then along the conveyor belt trans

The samples are fed into a machine for supplying sterile compressed air. Then, an automatic dosing device fills the cylinder with concentrate, after what with him is being deleted air. For these goals The automatic head dispenses 1-2 drops of the generated propellant, which, evaporating, displaces the air in the cylinder. The cylinders are then sealed. (Fig. 13.7).



Node hermetic seals aerosol bottles

This process is carried out by a valve fastening device. The valve can be fastened in two ways: using clamping collets or by rolling by wrapping the rollers around the neck of the cylinder. After that, they are fed to the dispensers, which inject the propellant (refrigerant) into them under pressure. Portion dispensers can be of the

rotary or linear type. After filling the cylinders with propellant, they are tested for strength and tightness in a water bath at a temperature of 45±5 °C for 15-20 min (for glass) or 5-10 min (for metal cylinders). When the cylinders are heated in a bath, increased pressure is created in them, and they either explode or release propellant, noticeable by bubbles rising in the water. Defective cylinders are removed from the bath. Some production lines aerosols equipped with special detectors with gas analyzers that monitor the minimum amount of propellant leakage from the cylinders. Leaking cylinders are automatically rejected.

Further, the cylinders enter the drying tunnel on a conveyor and are dried after water, and then they are checked for weight on automatic scales. If the mass does not match, the cylinders are automatically rejected. If aerosol packaging contain as propellant compressed gas, then their Check for gas pressure using a pressure gauge. Cylinders that do not contain gas are automatically rejected.

The cylinders are equipped with sprayers, the quality of which is checked on a special automatic device. Using an automatic orienting device, protective caps are put on the cylinders. The machine marks the cylinders (series, expiration date and other data). After that, the cylinders are sent to the packaging line, where they are placed in packs and instructions for use are added. Then these packs are packed in transport containers.

STANDARDIZATION AND STORAGE MEDICATIONS, WHAT WILL HAPPEN UNDER PRESSURE ?

Standardization of aerosol packaging at enterprises is carried out in accordance with the ND and includes several types of control: organoleptic, physicochemical, chemical and biological (if the composition contains cardiac glycosides and other substances).

The State Pharmacopoeia of Ukraine provides for the control of pressurized medicinal products according to the following indicators: *opus* ; *checking the tightness of the container* ; *measuring the thickness of the container* ; *determining the percentage of leakage of the container contents* ; *identification* ; *accompanying impurities* ; *microbiological sensitivity* ; *quantitative determination of API and*

antimicrobial preservatives ; *checking the valve operation* .

For aerosol packages equipped with a metering valve, *the average mass of the drug in one dose and the number of doses administered are additionally controlled* . For drugs intended for general action, in the form of suspensions or emulsions, which are under pressure with a metering valve, *the uniformity of dosing is additionally controlled* . For drugs, which are under pressure in the form of suspensions, intended for administration into the bronchi and lungs, *the particle size is additionally controlled* .

Foams obtained from aerosol packages are additionally evaluated according to the following indicators: *relative foam density*, *expansion time* (the time to reach maximum volume should not exceed 5 min).

The internal pressure in the aerosol container must comply with the requirements of a separate ND. It is determined by a manometer, the accuracy class of which must be 2.5. Filled containers are checked for strength and tightness. Percentage of the aerosol container contents X , %, analyzed by the formula

$$X = \frac{m_1 - m_4}{m_5} \cdot 100, \qquad (13.1)$$

de m_1 — mass of the entire package with contents, g; m_4 — mass of the empty cylinder, g; m_5 - mass of the contents indicated on the label, g.

Value average masses drug in one dose m_{sir} calculate by the formula

$$m_{cp} = \frac{m2 - m3}{n}, \qquad (13.2)$$

where m_2 is the mass of the cylinder after the first five presses, g; m_3 is the mass of the cylinder after 10-20 presses, g; n — the number of presses specified in a separate ND.

Deviation in dose allowed not more ± 20%, if no other instructions in individual ND.

The number of drug doses dispensed from the container is calculated using the formula

$$N = \frac{m1 - m_4}{m_{cep}}$$

High-quality aerosol containers are sent to the packaging line. Aerosols are packed in sturdy boxes if the product is flammable, for less hazardous products, cardboard transport packaging is allowed.

Aerosol cans have specific conditions when transported compared to the current rules adopted for other dosage forms. The storage conditions specified on the packaging and in the ND must be observed (avoid shocks, direct sunlight and high temperatures).

PATHS IMPROVE AEROSOL PACKAGING

In connection with the ongoing discussion about the harmful effects of fluorocarbon propellants on the environment and their possible ban, intensive development of alternative packaging is underway. This work is aimed at: creating packaging with a mechanical pump-type sprayer; using harmless displacers (propellants); developing new spraying methods; improving existing aerosol container designs, etc.

In the search for an adequate propellant, about 15,000 substances were studied. And only hydrofluorocarbons were recognized as the only substances capable of replacing freons. Unlike freon, hydrofluorocarbons do not contain a chlorine atom, do not destroy the ozone layer, practically do not cause a "greenhouse effect", and are absolutely non-toxic. This is especially important when using freon-free metered dose aerosol inhalers (MDIs), which improve the reproducibility of the inhaled dose, its delivery, and simplify the inhalation technique.

In the field of creating various aerosol packaging, packaging called "barrier" is becoming increasingly widespread. Its essence is that the product is separated from the propellant by a barrier - a movable partition, which prevents contact between them. At this sharply Packaging possibilities are expanded , as chemical interaction between the propellant and the product is eliminated, and it also becomes impossible for the propellant to enter the atmosphere. Structurally, two-chamber aerosol packages are available in various versions: with a piston, with a liner, with an inner bag (Fig. 13.8), etc.

Figure 13.8. Valve with a bag for barrier packaging

Number propellant in such packaging small, ago jet, What is produced from them, is not sufficiently dispersed. To increase the dispersion, low-viscosity formulations are selected, the cross-sections of the holes and valve channels are reduced, or very small amounts of propellant are introduced into the preparation.

Also widely used are compression cylinders made of elastic polymers (polyolefins, acrylonitrile, polyester, polyurethane and other resins). The principle of their operation is based on the action of muscular force squeezing such a cylinder and squeezing the product through a small-section hole. Such packages are the cheapest, but they require significant effort to activate them and emit coarse aerosols .

To everyone listed packaging inherent one vigilant blemish: the inability to achieve sufficient internal pressure compared to the pressure created by conventional aerosol cans with liquefied propellants.

SUCH A CH I SYS T EMI ADDITIONAL TAB KEY A E P OZOLNYKH P P EP A PATIB

Now in clinical practice for inhalation are used sprat aerosol drug delivery systems **:**

- dosed aerosol inhalers under pressure (freon and Freon-free);
- combination dosed aerosol inhalers (SAI) from spacer;

- dosing powder inhalers (DPI);
- nebulizers.

With the help of the above devices, liquid or solid drugs in the form of vapors or aerosols are introduced into the lungs in order to achieve a local or systemic effect. The size of the aerosol particles for inhalation is selected in such a way that a significant part of them is deposited in the lungs.

Spacer (aerosol tank) — volumetric cell, which connects GAI with the patient's airways. Particles of the drug enter the spacer from the inhaler and remain suspended inside the chamber for about 20 seconds. During this time, the patient can inhale the medication in one or more breaths without worrying about coordinating the inhalation with pressing the inhaler valve.

Spacers greatly simplify the inhalation technique, which allows the use of GAI for almost all patients, including children, the elderly and people with poor technique for performing inhalation procedures. In children under three years of age, spacers equipped with masks are used. The main disadvantage of spacers — their relative bulkiness, which makes it difficult their use by patients outside the home.

In ***metered dose inhalers,*** the drug is used in the form of a finely dispersed powder placed in double foil blisters, which are symmetrically arranged on a disk. For effective use of the DPI, the patient must inhale through the inhaler with maximum effort.

Advantages of DPI: portability; convenience and relative ease of use; absence of propellants; absence of the need to synchronize inhalation with pressing the inhaler valve; possibility of use by children starting from the age of five.

However, DPI has its drawbacks: the need for a sufficiently powerful airflow during inhalation, which complicates their use in cases of suffocation and in children under five years of age; low reproducibility of particle size; detrimental the effect of humidity on the operation and storage of DPI; the inability to use a spacer; poor receptivity to inhalation of powdered forms by some patients, in whom coughing

and/or bronchospasm occur.

Nebulizers **(** from Latin *nebula)* — fog, or cloud) have been used in medical practice for almost 150 years. Advantages of nebulizers: ability to generate aerosol particles of respirable size (1-5 microns); ability to deliver a large dose of the drug over a short period of time (usually 5-10 min); low oropharyngeal deposition drugs; simple inhalation technique, which is carried out in the "calm breathing" mode, since there is no need to coordinate inhalation with the arrival of the aerosol and no need for forced inhalation; possibility of including oxygen supply in the nebulizer circuit and performing artificial lung ventilation; possibility using systems at the hardest states (asthmatic status) in elderly people and children, with motor disorders and impaired consciousness; no propellant is required for nebulization.

Disadvantages inherent in most nebulizers: the drug cannot be used completely during nebulization, since part of it remains in the so-called dead space of the nebulizer, even if its chamber is almost completely drained. The residual volume depends on from constructions nebulizer and usually is located in within 1 ml. Taking into account this value, the filling volume of nebulizers should be at least 2 ml. In nebulizers with a residual volume of more than 1 ml, the initial volume should be about 4 ml, which significantly increases the drug consumption. The residual volume can be reduced by gently shaking the nebulizer chamber at the end of the procedure, while large drops of solution from the walls of the chamber return to the working area, where it is again subjected to nebulization. In general, the larger the initial volume of the solution, the greater the proportion of the drug is inhaled. However, the nebulization time also increases. In addition, it should be taken into account that most drugs for nebulization packaged on 2.2 ml. Ago Increasing the filling volume may require additional consumables, which will increase the cost of therapy.

R. Carsten and colleagues from Ludwig-Maximilians University (Munich, Germany) have proposed a new aerosol dosage form, called ***nanomagnetosol*** . In it, the drug substance is mixed with nanoparticles of nitric oxide, which provides the magnetic properties of the new dosage form. with formation sol in in the form of

microdroplets in size approximately 50 nm. The new form of aerosol was tested in experiments on mice. Inhalations were carried out under the control of an external magnetic field, which allowed directing the aerosol to the desired area of the lungs. At the same time, the efficiency of its delivery to the bronchi was increased eightfold. scurrying today inhalers deliver in lungs not more 4 %

medical substances. It forces doctors significantly increase its dose, which carries a high risk of unwanted side effects.

It is too early to predict how effective nanomagnetozole will be in humans due to the much more developed bronchial system. In addition, the problem of creating magnetic field gradients around the human chest, which is much more difficult, will also have to be solved. than in small animals.

The progressive direction of development of pressurized drugs is Development by specialists from the Korean Institute of Radiology and Medicine of a spray made from stem cells from the victim's skin. The drug allows for the effective treatment of significant skin lesions from burns and radiation exposure.

Thus, currently, pressurized drugs are becoming increasingly common in medicine for the treatment of various pathological conditions of the human body and are constantly being improved.

Materials for activating higher education students during lectures: questions, situational tasks, etc.:

Question:

1. What are the methods for creating medical sprays?
2. What aerosol system technologies exist?
3. Describe aerosol solutions.

5. What is the difference between aqueous, aqueous-alcoholic foams, and non-aqueous foams?

6. How to characterize aerosol suspensions?

7. What are the methods of pressure filling?

8. How are drugs standardized and stored under pressure?

9. What are the ways to improve aerosol packaging?

10. Provide examples of modern aerosol drug delivery systems.

11. Describe spencers and nebulizers.

General material and methodological support for the lecture:

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

Questions for self-control:

1. How can medical sprays be characterized?
2. How is the concentrate prepared?
3. What classes are foams divided into?
4. How to fill cylinders with propellant.
5. What is the pressure filling method?
6. What are spencers and nebulizers?

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Main:

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Lecture No. 10

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

Relevance of the topic: Drug technology (industrial drug technology) is one of the fundamental technological sciences. It consists of several key aspects that are important for modern medicine and patients: Efficacy and safety - Modern technologies allow the production of drugs with high efficiency and safety for patients. Accurate dosing, quality control and the absence of impurities make drugs more effective and safe. Innovations in the medical field: 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 treatment. Minimization of side effects: Technologies allow the development of drug formulas that minimize side effects and negative effects on the body. This provides more comfortable and safe treatment for patients. Fast production and delivery process: The use of modern technologies allows the acceleration of the production process of drugs, which is especially important in a rapidly changing medical environment, such as the spread of diseases or epidemics. Personalized medicine: Technology enables the development of 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 accessibility Improved manufacturing technologies can reduce production costs, making medicines more accessible to a wider range of patients, ensuring cost-effectiveness in the healthcare sector. Thus, the use of modern technologies for the manufacture of medicines is an important factor in improving the effectiveness of treatment, patient safety and the overall state of public health.

Purpose: The discipline provides, on the basis of general knowledge and principles, regularities of factory production technology, to form in students knowledge about: theoretical foundations, acquisition of professional skills and abilities in the preparation of dosage forms, phased 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 facilities and personnel. To get acquainted with the main stages of industrial production of dosage forms and the discipline "Technology of Medicines", to characterize the production of drugs. To get acquainted with the main stages of industrial production of dosage forms and the discipline "Technology of Medicines", to characterize production of powders, tablets by direct compression and pre-granulation and describe the current state of the pharmaceutical industry of film-coated tablets and medical capsules .

Basic concepts:

Specific surface area *is* the total surface area occupied by a powdery substance,

and contact surface area 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 same chemical and pharmaceutical production.

Bulk (volumetric) density is the mass per unit volume of free powder and depends on the density of the substance, the shape and size of the particles, and their arrangement.

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

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

Pressing (properly tableting) is the process of forming tablets from granular or powdered material under pressure.

Direct pressing – This is a process of pressing non-granulated powders. Direct pressing eliminates 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 exiting the press.

Granulation – directional particle enlargement, i.e. the process of transforming powdered material into grains of a certain size, which is necessary to improve the flowability of the tablet mixture and prevent its delamination.

Lecture plan and organizational structure:

No. 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. II 3. III 4.	*Preparatory stage* Defining learning goals. Providing positive motivation. *Main stage* Presentation of lecture material. Plan: 1. Characteristics of tablets as a dosage form. Types and groups of tablets. 2. Properties of powdered medicinal substances. 3. Main groups of excipients in the production of tablets. 4. Objectives and main types of granulation in tablet production. 5. Coating tablets with shells. 6. Ways to improve tablets as a dosage form. *Final stage* Lecture summary, general conclusions. The lecturer's answers to possible questions. Tasks for student self-study.	 I II III	Combined lecture Slides Bibliography, questions, assignments.	1% 2% 90% 2%

5. 6.				3% 2%

Structural and logical diagram of the lecture content

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

1.1 Effervescent, soluble and dispersible tablets.

1.2 Modified-release tablet .

2. Properties of powdered medicinal substances.

 2.1 physical, chemical technological (pharmaco-technological) structural-mechanical properties.

2.2 Physical properties: Specific surface area ,contact surface , true density, wettability, kyophilicity, hygroscopicity, water of crystallization.

2.3 Electrical properties.

2.4.Technological properties

2.5 Main groups of excipients in the production of tablets.

3.1 Particle shape and size.

3.2 Shapes: elongated , lamellar ,equiaxial.

4. Objectives and main types of granulation in tablet production.

5. Coating tablets with shells.

6. Ways to improve tablets as a dosage form.

Content of the lecture material (lecture text)

Tablets (*Tabulatea* , from Latin *tabula)* — board, *table* — board, tile) — A tablet containing a single dose of one or more active ingredients, obtained by compressing a specific volume of particles. Most tablets are intended for oral administration. Some tablets are swallowed whole, some — are chewed beforehand, while others are dissolved or dispersed in water before use or left in the mouth, where the active substance is released. Even in the “Canon of Medicine” by Abu Ali ibn Sina, such LFs as cakes (the prototype of modern tablets) were mentioned, which, depending on the purpose and dosage , were divided into ***dosage*** forms for direct

use and ***non-dosed*** for storage and further use. The first information about pills appeared in the middle of the 19th century. In In 1844, Brokedon received a patent in England for the preparation of potassium bicarbonate tablets by pressing. In 1846-1897, tablet production began in the USA, France, and Switzerland. In 1872 In Germany, the manufacture of tablets was first proposed by Rosenthal. In 1901, tablets were first included as a dosed drug in the Swedish Pharmacopoeia . Tablets produced by the pharmaceutical industry constitute a significant portion of the total number of oral contraceptives. Industrial tablet production is constantly increasing worldwide.

CHARACTERISTIC I CLASSIFICATION I KAT I I TABLET O K

Tablets as a dosage form have become widespread throughout the world, thanks to the following ***positive qualities*** :

- an appropriate level of mechanization at the main stages and operations, which ensures high productivity, cleanliness and hygiene of production;
- precision dosage medical substances, What are introduced in tablets;
- portability tablets, What provides convenience their application, storage and transportation;
- continued stability medical substances in compressed condition;
- possibility causing shells for protection unstable substances;
- possibility disguise unpleasant organoleptic properties (taste, smell, color) achieved by applying coatings;
- combination of drugs that are incompatible in terms of physicochemical properties in other dosage forms;
- localization of the action of the medicinal substance in a certain part of the gastrointestinal tract by applying coatings soluble in an acidic or alkaline environment;
- prolongation API actions (by causing certain coatings, using special technology and composition of core tablets);
- regulation of sequential absorption of several LRs from a tablet at certain intervals of time (multilayer tablets);

- preventing medication errors — by applying appropriate inscriptions to the surface of the tablets.

However, tablets also have some ***disadvantages*** : the action of LRs in tablets develops relatively slowly; during storage, they can cement, thereby increasing the disintegration time; the composition of tablets may include excipients that have no therapeutic value and sometimes cause some side effects (for example, talc irritates the gastric mucosa); some LRs form highly concentrated solutions in the dissolution zone, which can cause severe irritation of the mucous membranes; tablets cannot be administered to a patient who is vomiting and unconscious; not all patients, especially children, can freely swallow tablets.

Tablets classify by different signs:

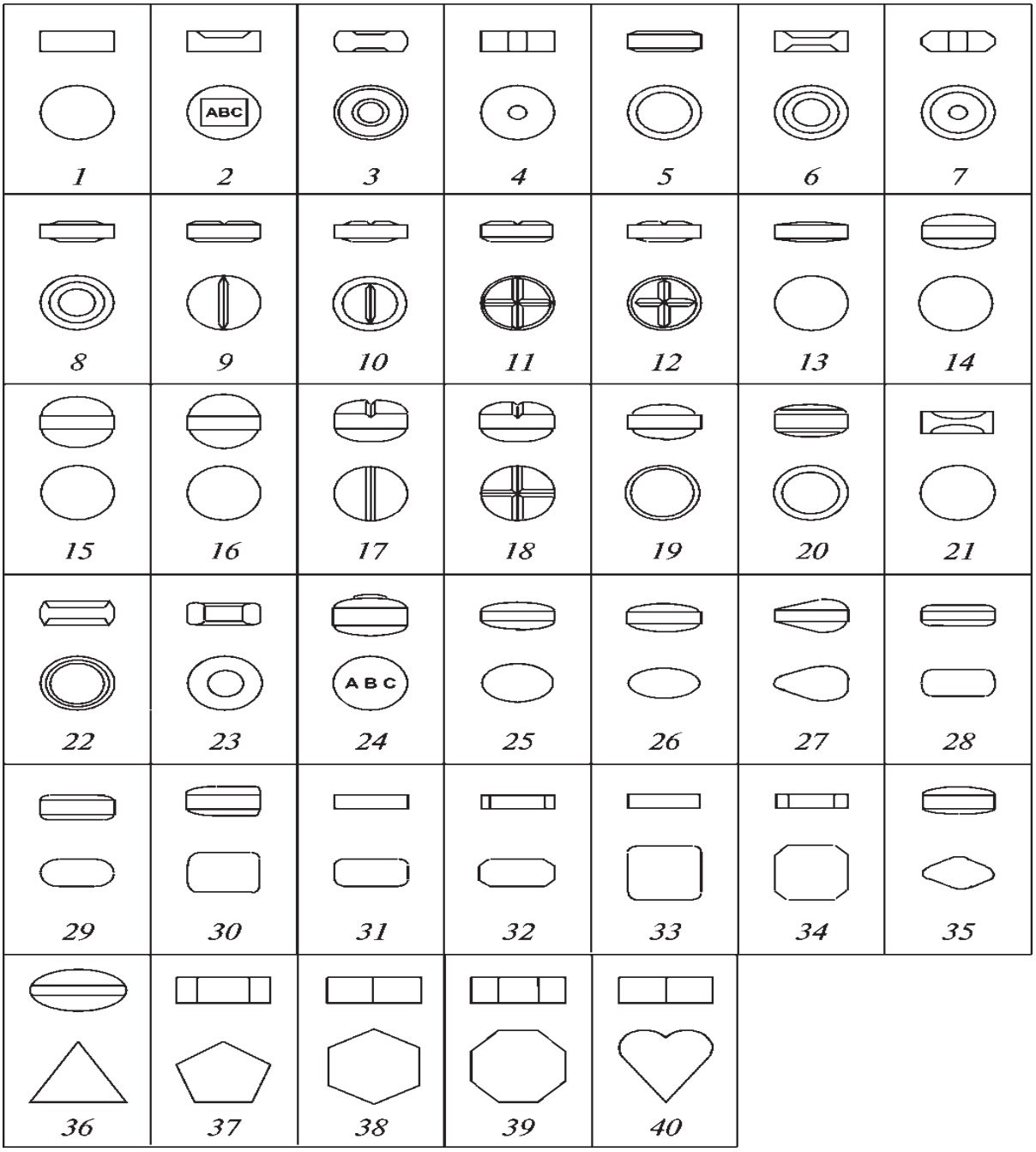
- by composition: ***simple*** (single-component) and ***complex*** (multicomponent);
- structure structures: ***single-layer, multilayer*** (not Less two layers) and ***frame , without shells (coating)*** **or** ***covered shell*** ;
- in the form of: ***round , oval , longitude , polygonal , of a specific form*** ;
- by appointment and in a way application.

Single-layer tablets are folded with pressed mixtures LR and excipients and are homogeneous throughout the entire volume of the LF. In multilayer tablets, LR are arranged in layers. When using chemically incompatible substances in multilayer tablets, their minimal interaction is ensured.

The size of the tablets ranges from 4 to 25 mm in diameter. Tablets with a diameter of more than 25 mm are called ***briquettes*** . The most common are tablets with a diameter of 4 to 12 mm. Tablets with a diameter of more than 9 mm have one or two lines, applied perpendicular to each other, which allow dividing the tablet into two or four parts and thus varying the dosage of the API. The weight of the tablets is mainly 0.05-0.8 g, which is determined by the dosage of the medicinal substance and the number of excipients in their composition. The shapes of tablets produced by the pharmaceutical industry are very diverse. The most common are the flat-cylindrical shape with a chamfer (a surface formed by the bevel of the edge of the tablet) and the

biconvex shape, which is convenient for swallowing. In addition, the press tool for the production of tablets of such shapes is very simple, therefore it does not cause any special difficulties when installing it on tablet machines. The flat-cylindrical shape of tablets without a chamfer is not recommended for production, since during packaging and transportation the sharp edges of the tablets are destroyed, as a result of which their presentation is lost. The tablets must have the correct shape, be whole, without chipped edges, their The surface must be smooth and uniform, and the tablets themselves must be strong enough not to crumble. The geometric shape and dimensions of the tablets are determined standard. By abroad choice forms tablets lot Larger plano-cylindrical tablets are available with a diameter of from 4.0 to 20.0 mm; biconvex pills without coverage — from 4.0 up to 13.0 mm, coated tablets — from 5.0 to 10.0 mm. The diameter of the tablets is determined by their mass. The height of the flat-cylindrical tablets should be within 30-40 % of diameter. Oblong tablets are called " ***caplets*** " **.** The specific shape of the tablets is determined by the method of application of the drug or its pharmacological action.

Some tablets have inscriptions on the surface with the name of the drug, which are applied in the form of concave prints, since the convex letters on the end of the tablets quickly wear out and collapse. Tablet shapes: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Conditional marks :

1 — flat-cylindrical, simple;

2 — flat-cylindrical with in-depth panel;

3 — flat-cylindrical with in-depth centers;

4 — flat-cylindrical with carved center;

5 — flat-cylindrical with chamfer;

6 — flat-cylindrical with chamfer and in-depth centers;

7 — flat-cylindrical with chamfer and carved center;

8 — flat-cylindrical with reinforced chamfer;

9 — flat-cylindrical with chamfer and one dash;

10 — flat-cylindrical with reinforced chamfer and one a dash;

11 — flat-cylindrical with chamfer and two dashes;

12 — flat-cylindrical with reinforced chamfer and two dashes;

13 — flat-cylindrical with small sphere;

14 — flat-cylindrical with normal sphere;

15 — flat-cylindrical with deep sphere;

16 — flat-cylindrical spherical;

17 — round with normal sphere and alone with a dash type "AND";

18 — round with normal sphere and two dashes type "AND";

19 — dragee-shaped simple;

20 — round with chamfer and sphere;

21 — round with in-depth centers;

22 — round flat with rim;

23 — round with rim and carved center;

24 — round with normal sphere and inscription;

25 — spherical ellipsoidal;

26 — spherical oval;

27 — spherical almond-shaped;

28 — spherical capsule-shaped;

29 — spherical capsule-shaped with commodity sign;

30 — spherical spherical;

31 — flat rectangular from rounded corners;

32 — flat rectangular with diamond-shaped corners;

33 — flat square from rounded corners;

34 — flat square with diamond-shaped corners;

35 — spherical diamond-shaped;

36 — spherical triangular;

37 — flat pentagonal;

38 — flat hexagonal;

39 — flat octagonal;

40 — flat heart-shaped

State Federal University ***pill for acceptance in the middle*** classified as:

— tablets without a shell;

— coated tablets ;

— pills "effervescent";

— pills soluble;

— pills dispersed;

— pills enteric- coated;

— pills with modified release;

— pills for application in oral cavity (oromucosal);

— oral lyophilisates.

"Shupuchi" tablet - uncoated tablets, the bulk of which consists of acids and carbonates or bicarbonates that react rapidly in the presence of water with the release of carbon dioxide. Effervescent, soluble and dispersible tablets are intended for dissolution or dispersion in water to form a solution or a homogeneous suspension, respectively, before administration.

Modified-release tablet — tablets with or without a coating, containing special excipients or obtained by methods that involve regulating the rate, location or time of release of the active substances. These include tablets with prolonged, delayed and pulsatile release.

The names of prolonged-release tablet preparations may include the terms " ***retard*** **" and "** ***depot*** **,"** which mean the release of LR at a reduced rate. " ***Rapid-retard***

" tablets are also available, with in which one part of the active ingredient is released quickly and the other slowly.

Depending on the dosage of LR, tablets are divided into **" *mitte* "**, **" *semi* "** and **" *forte* ".** — tablets, respectively, with minimum, medium and high dosage and minimum, medium and strong effect of the medicinal substance .

Chewable tablets are produced *that* quickly disintegrate when chewed into uniform pieces, the fillers of which are mannitol, sorbitol, lactose, dextrose, maltose, glucose or xylitol with the addition of dyes and flavors. Large chewable tablets are especially advisable for children and adults who have difficulty swallowing solid dosage forms.

Until recently, in addition to tablets pressed on tablet machines, ***molded* (*tructured*)** tablets were obtained, which were molded on special machines from plastic mass moistened with ethanol (40-95%). %), by rubbing it into perforated plates with subsequent extrusion of the rubbed mass by a punch system and drying. Molded tablets by mass to 0.05 g contained small doses medical substances and diluents (lactose, sucrose, glucose, starch). In the 21st century, due to the improvement of tablet machine designs, ***molded tablets are no longer produced!*** A new technology has been developed for obtaining tablets without pressing, the so-called **" *oral lyophilizates* ",** by dividing them into individual doses, freezing and drying solutions or suspensions of LR. Oral lyophilizates are intended for placement in the oral cavity, dissolution or dispersion in water before use.

1.1. PROPERTIES POWDER-LIKE MEDICINAL SUBSTANCES

The properties of the starting medicinal substances largely determine the rational method of obtaining tablets. As starting 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:

- 1. ***physical*** - density, shape, size and nature of the surface of particles, specific surface area of particles, forces of adhesion (sticking together on the surface) and cohesion (sticking together of particles inside the body), surface activity, melting point, etc.;

- 2. ***chemical*** — solubility, reactionary ability, etc.;
- C. ***technological*** (pharmaco-technological) - bulk volume and bulk density before shrinkage, shrinkage capacity, volume and density after shrinkage, degree of compaction, flowability, moisture content, fractional composition, dispersion, porosity, compressibility, etc.;
- 4. ***structural and mechanical*** — plasticity, strength, elasticity, viscosity of crystal lattices, etc.

These properties often divide on two big groups: physicochemical and technological.

Physico-chemical properties

Particle shape and size. Powdered drug 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.

Many API particles *are anisodiametric* (asymmetric, non-axial). They can be elongated in shape, where the length significantly exceeds the transverse dimensions (rods, needles, etc.). etc.), or lamellar, when the length and width are much greater than the thickness (plates, scales, plates, leaflets, etc.). A smaller part of powdered substances has *isodiametric* (symmetrical, equiaxed) particles - These are spherical formations, polyhedra, etc.

Form and particle size powders depend: in crystalline substances - from the structure of crystal lattices and the conditions of particle growth in the process of crystallization, in crushed plant materials - from the anatomical and morphological features of the ground plant organs and the type of grinding machine. The size of the powder particles is determined by their length and width, which are measured using a microscope equipped 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, the particles are conventionally divided into three main types:

elongated — length to width ratio — more than 3 : 1;

lamellar — the length exceeds the width and thickness, but not more than 3 times;

equiaxed — have a spherical, polyhedral shape, close to isodiametric.

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

The largest number of crystalline products is made up of substances of the monoclinic system - about 40%, cubic — 10, hexagonal - 7, tetragonal — 5, rhombic — 28, triclinic — 10 %. It is known that What only substances, belonging to the cubic system (sodium chloride, potassium bromide) are pressed into tablets directly, i.e. by direct pressing, without granulation and auxiliary substances. Usually, powders that have the form of particles in the form of rods are characterized by fine dispersion, good compaction and sufficient porosity (analgin, norsulfazole, akrihin, etc.).

Powders with equiaxed particle shape — coarse-dispersed, with a slight degree of compaction, low porosity (lactose, hexamethylenetetramine, salol). The more complex the surface of the powder particles, the greater the adhesion and the lower the fluidity, and vice versa.

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

Specific surface area — the total surface area occupied by the powdery substance, and ***the contact surface*** — a surface that is formed when powder particles collide with each other.

The true density of a powder is determined by the ratio of the mass of the preparation to its volume at zero porosity of the powder. Any liquid that wets but does not dissolve the powder is used as a filler. The determination is carried out using a volume meter (pycnometer - for powder-like solids).

The chemical properties of the starting materials are also important for tableting , such as solubility, wettability, hygroscopicity and the presence of water of crystallization.

3wettability. The wettability of powdered LRs is understood as their ability to interact with various liquids (lyophilicity) and primarily with water (hydrophilicity). The surface of solid particles of medicinal substances contains a certain number of hydrophilic groups (—OH, —COOH, etc.). etc.) or oxygen atoms, which are structural elements of their crystal lattices, therefore the wettability of the surface of powders has a different value depending on the intensity of the interaction of intermolecular forces. Hydrophobic (non-wettable by water) substances can be well wetted by other liquids -

for example, organic solvents.

Cyophilicity of powders substances, subject to tableting, is determined coefficient philosophies that represents relation 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 a wetting liquid on the surface of a solid particle is always accompanied by the release of the so-called heat of wetting. The practical significance of wettability is that water easily penetrates into a tablet obtained by pressing well-wettable 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 powder mass prepared for tableting will begin to absorb vapor from the air and spread in the absorbed water. The kinetics of moisture absorption is determined by the mass method under normal conditions, under extreme conditions (100% relative humidity) or in a climatic chamber. If the substance is very hygroscopic, this necessitates the use of auxiliary substances - moisture regulators.

Water of crystallization. Molecules of water of crystallization determine the mechanical (strength, plasticity) and thermal (dependence on air temperature) properties of the crystal and significantly affect the behavior of the crystal under pressure. The phenomenon of increasing the strength of tablets during storage ("cementation") is also closely related to the presence of water of crystallization in tableted substances.

Electrical properties. The phenomenon of electrification of powdered LRs during their processing and pressing gives grounds to conclude that, considering the nature of the bonding of particles in tablets, in addition to deformation characteristics, it is necessary to take into account dielectric characteristics. Under mechanical action, all asymmetric crystals containing polar groups in their structure or in the adsorbed water film will be subject to polarization. For non-polar substances, the formation of surface charges is impossible.

Technological properties

The technological properties of powdered LRs depend on their physicochemical properties.

The fractional (granulometric) composition, or the percentage distribution of powder particles by size, affects the degree of its free flowability, and therefore the

rhythmic operation of tablet machines, the stability of the mass of the resulting tablets, the accuracy of the dosage of the LR, as well as the qualitative characteristics of the tablets (appearance, disintegration, strength, etc.).

The fastest and most convenient method for determining dispersion is sieve analysis. The technique of this analysis consists in sifting 100.0 g of the powder under study through a set of sieves (hole diameter 2.0; 1.0; 0.5; 0.25 and 0.1 mm). A portion of the material is placed on the sieve with the largest holes (top) and the entire set of sieves is shaken (manually or on a vibrating machine) for 5 min, and then determine the mass of each fraction and its percentage content.

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

It is important to determine such volumetric parameters of powders as bulk volume, bulk density before shrinkage, shrinkage capacity, volume and density after shrinkage, relative density and porosity.

Bulk volume (volume before shrinkage) — volume of 100.0 g of powder poured without compaction. ***Bulk density*** (density before shrinkage) — mass of a unit volume of freely poured powder. It depends on the density and humidity of the substance, the shape and size of the particles, their arrangement. The bulk density value can be used to predict the nature of the excipients used and the volume of the matrix channel of tablet machines, since the dosage of masses (powders and granules) of tablets in them is carried out by volume. Medicinal powders are usually light, the error in measuring their bulk volume is higher than that of heavy bulk materials. Therefore, the volume and density of powders after shrinkage during mechanical shaking are also determined. The difference between the bulk volume of the bulk material and the volume after shrinkage shows ***the ability of the material to shrink*** **.** The determination of such indicators is carried out on a device that consists of: a graduated cylinder with a capacity of 250 ml with a division value of 2 ml, which is installed on a special stand, and shaking device, What provides 250±15 cylinder jumps per minute from a

height of 3±0.2 mm. The method for determining these indicators is given in the State Federal University (SFU, p. 2.9.34).

Bulk density r_n, g/ml, and density after shrinkage Russian , g/ml, calculated by the formula

$$\rho_{n(inc)} = \frac{m}{V}, \quad (3.1)$$

0(1250;2500)

where *m* — mass weights loose material, g.

Depending from density after shrinkage distinguish powders like this in the following way:

- $r_n > 2000$ kg/m ^{3} — very heavy;
- $2000 > r_n > 1100$ kg/m ^{3} — heavy;
- $1100 > r_n > 600$ kg/m ^{3} — medium;
- $r_n < 600$ kg/m ^{3} — easy.

Determination of bulk density and density after shrinkage can also be carried out according to the State Federal Institute of Physics and Technology by other methods, using a volume meter and a stainless steel vessel with a capacity of 100 ml.

Relative density τ — ratio of density after shrinkage p_{us} to actual density p:

$$\tau = \frac{\rho_{mous}}{\rho} \cdot 100.$$

***Porosity* is** the volume of free space (pores, cavities) between powder particles. Porosity *P* is determined based on the values of the density after shrinkage and the true density:

$$P = \left(1 - \frac{\rho_{yc}}{\rho}\right) \cdot 100 \text{ or } P = 100 - \tau. \quad (3.3)$$

The ability of the powder to compress under pressure depends on these

volumetric characteristics.

Compression *ratio* — powder height ratio in the matrix H_1

to the height of the resulting tablet H_2: K_{szh} □

The determination is carried out using a matrix. The matrix channel is filled with

powder and pressed at a pressure of 120 MPa. The resulting tablet is pushed out with a punch and the height is measured. The ability of powdered preparations to compress is affected by the shape of the particles, the ability of the latter to move and deform under pressure. The compaction coefficient is an essential technological factor; in particular than he higher, that more time is spent on pressing.

H_1 . H_2

At the same time, more effort is spent on pushing the tablet out of the depth of the matrix channel.

At tableting the most important technological properties There is fluidity, compressibility and slip, which allows the tablet to be easily pushed out of the die.

Flowability (fluidity, fluidity) — the ability of a powdery material to pour out of a funnel or "drain" under the action of its own weight and ensure uniform filling of the matrix channel. A material that has poor flowability in the funnel sticks to its walls, which disrupts the rhythm of its flow into the matrix. This leads to the fact that the specified mass and density of the tablets will fluctuate. The flowability of powders is a complex characteristic determined by the dispersion and shape of the particles, the humidity of the masses, the particle size distribution, the coefficient of interparticle and external friction, and the bulk density. This technological characteristic is taken into account when choosing a tableting technology. Powdery mixtures containing 80-100 % of the fine fraction (particle size less than 0.2 mm) are poorly dosed, therefore it is necessary to carry out directed particle enlargement of such masses, i.e. granulation. If the fine fraction contains up to 15 %, it is possible to use the direct pressing method.

The following methods are used to determine flowability: ***nozzle flow rate ; angle of natural slope ; compressibility index or Fausner coefficient ; shear cell methods*** . Monitoring the flow rate of the material through the nozzle is considered one of the best methods for measuring the flowability of a powder. However, this

method is used only for freely flowing materials. Nozzle flow rate is usually measured as the ratio of mass and pouring time from any different type of container (funnels, cylinders) on special devices from the Sotax FT300 company (Switzerland), the PTG-S3 model from the Pharma Test company, the GTB series from the Erweka company (Germany), etc. Method definition these indicators given in pharmacopoeia (SFU, (paragraph 2.9.36).

Indirect flow characteristic - angle of natural slope - the angle a between the generator of the cone of the bulk material and the horizontal plane is determined from the equation tg a = cone height/(0.5 x base diameter). For example, to determine the angle of natural slope, the GTB series devices from Erveka are equipped with a small table onto which powder or granulate is poured from a funnel, forming a cone. The laser built into the device determines the dimensions of the cone, from which the angle of slope is calculated. The angle of natural slope varies within wide limits - from 25 to 30° for well-flowing powders and 60-70° for bound materials. Hence, the smaller the slope angle, the higher the flowability.

The degree of compressibility of the powder. The interactions between particles that affect the bulk properties of the powder also affect the fluidity of the material. For a freely flowing powder, less interaction between particles is characteristic, and the values of bulk density and density after shrinkage will be close. For less fluid materials, significant differences are observed between bulk density and density after shrinkage. Therefore, fluidity can be estimated from the compressibility index of the powder **(** Carr index) and the Hausner coefficient. ***The compressibility index*** , or ***Carr index*** *C* , %, is a quantity calculated by formula (3.5) or alternatively by formula (3.6):

C □ V 0 □ V 1250(2500) ____ □100 ;

V 0

WITH □ □ mous □ □ n _____ □100 .

□ mous

Coefficient Hausner calculate by formula :

$HR = V0 / V1250_{(2500)}$;

HR = Rus/RN.

The more the powder is compacted in the cylinder on the shaking device, i.e. the higher the Carr index and the Hausner coefficient, the smaller the fluidity powder. Classification fluidity, developed by R. L. Carrom.

Fluidity scale

Fluidity	Angle natural slope, hail	Compressibility index (indicator Carr)	Coefficient Hausner
Very good (excellent)	25— 30	1— 10	1.00— 1.11
Good	31— 35	11— 15	1.12— 1.18
Satisfactory	36— 40	16— 20	1.19— 1.25
Permissible (powder can hang in the funnel)	41— 45	21— 25	1.26— 1.34
Not satisfactory (powder trace shake off, to mix)	46— 55	26— 31	1.35— 1.45
Bad	56— 65	32— 37	1.46— 1.59
Very bad	Over 66	Over 38	Over 1.60

Methods sliding cell allows more exactly evaluate powder flowability, although methods enough labor-intensive. One from types shear A cell is a cell consisting of a horizontal base and rings that form plane shift between lower stationary basis and upper by the moving part of the shear cell ring. After compacting the powder layer in the shear cell, the force required to shear the powder layer by the moving ring is determined.

Compressibility — the ability of powder particles to cohesion under pressure, i.e. the ability of particles under the action of electromagnetic forces (molecular, adsorption, electrical) and mechanical interlocking to attract each other to form a

stable, strong compressed product. There are no direct methods for determining compressibility, but it is characterized by the strength of a model tablet after pressure is removed. The greater the compressibility of the powder, the higher the strength of the tablet. If the compressibility is poor, the tablet is formed weakly, and sometimes completely breaks when pushed out of the matrix.

When determining the compressibility of powder (granulate), a sample weighing 0.3 or 0.5 g are moving in matrices by with help punches diameter 9 and 11 mm on a hydraulic press at a pressure of 120 MPa. The resulting tablet is weighed, the height is measured with a micrometer and the compressibility coefficient $K_{compress}$, g/mm, is calculated by the formula

To the press —

□ m, H

(3.9)

where *m* — mass pills, g; *N* — height pills, mm.

Compressibility can be assessed by the tablet's resistance to crushing. The resistance is determined on devices (such as the TVN from the company "Erveka") and "Pharma-test"), which allow measuring the force required to break tablets (in Newtons). The higher the tablet's resistance to crushing, the better the compressibility and formability of the tablet mass.

It is established, What for substances from stability tablets to crushing:

- over 70 N — pure solvents are used for the granulation process; if these are finely dispersed powders with good flowability, they are processed directly, i.e. by direct processing;
- 40—70 N — enough application ordinary binding agents;
- 0—40 N — it is necessary to use highly effective binding agents.

conclusion about technology tableting.

The force of screwing tablets out of the matrix. To push a compressed tablet out of the matrix, it is necessary to apply a force to overcome the friction and adhesion between the lateral surface of the tablet and the wall of the matrix. Considering the magnitude of the push-out force, antifriction additives are predicted (sliding or lubricating) substances. For definition forces extrusion a portion of powder weighing 0.3 or 0.5 g is pressed into a die with diameter in accordance 9 and 11 mm on hydraulic press at pressure 120 MPa. The pressed tablet is ejected by the lower punch. The ejection force is recorded on the press manometer.

The nature of particle bonding in tablets . Tableting is based on the use of the properties of powdered LR to compact and solidify under pressure. In this case, the weakly structured material is transformed into a cohesive-dispersed system with a certain amount of porosity. Such a system is in many ways close in its properties to a compact body in which certain adhesion forces act.

Powder compressibility, as already it was noted earlier, it the ability of its particles to cohesion and adhesion under pressure to form a strong compact tablet. Under pressure, the powder particles seem to fuse, stick together, and adhere between by myself, in result weakly structured dispersed the system transforms into a homogeneous solid.

Objectives and main types of granulation in tablet production.

Granulation is the directed enlargement of particles, that is, the process of converting powdered material into grains of a certain size.

Granulation is necessary to improve the flowability of the tableted mass, which occurs as a result of a significant reduction in the total surface area of the particles when they stick together into granules and, therefore, a corresponding reduction in the friction that occurs between the particles during movement.

Currently existing granulation methods are divided into the following 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 adhesives in enameled mixers with subsequent drying to a granular mass. Then the mass is converted into a coarse powder using rollers or an Excelsior mill. Granulation by grinding is used in cases where the moistened material reacts with the material when rubbed. 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 introduced into the composition of the tableted powder mass, 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 rubbing the mass with moisture, is carried out in order to compact the powder and obtain uniform grains - granules with good flowability.

This method of granulation is suitable for powders that have poor flowability and insufficient adhesion between particles.

In both cases, bonding solutions are added to the mass to improve adhesion between particles.

The wet granulation method includes the following operations:

1) mixing 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 powders . This is done to achieve a homogeneous mass and uniform distribution of the active ingredient in the tablets.

Mixers of various designs are used to mix and moisten powdered 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, previously sifted through a sieve, add to the mass in separate portions in the form of triturations, that is, diluted with a filler at a concentration of 1:100;

- colored substances and substances with a high specific load the mass into the mixer last;

- volatile essential oils should be introduced into dry granulation bath mass before pressing at the powdering stage, in avoid their weathering.

The practice of tablet production shows that the time required to mix 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 humectant is added to the mass in separate portions, which is necessary to prevent it from clumping.

When wet mixing powders, the uniformity of their distribution is significantly improved, there is no separation of particles and stratification of the mass, and its plasticity is improved. Mixing wetted powders is accompanied by some compaction of the mass due to the displacement of air, which allows you to obtain denser solid granules. Mixing time of wet mass: for simple mixtures 7-10 min, for complex ones - 15-20 min. The optimal amount of humectant is determined experimentally (based

on the physicochemical properties of the powders) and is specified in the regulations. An error can lead to a defect: if you add too little humectant, the granules will crumble after drying, if too much - the mass will be viscous, sticky and poorly granulated. The mass with optimal humidity is a moist, dense mixture that does not stick to your hands, but crumbles into separate lumps when squeezed.

Granulation of wet mass . Wet mass is granulated on special granulator machines, the principle 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 tablet production, but it has a number of disadvantages:

— prolonged exposure to moisture on medicinal and auxiliary

corrosive substances;

— deterioration of the disintegration (solubility) of tablets;

- the need to use special equipment;

- duration and complexity of the process.

Drying wet granules. Different types of dryers are used:

1) shelf dryers with forced air circulation;

2) dryers with silica gel column.

If it is necessary to regenerate the liquids contained in the materials being dried, dryers are used in which air is passed through silica gel. In this case, valuable vapors are adsorbed, and the warm air is used again to dry the material.

Infrared rational dryers . Special mirror lamps, nichrome filament spirals placed at the focus of a parabolic reflector, metal and ceramic panel radiators with electric, steam or gas heating are used as heat emitters in such dryers.

Freeze dryers . In recent years, the method of drying materials in a frozen state under conditions of deep vacuum has been widely used in industry. It is called freeze drying, or molecular drying. The method allows you to preserve the basic biological qualities of the dried material, when the solid evaporates 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.

Dried granules must have some moisture before pressing, which is called residual moisture.

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 the GF, and the strength - the highest compared to tablets obtained from granules of the same drug with a different degree of humidity.

Underdried granules stick to the punches, fill the matrix unevenly, and require increased amounts of antifriction agents. Overdried granules are difficult to compress, and tablets may have broken edges.

Processing of granules **.** During the drying process, the granules may clump together into individual lumps. In order to ensure a uniform fractional composition, the dried granules are passed through granulators with mesh sizes of 1.5 mm, which largely ensures a constant weight of tablets. Then the granules are powdered by adding antifriction agents and transferred to the tableting stage.

Structural granulation. Has a characteristic effect on moistened material, leading to the formation of rounded, and under certain conditions, fairly uniform in size granules.

Currently, there are three methods of granulation of this type used in pharmaceutical production: granulation in a coating pan; spray-drying granulation and structural granulation.

For granulation in a dragee , a mixture of powders is loaded into a boiler and, when the boiler rotates at a speed of 30 rpm, moistening is carried out by feeding a solution of a binder through a nozzle. The powder particles stick together, are dried with warm air and, as a result of friction, acquire approximately the same shape. At the end of the process, lubricants are added to the dried granulate.

Materials for activating higher education students during lectures: questions, situational tasks, etc.:

Question:

1. What types and groups of tablets are there?
2. List the properties of powdered medicines.
3. On what grounds? classify pills?
4. What are the physical properties of powders?
5. What are the main groups of excipients in the production of tablets?
6. What form of tablets are produced?
7. What are the purposes and main types of granulation in tablet production?
8. Describe ways to improve tablets as a dosage form.

General material and methodological support for the lecture:

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

Questions for self-control:

1. How to characterize types and groups of tablets?
2. What properties do powders have?
3. How can tablets be classified by shape?
4. Name the main types of granulation.

List of sources used:

1. A textbook for independent work of students of the Faculty of Pharmacy for the licensing exam "Step 2. Pharmacy" / V.Yu. Anisimov, O.I. Belyaeva, G.G. Vidavska, V.O. Helmboldt, A.V. Zamkova, I.V. Lytvynchuk, A.V. Nikitin, B.V. Prystupa, I.B. Petkova, Ya.V. Rozhkovsky, S.B. Strechen, L.M. Unguryan, N.S. Fizor Odessa: Odessa National Medical University. 2020. - 240 p.

Access mode 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: basic textbook for students of higher. educational. pharmaceutical institutions (pharmac. faculties) / E.V. Gladukh, O.A. Ruban, I.V. Saiko and others. - Kh.: NPhU: Original, 2016. - 632p. : Named after. - (Series "National textbook")

2. Workshop on industrial technology of medicines, specialty "Pharmacy" / Edited by Ruban O.A. - Kh .: National University of Physics and Technology, 2015. - 374 p.

3. INDUSTRIAL technology of medicines : a manual for independent work of students / O. A. Ruban , V. D. Rybachuk , L. M. Khokhlova etc. – KH.: NATIONAL UNIVERSITY OF PHYSICS AND TECHNOLOGY, 2015. – 120 p.

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5. Technology of industrial drug production: a textbook for students of higher education institutions: in 2 parts / V. I. Chuyeshov, E. V. Gladukh, I. V. Sayko and others – 2nd ed., revised and supplemented – Kh.: National University of Physics and Technology: Original, 2012. – Part 1. – 694 p.

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7. Modern pharmaceutical technologies: teaching aids for laboratory classes of undergraduates of full-time, evening and correspondence forms of study in the specialty 8.110201 "Pharmacy" / edited by O. A. Ruban. – Kh.: Publishing house of the National University of Physics and Technology, 2016. – 256 p.

8.Encyclopedia of Pharmaceutical Technology: 3-d Ed. / ed. by J. Swarbrick. – New York; London: Informa Healthcare, 2007. – 4128 p.

9.European Pharmacopoeia 8.0 [8th edition] / European Directorate for the Quality of Medicines & Healthcare. - Strasbourg, 2013. - 3638 p.

10. Handbook of Pharmaceutical Excipients, 6th edition / RC Rowe, PJ Sheskey, ME Quinn. - Pharmaceutical Press and American Pharmacists Association, 2009. - 521 p.

11. State Pharmacopoeia Ukraine / State enterprise « Ukrainian scientific officinal center qualities medical " means " - 2nd ed . – Kharkiv : State enterprise « Ukrainian scientific officinal center qualities medical means ", 2015. – T. 1. – 1128 p .

12. State Pharmacopoeia Ukraine / State enterprise « Ukrainian scientific officinal center qualities medical " means " - 2nd ed . – Kharkiv : State enterprise « Ukrainian scientific officinal center qualities medical means ", 2014. – T. 2. – 724 p .

13. State Pharmacopoeia Ukraine / State enterprise « Ukrainian scientific officinal center qualities medical " means " - 2nd ed . – Kharkiv : State enterprise « Ukrainian scientific officinal center qualities medical means ", 2015. – T. 3. – 732 p .

14. On medicinal products: Law of Ukraine dated 4.04.96 No. 123/96 // Bulletin of the Verkhovna Rada of Ukraine. – 1996. – .№ 123