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«STUDY GUIDE FOR PREPARATION FOR PRACTICAL CLASSES IN THE DISCIPLINE "DRUG TECHNOLOGY" (INDUSTRIAL TECHNOLOGY OF MEDICINES) FOR FULL-TIME, PART-TIME AND DISTANCE LEARNING STUDENTS (1 PART)»

(for full-time, part-time and distance learning students)

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In accordance with the content of the Drug Technology programme, this textbook presents the main theoretical issues required for the course, as well as test tasks to check the students' mastery of the educational material.

The publication is recommended for students of pharmaceutical faculties, as well as for students of medical universities.

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Topic: "Regulatory documentation in the production of medicinal products"

The pharmaceutical industry in the European Union operates in accordance with standards that contain high requirements for ensuring the quality of medicines in their development, production and control. The marketing authorisation system requires all medicinal products to undergo an expert evaluation by a competent authority to ensure that they meet the latest safety, quality and efficacy requirements. The system of manufacturing authorisation ensures that all products authorised for sale on the European market are manufactured only by licensed manufacturers whose activities are regularly inspected by the competent authorities. Manufacturing licences are mandatory for all pharmaceutical manufacturers in the European Community, regardless of whether the products are sold within or outside the Community.

The Commission has adopted two directives establishing the principles and rules of good manufacturing practice (GMP) for medicinal products. Directive 2003/94/EC concerns medicinal products for human use, and Directive 91/412/EEC concerns medicinal products for veterinary use. Detailed rules (requirements) that are consistent with the principles of these directives are set out in the Good Manufacturing Practice guidelines used to assess applications for manufacturing licences and inspect manufacturers of medicinal products.

The GMP principles and detailed rules apply to all processes requiring licensing in accordance with Article 40 of Directive 2001/83/EC and Article 44 of Directive 2001/82/EC, as amended by Directives 2004/27/EC and 2004/28/EC respectively. In addition, they apply to all batch manufacturing of medicinal products, including hospital manufacturing and manufacturing of medicinal products for clinical trials.

All EU Member States and industry representatives have agreed that the requirements for good manufacturing practice for medicinal products for use in veterinary medicine should be the same as for human medicinal products. Some more detailed GMP rules specific to the manufacture of veterinary medicinal products and immunobiological products for veterinary use are set out in two annexes.

This Guideline consists of two parts: the basic requirements and the specific annexes. Part I contains GMP principles for the manufacture of medicinal products. Part II covers the GMP principles for the manufacture of active substances used as starting materials.

The chapters of Part I on "basic requirements" begin with the principles set out in Directive 2003/94/EC and Directive 91/412/EEC. Chapter 1, Quality Management, sets out the fundamental concept of quality assurance in the manufacture of medicinal products. According to it, each of the chapters formulates in general terms a principle focused on ensuring the aspect of quality to which that chapter is devoted and provides the text of rules set out in sufficient detail to enable manufacturers to understand and comply with the principle.

Part II was recently developed on the basis of guidance developed by the ICH and published as ICH Q7a on "active pharmaceutical ingredients", which was incorporated into the GMP Manual as Annex 18 for voluntary use in 2001. According to the revised Article 47 and Article 51 of Directive 2001/83/EC and Directive 2001/82/EC respectively, as amended, the Commission adopts and publishes detailed rules to the GMP principles for active substances used as starting materials. The former Annex 18 has been replaced by the new Part II of the GMP Guidelines, which applies to medicinal products for human and veterinary use.

In addition to the basic principles and rules of good manufacturing practice set out in Parts I and II, the guideline includes a number of annexes that provide more detailed rules for specific industries. For some manufacturing processes, more than one annex should be applied simultaneously (e.g. annexes for the manufacture of sterile medicinal products, radiopharmaceuticals and/or biological products).

The annexes are followed by a glossary of some of the special terms used in this guideline.

The guideline does not address the safety of personnel involved in manufacturing. These issues can be very important in the manufacture of certain medicinal products, such as potent, biological and radioactive products. They are regulated by other Community regulations or national legislation.

The Guideline stipulates that the holder of a manufacturing licence systematically incorporates the requirements of the marketing authorisation relating to the safety, quality and efficacy of medicinal products into all manufacturing, control and authorisation activities.

For many years, the production of medicinal products has been carried out in accordance with the rules of good manufacturing practice; the production of medicinal products is not regulated by CEN/ISO standards. The harmonised CEN/ISO standards adopted by the European Organisation for Standardisation can be used at the discretion of manufacturers as a tool for implementing quality systems in the pharmaceutical sector. In this third edition of the guideline, the CEN/ISO standards have been taken into account, but the terminology of these standards has not been applied.

It is acknowledged that there are other acceptable methods, other than those described in this guideline, by which the principles of quality assurance can be met. The guideline is not intended to restrict in any way the development of any new concepts or new technologies that have been validated and guarantee a level of quality assurance at least equivalent to that set out in this guideline. This Guideline will be reviewed regularly.

Industrial production of medicinal products is regulated by the relevant regulatory and technical documentation (R&D) approved in accordance with the established procedure.

The regulatory and technical documentation should ensure the improvement of the quality and efficacy of medicinal products, be constantly improved based on the achievements of science and technology and be reviewed in a timely manner to replace outdated indicators in accordance with the needs of public health, national defence and export.

Regulatory documents are documents that establish rules, general principles or characteristics relating to various activities or their results.

The following categories of regulatory documents for medicinal products, medicinal plant materials and medical devices are divided into:

1. Technological and technical regulations.

2. State Pharmacopoeia (SP).

3. Analytical normative documentation.

4. State standards (GOST, DSTU).

5. Industry standards (OST), Industry Standard of Ukraine (GSTU).

6. Technical specifications (TU U).

7. Guiding regulatory document (GD) - instructions, guidelines, etc.

8. Production technological instructions.

A technological regulation is a regulatory document that sets out the technological methods, technical means, standards and norms for the manufacture of a medicinal product.

The technological regulations are the basis for the batch production of chemical and pharmaceutical products.

The technological process of manufacturing medicinal products consists of separate, successive stages of production.

A production stage is a set of technological operations that lead to the production of an intermediate product (at the final stage - a finished product). For example, the tablet manufacturing process includes the following production stages: mixing, granulation, and pressing. Each stage, in turn, is a combination of a number of sequential technological operations.

The production flow chart should clearly (graphically in the form of a flow chart) reflect the sequence of work in this production with their subdivision by stages and operations of the technological process, indicating the main material and energy communications (raw material supply, steam, water supply, waste, wastewater, air emissions).

Technological operation is a part of the technological process associated with the maintenance of one of the main types of equipment. For example, in the production of tablets, such operations are: grinding ingredients, weighing, sieving, moistening the mixture to be granulated, etc.

The technological operation is depicted separately with an indication of its belonging to a certain stage. Each stage and operation shall be characterised by a name

and an index consisting of a symbol and a serial number. Stages are numbered in the order in which they are performed during the technological process, starting with the receipt and preparation of raw materials and ending with the shipment of finished products.

The following stage designations are used in the flow chart:

"AW" - stages of auxiliary works

" TP" - stages of the main technological process

"RofW" - stages of recycling of used waste

"WD" - stages of waste disposal

"NPVEA" - Stages of neutralisation of process and ventilation emissions into the atmosphere

"PLS" - packaging, labelling and shipment of the finished product

If auxiliary works (dissolution and drying of raw materials, preparation of solutions of a given concentration) are carried out in separate equipment for one stage of the main technological process, then such auxiliary works are included in this stage of the main technological process.

Auxiliary activities carried out in separate equipment for several stages of one or more production processes are separated into independent stages of auxiliary activities (for example, preparation of purified water, acid or alkali solutions with a given concentration for the entire workshop).

If waste treatment or disposal is carried out as a separate activity, it may not be included in the production flow chart. In this case, an arrow on the flow chart indicates where the waste is sent for processing (neutralisation).

Analytical regulatory documentation (ARD) — pharmacopoeial articles, documents on analysis methods, as well as other analytical documentation that allows to control the quality of the medicinal product. The ARD is an integral part of the registration documents - a set of materials for a medicinal product, the specialised evaluation of which allows to draw conclusions about the possibility of its state registration, the need for pre-registration studies or quality control of samples of the medicinal product.

Standard - a regulatory document that sets out rules, requirements, general principles or characteristics relating to various activities or their results for general and repeated use to achieve an optimal degree of orderliness in a particular area.

Technical specifications are a regulatory document that sets out requirements for specific products or services and regulates the relationship between the supplier and consumer of the products.

Technological regulation is a regulatory document that sets out the technological methods, technical means, standards and norms for manufacturing a medicinal product.

Technical regulation is a regulatory document that sets out the conditions for a specific set of technological equipment that ensure the production of intermediate products or medicinal products of a particular dosage form of a given quality.

Material balance - the ratio between the amount of raw materials, materials, intermediate products and intermediate products (C1) used in production and the amount of actually obtained finished products (C2), by-products (C3), waste or refuse (C4) and losses (C6), i.e. the ratio of theoretically possible and actually obtained output of finished products. If there are no by-products, the material balance equation is simplified:

$$C1=C2+C6.$$

Material losses in the production of medicines are of different origin, so they are divided into several

groups:

* mechanical losses, which occur mainly in the absence or insufficient mechanisation of material handling during processing (liquid spillage, spraying, crushing, bruising, etc.)

* physical and chemical, which are observed when the technological process is carried out without taking into account the physical and chemical properties of medicinal substances (incomplete extraction of active substances from medicinal plant material, loss of volatile solvents during filtration, essential oil during evaporation, etc;)

* chemical, which are possible as a result of non-compliance with or incorrect choice of chemical reaction (synthesis) parameters.

The material balance sheet is of great practical importance, as it determines the degree of sophistication of the technological process. The more complete it is, the more thoroughly the technology of a given drug is studied. The fewer losses of various kinds in the balance sheet, the more correct the production process is. And vice versa, the more material losses are included in the balance sheet, the less perfect the technology of the drug is considered to be.

1. Name the main regulatory and technical documents that regulate the activities of a technologist and are used for the preparation of medicines;

2. What are the general principles of production of finished dosage forms;

3. What are the categories and structure of regulatory documents.

4. Conditions of industrial production of drugs in accordance with the GMP rules.

5. Name the main terms used in the manufacture of medicines.

6. How to plan the technological process, production regulations, technical and economic balance;

7. Identify the characteristics, requirements for medicines;

8. List the stages of the technological process (general and partial);

9. What is the current appearance of packaging, quality assessment and prospects for further improvement of its manufacturing technology.

Topic: "Requirements for sterile products. Determination of the main quality indicators of ampoule glass"

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

Medicinal products are administered by injection (small volume injection), infusion (infusion of more than 100 ml at a time by drip or stream) or implantation with the help of special devices that violate the integrity of the skin or mucous membranes. Such use is quite painful, so recently less painful methods of needleless administration of injectable solutions in the form of a thin (about 0.1-0.12 mm in diameter) jet under high pressure, which is sprayed out of the hole of a special injector at a speed of 300 m/s and penetrates the skin to a depth of 3 cm. For this purpose, manual injectors such as "Bee", "Hynospray", "Jetinjection" are used.

According to the SFS, medicinal products for parenteral use are classified into the following groups:

1) injectable medicinal products;

2) intravenous infusion medicinal products;

3) concentrates for injectable or intravenous infusion medicinal products;

4) powders for injectable or intravenous infusion medicinal products;

5) implants.

The requirements of this Article shall not apply to medicinal products made from human blood, immunological and radiopharmaceutical products, implantable prostheses.

Injectable medicinal products are sterile solutions, emulsions or suspensions. Solutions for injection must be transparent and free of particles. Emulsions for injection should not show signs of stratification. Sediment may be present in suspensions for

injection, but it should disperse instantly on shaking to form a suspension. The resulting suspension should be sufficiently stable to provide the required dose when administered.

Intravenous infusion medicinal products are sterile aqueous solutions or emulsions (water as a dispersion medium) that are free of pyrogens and usually isotonic to blood. They are intended for use in large doses and should therefore not contain any antimicrobial preservatives,

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

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

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

Parenteral administration of medicinal products involves skin disruption, which is associated with possible infection with pathogenic microorganisms and the introduction of mechanical inclusions. Therefore, sterile manufacturing, compared to other industries, has specific features dictated by the requirements for injectable dosage forms. The main ones are the absence of mechanical impurities, sterility, stability, apyrogenicity, etc., and for some drugs - isotonicity, osmolality or osmolarity, isoionicity, isohydricity, viscosity, which is specified in the relevant regulatory and technical documentation.

Sterile products are produced in special primary packaging (vessels) made of glass (ampoules, vials) or polymeric materials (vials, flexible containers, syringe-ampoules).

Vessels for injectable drugs are divided into 2 groups:

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

- multi-dose vessels, which provide the possibility of repeated withdrawal of a certain amount of drug from the vessel without compromising sterility.

The volume of the injectable medicinal product in a single-dose container should be sufficient to withdraw and administer the nominal dose using the usual method of administration.

Multidose aqueous injectable medicinal products contain an appropriate antimicrobial preservative in the required concentration, except for medicinal products with appropriate antimicrobial properties. When a drug for parenteral administration is released in a multi-dose container, it is necessary to indicate the safety precautions for its administration and especially for storage between doses.

The most common type of disposable container is the ampoule. Ampoules are glass vessels of various capacities and shapes, consisting of an expanded body (bulb) and a capillary (stem). In the pharmaceutical industry, the most common ampoules are 1, 2, 3, 5 and 10 ml; 20 and 50 ml are typical for veterinary medicine. The capillaries of the ampoules can be smooth or with a crimp. The most rational are ampoules with a crimp, so the liquid from the ampoule cannot get into the capillary, which is important when opening the ampoules. Notification 0712.1-98 on changes to TU U 480945-005-96 introduced new ampoules with a coloured break ring.

In our country, syringe and vacuum-filled ampoules are produced with the appropriate labelling:

Vacuum-filled ampoules: VPO - vacuum-filled with a pinch open; VO - vacuum-filled without a pinch open;

Syringe-filled ampoules: IP-O - open syringe filling; IP-S - open syringe filling with a socket;

C - paired;

G - for glycerin

Along with the letter designation, the capacity of the ampoules, the glass grade and the number of regulatory and technical documentation (standard) are indicated. In terms of quality and size, the ampoules must meet the requirements of TU U 480945-005-96 (Annex D, Fig. 1-5) or OST 64-2-485-85.

An example of the designation of an IP type ampoule with a nominal capacity of 1.0 ml, shape B, without a coloured break ring, made of USP-1 glass:

Ampoule IP-1B USP-1 TU U 480945-005-96.

An example of the designation of an IP type ampoule of nominal capacity of 1.0 ml, shape B, with a coloured break ring made of USP-1 glass:

Ampoule IP-1B KI USP-1 TU U 480945-005-96.

A syringe ampoule is a disposable container. These are tubes made of polymeric materials with an injection needle protected by a cap. As a rule, they have a special purpose and are called differently in different countries - cytolem, mayol, ampoule, etc.

Examples of multi-dose vessels are vials for infusion solutions with a capacity of 50, 100, 250, 500 ml, made of glass or polymeric materials. Flexible containers made of polyvinyl chloride (PVC) are promising vessels for infusion solutions.

Glass vessels for injectable solutions are made of medical glass, which is a solid solution (alloy) of silicates, metal oxides and some salts. By varying the composition of the components and their concentration, glass with specified properties can be produced.

Depending on the qualitative and quantitative content of additives and the resulting properties, there are 2 classes and several grades of glass used in the production of ampoules.

Since 1996, Ukraine has been producing ampoules from medical grade glass - USP-1 (TU U 480945-002), which corresponds to water resistance class 1/121. The ampoules are not allowed to have internal residual inclusions that create a specific difference in beam path of more than 8 million "1, chips, unwashable dirt and glass dust. USP-1 ampoules must be thermally stable and withstand a temperature difference of at least 130°C; chemically stable - the change in pH of water after ampoules are treated in a steriliser should not exceed 0.8.

It is allowed to manufacture ampoules from other grades of medical glass that do not impair product quality. Glass grades belong to the first class: NS-3, NS-1, and NS-2, AB-1, to the second class.

Ampoules are produced at glassworks from glass tubes (glass wire) of the above glass grades and grades. The glass wire is a 1 to 1.5 metre long tube with fixed inner and

outer diameters. Calibration of the wire is very important to obtain ampoules that are uniform in size, have the specified capacity and are the same for the entire series. The quality of the wire is strictly regulated by the following indicators: taper, difference, straightness, ovality, bending, and contamination.

In addition, there must be no mechanical inclusions, air bubbles or other glass defects.

After manufacturing and sorting, the wire is washed. There are several ways of washing:

1. Chamber
2. Ultrasonic
3. Contact-ultrasonic

Drying of glass wires is carried out with hot filtered air or using the tunnel method.

All types of ampoules are made from glass wires on rotary glass-forming machines or semi-automatic machines of various companies IO-8 "TUNGSRAM" (Hungary), "AMBEG", "MATWER" (Germany). The disadvantage of this method of manufacturing ampoules is the formation of internal stresses when the length of bonds between the molecules of the glass composition is redistributed, which can lead to mechanical destruction of the product or the appearance of microcracks under adverse conditions (high temperature, sudden temperature changes, vibration, etc.). Therefore, after manufacturing, the residual stresses are removed by annealing the ampoules in special ovens. The annealing process involves heating the ampoules or vials to a temperature close to the glass softening point, keeping them at this temperature for 7-10 minutes and gradually cooling them down.

The American company Corning-Glass has developed a new method of manufacturing ampoules without the intermediate use of wire. The process of forming glass products on these machines is a jet-blowing method that ensures a high degree of uniformity in the distribution of glass mass in the walls of finished products.

The following requirements are imposed on glass for ampoules

- transparency - for visual and optical inspection for the absence of mechanical inclusions;

- colourlessness - allows detecting discolouration of the solution in addition to mechanical inclusions;

- fusibility - necessary for high-quality sealing of ampoules at a relatively low temperature to avoid heating of the solution;

- thermal stability - the ability of glass products not to be destroyed by sudden temperature fluctuations;

- chemical resistance, which guarantees the preservation of medicinal substances and other components of the drug, showing the ability of glass to leach;

- mechanical strength - to withstand loads during ampoule handling during production, transportation and storage. This requirement must be combined with the necessary fragility for easy opening of the ampoule capillary.

- the specific surface area of contact between the solution and the glass, because the higher this value is, the higher the chemical resistance of the glass should be.

Preparation of ampoules for filling includes the following operations: opening capillaries, determining the quality of ampoules, washing, drying and/or sterilising ampoules.

The quality of ampoule glass and ampoules is assessed by the following parameters:

1. Water resistance
2. Alkali resistance
3. Residual stresses
4. Thermal stability
5. Chemical resistance
6. Light protection properties (for SNS-1 glass)
7. Visual inspection of ampoules
8. Radial runout of the ampoule stem relative to the body
9. Deviation from the roundness of the ampoules
10. For vacuum-filled ampoules, the depth of vacuum is determined to ensure accurate filling of the ampoules using a vacuum.
11 . For ampoules with a coloured break ring, the break strength is determined.

Table 1.2 shows the comparative characteristics of different grades of ampoule glass.

The radial runout of the ampoule stem relative to the body axis and the radial runout of the conical ends relative to the axis of the cylindrical part of the G-type ampoule is checked using a universal stand type ST according to GOST 10197 or TU 2-034-623, a test prism according to TU 2-034-439 or TU 2-034-812 and a clock-type indicator according to GOST 577.

Table 1.2 Comparative physical and chemical properties of glass

Characteristics	USP-1	NS-1	NS-3	NS-2
Thermal resistance, °C not less than	170	150	150	145
Temperature coefficient of linear expansion in the temperature range 20-400°C, L - 1 07 deg'1	60-65	68-72	63-67	78-82
Density, g/cm3	2,4-2,5	2,44-2,46	2,42-2,44	2,44-2,46
Water resistance. mg Na2O per 1 g of glass	0,02-0,062	0,06	0,05	0,15
Resistance to bases, mg/dm^2	75-140	85	100	85

Place the ampoule on a prism, bring the indicator tip to the capillary of the ampoule, and for type G ampoules - to the conical end, and rotate the ampoule 360°. Radial runout of the ampoule stem should not exceed:

1.0 mm - for IP type ampoules with a capacity of 1-2 ml;

1.2 mm - for IP type ampoules with a capacity of 3 ml;

1.5 mm - for IP type ampoules with a capacity of 5, 10, 20 ml;

1.5 mm - for 0.3 ml type G ampoules;

1.7 mm - for ampoules of type VO and C with a capacity of 1, 2, 3 ml;

2.0 mm - for 5 ml ampoules of type VO and C;

2.0 mm - for 10 ml ampoules of type IDP.

The deviation from the roundness of the ampoules, which is determined by the difference of two mutually perpendicular diameters, should not exceed the maximum deviations per diameter.

The bottom of the ampoules, except for ampoules of type G, must ensure the stability of the empty ampoule with the stem cut off on a horizontal plane. The concavity of the bottom of ampoules of type VPO-10 is allowed to be no more than 2.0 mm.

The breaking force of ampoules with a coloured ring is determined on the installation, the scheme of which is shown in Fig. 1, with the following characteristics:

Test speed - 10 mm/min; force measurement limit - 200 N; temperature of the ampoule under test - 20 ± 5 ° C.

The distance between the prisms is set depending on the ampoules being tested.

The ampoule is placed on the prisms so that the force is applied at an angle of 90° to the axis of the ampoule at the location of the coloured fracture ring. The force is applied until the ampoule stem breaks off. At the moment of fracture, the numerical value of the fracture force is determined, which must correspond to the following values:

Номінальна вмістимість	Length L = її + Ь, mm	Power to evil, H
1	36=18+18	30 to 70 incl.
2	36=18 + 18	30 to 70 incl.
10	60 = 22 + 38	30 to 90 incl.

The number of ampoules with a coloured breakage ring to determine the breakage strength should be at least 0.01% of the batch. A batch is a number of ampoules of the same type, capacity and glass grade, documented in one document.

The accuracy of vacuum filling depends on the pressure difference between the vacuum inside the ampoule created by the apparatus and the ambient air pressure. Atmospheric pressure often varies and ampoules of the same nominal volume have different sizes, so chemical and pharmaceutical plants draw up tables of the required

degree of vacuum depending on atmospheric pressure, ampoule size and required filling volume.

In cases where such tables are not available, the ampoules are filled at the operating vacuum, which results in a filling volume slightly less and/or more than the required volume, and the desired filling depth is calculated by interpolation. With the found value, control fills are made and the correctness of the calculations is checked by the difference in the mass of the ampoules with its subsequent conversion to the volume before and after filling or by measuring the volume using a calibration syringe.

Light protection properties are tested for ampoules made of light-protective glass by measuring light transmission in the spectral range from 290 to 450 nm.

Methods for determining other quality characteristics of ampoules are described in the laboratory work.

After determining the quality of the glass, the ampoules are subjected to external and internal washing. External washing is most often carried out using the internal washing method. For internal washing, the following methods are used: syringe, vacuum (turbo-vacuum, vortex, vapour-condensation), vibration, thermal, ultrasonic (vibro-ultrasonic, contact-ultrasonic). After washing, the ampoules are transferred for drying or sterilisation by the shortest possible route and quickly enough to prevent contamination, depending on the conditions of the ampoule. The washed, dried or sterilised ampoules and vials are transferred to the ampouling stage.

Тема: «Industrial production of injectable solutions»

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

Today, parenteral medicines account for almost ZO% of all finished medicines produced by the domestic pharmaceutical industry. Injectable dosage forms occupy a prominent place in the nomenclature of medicines. Injectable drugs account for 10% to 15% of the world's pharmacopoeias.

Parenteral medicinal products (PMPs) are a relatively young dosage form.

The parenteral route of drug administration has a number of advantages over other methods:

— rapid action and full bioavailability of the medicinal substance;

- accuracy and convenience of dosage;

- the possibility of administering the medicinal substance to a patient who is unconscious or when the medicine cannot be administered by mouth;

- absence of influence of gastrointestinal secretions and liver enzymes, which occurs when medicines are taken internally;

- the possibility of creating large stocks of sterile medicines, which facilitates and speeds up their release from pharmacies.

Along with its advantages, the parenteral route of administration has some disadvantages:

- when injecting liquids through damaged skin, pathogenic microorganisms can easily enter the bloodstream;

- air can be injected into the body along with the drug for injection, which can cause vascular embolism or cardiac disorders;

- even a small amount of impurities can have a negative impact on the patient's body;

- the psycho-emotional aspect associated with the painfulness of the injection route;

- sterile medicines should be administered only by qualified professionals.

The administration of drug products is carried out by injections (injection of a small volume), infusions (infusion of more than 100 ml at a time by drip or stream) or implantation with the help of special devices with violation of the integrity of the skin or mucous membranes. Such use is quite painful, so recently less painful methods of needleless administration of injectable solutions in the form of a thin (about 0.1-0.12 mm in diameter) jet under high pressure, which is sprayed out of the hole of a special injector at a speed of 300 m/s and penetrates the skin to a depth of 3 cm. For this purpose, manual injectors such as "Bee", "Hynospray", "Jetinjection" are used.

According to the SFS, medicinal products for parenteral use are classified into the following groups:

1) injectable medicinal products;

2) intravenous infusion medicinal products;

3) concentrates for injectable or intravenous infusion medicinal products;

4) powders for injectable or intravenous infusion medicinal products;

5) implants.

The requirements of this Article shall not apply to medicinal products made from human blood, immunological and radiopharmaceutical products, implantable prostheses.

Injectable medicinal products are sterile solutions, emulsions or suspensions. Solutions for injection must be transparent and free of particles. Emulsions for injection should not show signs of stratification. Sediment may be present in suspensions for injection, but it should disperse instantly on shaking to form a suspension. The resulting suspension should be sufficiently stable to provide the required dose when administered.

Intravenous infusion medicinal products are sterile aqueous solutions or emulsions (water as a dispersion medium) that are free of pyrogens and usually isotonic to blood. They are intended for use in large doses and should therefore not contain any antimicrobial preservatives,

Concentrates for injection or intravenous infusion are sterile solutions intended for injection or infusion after dilution. Before use, the concentrates are diluted to the

specified volume with an appropriate liquid. After dilution, the resulting solution must meet the requirements for injectable or infusible medicinal products.

Powders for injectable or intravenous infusion medicinal products are sterile solid substances placed in a sterile container. When shaken with a specified volume of appropriate sterile liquid, they should rapidly form either a clear, particle-free solution or a homogeneous suspension. Once dissolved or suspended, they must meet the requirements for injectable or infusible medicinal products.

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

Parenteral administration of medicinal products involves skin disruption, which is associated with possible infection with pathogenic microorganisms and the introduction of mechanical inclusions. Therefore, sterile manufacturing, compared to other industries, has specific features dictated by the requirements for injectable dosage forms. The main ones are the absence of mechanical impurities, sterility, stability, apyrogenicity, etc., and for some drugs - isotonicity, osmolality or osmolarity, isoionicity, isohydricity, viscosity, which is specified in the relevant regulatory and technical documentation.

Solutions for injection are manufactured in special premises of A or C cleanliness class in compliance with all aseptic rules. Preparation of aqueous or non-viscous solutions for injection is carried out by the mass-volume method, using hermetically sealed reactors equipped with a jacket and a stirring device. In cases where the density of the solvent differs significantly from that of water, the mass method is used, in which both the drug substance and the solvent are taken by weight. Dissolution of slowly or hardly soluble drugs is carried out by heating and stirring.

The solution preparation stage includes the following operations: dissolution, isotonisation, stabilisation, preservatives, and filtration.

Depending on the properties of the medicinal substances, some of the operations may be excluded, such as isotonisation, stabilisation, and the addition of preservatives. Among injectable solutions, a special group includes isotonic solutions, which are

solutions with an osmotic pressure equal to the osmotic pressure of body fluids (blood plasma, lymph, cerebrospinal fluid, etc.).

The isotonic concentrations of drugs in solutions can be calculated by the following methods:

* method based on the Van't Hoff law;

* Cryoscopic method based on Raoul's law;

* The method of drug equivalents based on sodium chloride.

A graphical method for calculating isotonic concentrations is also used abroad, which allows the amount of sodium chloride required to isotonise a solution of a medicinal substance to be determined quickly, but with some approximation, using developed nomograms.

During the manufacture and storage of some medicinal products, changes in their properties are often observed, which occur at different rates and degrees. This is due to a decrease in the content of medicinal substances or a decrease in their pharmacological activity, changes in the properties of dosage forms, etc. Such changes affect the shelf life (storage) of drugs, which can range from several hours (antibiotic solutions) or days (enzyme solutions) to several years. The task of improving the stability of medicines is currently receiving special attention.

The processes occurring in medicines can be conditionally classified into physical, chemical and biological. The conventionality lies in their interconnection: chemical transformations can cause changes in physical properties, while physical changes cause undesirable chemical processes. Biological processes are accompanied by both chemical and physical transformations.

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

Chemical processes often occur in the manufacture of a drug, especially during thermal sterilisation, and are accompanied by various chemical reactions - hydrolysis, saponification, redox processes, photochemical and enzymatic transformations, less commonly polymerisation and isomerisation, etc.

Biological processes caused by the vital activity of microorganisms often lead to undesirable chemical transformations of active substances, sometimes to changes in the appearance of the dosage form.

Direct antioxidants:

1) Substances that prevent the formation of active radicals from hydroperoxides: Phenols, naphthols, aromatic amines, molecular iodine

indirect antioxidants; polybasic carboxylic acids; oxyacids (citric, salicylic, tartaric, etc.); ethylenediaminetetraacetic acid (trilon B); calcium salt of trilon B (tetacine); unitiol; amino acids, thiourea, etc.

Stabilisation of substances: apomorphine hydrochloride, ascorbic acid, sodium aminosalicylate, streptocide, etazol sodium stabiliser analgin, sodium sulfite; vicasol sodium salicylate, ascorb stabiliser: sodium metabisulfite;

novocainamide stabiliser: sodium bisulfite, vicasol, dicaine, novocain;

streptocide - stabiliser: sodium thiosulfate;

stabilising agents: thiamine bromide, thiamine chloride;

stabiliser: unitiol;

apomorphine hydrochloride - stabiliser: cysteine

The choice of preservative is determined by the composition of the medicinal product; pH of the medium; mode of administration

Requirements: pharmacological indifference, absence of general toxic and irritating effects.

Wide spectrum of antimicrobial activity at low doses.

Good solubility in dispersion medium.

Chemical indifference to drugs, packaging and excipients.

Stability in a wide range of pH and temperatures during the term of use.

No effect on organoleptics.

Sterile storage.

No ability to develop microbial resistance.

Application of the drug. Medicinal products for intracavitary, intraocular and cerebrospinal fluids, as well as for single doses of more than 15 ml, should not contain preservatives.

Characteristics of preservatives by the type of impact on microorganisms :

1. Bacteriostatic Nipagin Nipazole Butaben Benzoic and sorbic acids Chlorobutanol hydrate Mertyolate Cephiran Cephirole Phenylethyl alcohol

2. Bactericidal action Phenol Tricresol Cresol Chlorocresol

Chemical classification

1. Inorganic - silver water 1-10 mg/l

2. Organic alcohols: ethyl phenylethyl 0.3-0.5% benzyl 2%

Phenols: phenol 0253-0.3% chloroacetone 0.05-0.1%

Esters: n-hydroxybenzoic acid (nipagin nipazole) up to 0.5%

Organic compounds: benzoic sorbic acid 0.1-0.2%.

Essential oils: bay, lavender, anise, rose, lemon

Quaternary ammonium bases salts: benzalkonium chloride, dimethyldodecylbenzylammonium 0.01%.

Organometallic mertyolate 0.005% 0.02% 0.02% 0.1% sodium chloride

0.02% 0.1% salts of phenylmercury acetate or nitrate up to 0.2% and 0.001-0.004%

Tasks for the topic:

1. Draw up a working prescription for the preparation of 1000 ampoules of 1 ml of 20% sodium caffeine benzoate solution (ρ 20% 1.073, KZO = 0.65, Crash = 1.2).

2. Make a working prescription to obtain 1000 ampoules of 10 ml of 40% glucose solution (CBR = 0.69 at 10% humidity, 40% = 1.1498, Crash = 1.1).

3. Make a working prescription to obtain 20 ampoules of 1 ml of 20% solution of camphor in oil (20% = 0.926).

4. Prepare 250 ml of sodium caffeine benzoate solution. The analysis showed that

the solution contains 21% of the drug. How much water is required to obtain a 20% solution?

5. 250 ml of sodium caffeine benzoate solution was prepared. The analysis showed that the solution contains 19% of the drug. How much sodium caffeine benzoate should be added to get a 20% solution?

6. Draw up a material balance sheet for the manufacture of 1000 ampoules of eufiline 2.4%. The consumption factor is 1.12.

7. Draw up a working prescription for the production of 1000 ampoules of 1 ml of 20% sodium caffeine benzoate solution (ρ 20% 1.073, KZO = 0.65, Krash = 1.2).

8. Make a working prescription for obtaining 1000 ampoules of 10 ml of 40% glucose solution (CBR = 0.69 at 10% humidity, ρ 40% = 1.1498, Crash = 1.1).

9. Make a working prescription for 20 ampoules of 1 ml of 20% solution of camphor in oil (ρ 20% = 0.926).

Topic: «Industrial production of infusion solutions»

The purpose of manufacturing under aseptic conditions is to maintain the sterility of a product made from components that have been previously sterilised by one of the methods described above. This is achieved by using the conditions and equipment described above and designed to prevent microbial contamination.

The following stages of the manufacturing process may be carried out under aseptic conditions: filling and sealing of containers, mixing of ingredients followed by aseptic filling and sealing.

Sterility tests on an appropriate number of samples must be carried out before each batch of any medicinal product sterilised by filtration or manufactured under aseptic conditions is released.

Preparation of parenteral solutions that are not subject to heat sterilisation. Compliance with all aseptic conditions is particularly important in the manufacture of medicinal products for injection that cannot be heat sterilised in the final packaging. This applies to the preparation of injectable solutions from thermolabile substances (barbamyl, epinephrine hydrochloride, eufiline) or substances with pronounced bactericidal activity (amino zine, diprazine, hexamethyl enteramine, etc.).

Hexamethylenetetramine solutions are relatively stable at normal temperature and have a bactericidal effect. At higher temperatures, however, hexamethylene tetramine is hydrolysed to form formaldehyde and ammonia, so its 40% solution is prepared under aseptic conditions (purity class A) without heat sterilisation. The medicinal substance used to prepare the injectable solution should be of higher quality than the pharmacopoeial substance. It should not contain amines, ammonium salts and paraform. If there is no "for injection" grade available, hexa methyl enteramine is subjected to special purification.

To obtain stable solutions of eufiline, use an "injectable" grade with a higher ethylenediamine content (18-22% instead of 14-18%). The water for injection used to prepare eufiline solutions is subjected to carbon dioxide purification. These measures serve to prevent hydrolysis of eufiline. 12-24% eufiline solutions for injection are

prepared under aseptic conditions, without stabilisers, and the ampoules are filled and sealed in a nitrogen stream (gas protection).

Aqueous solutions of aminazine and diprazine are easily oxidised even when exposed to light for a short time, with the formation of reddish decomposition products. To obtain a stable preparation, antioxidants are added and sodium chloride is added to isotonise the solution. It is manufactured under strictly aseptic conditions without heat sterilisation.

The process of filtering through bacterial filters plays an important role in the preparation of injectable solutions that are not subject to heat sterilisation, as it removes microorganisms from the solution, thereby ensuring its sterility and apyrogenicity. Sterile filtration is achieved by using depth and membrane filters.

Infusion and dosage forms. Infusion drugs are the most complex group of parenteral dosage forms. They include the so-called physiological solutions, which, due to the composition of dissolved substances, are able to support the vital activity of cells and organs without causing significant shifts in the physiological balance in the body. Solutions that are as close as possible to human blood plasma in terms of their properties are called blood substitutes. In various pathological conditions accompanied by blood loss, shock, disturbances in the body's water-electrolyte and acid-base status, it becomes necessary to introduce significant volumes of infusion solutions into the bloodstream. Infusion therapy is based on the long-term parenteral administration of large volumes of medicines, which are sterile apyrogenic aqueous solutions or emulsions, usually isotonic to blood plasma, and have a selective and multifunctional effect on the body. Infusion solutions are divided into six groups depending on the function they perform when administered into the body:

1. Haemodynamic or anti-shock drugs. They are intended to treat shock of various origins, replenish the volume of circulating blood and restore haemodynamic disorders. This group includes polyglucin, rheopolyglucin, gelatinol, rheo-glumac, etc. Often, ethanol, bromides, barbiturates, narcotic substances that normalise the central nervous system disorders and inhibition are added to the antishock solutions; glucose, which activates the body's redox processes.

2. De-intoxication solutions. Many diseases and pathological conditions are accompanied by intoxication of the body (infectious diseases, extensive burns, renal and hepatic failure, poisoning with various toxic substances, etc.) Their treatment requires targeted detoxification solutions, the components of which should bind to toxins and be quickly excreted from the body. Such compounds include polyvinylpyro-lidone, polyvinyl alcohol, hemodesis, polydes neo-hemodesis, gluco-neodesis, enterodesis, etc.

3. Regulators of water-salt balance and acid-base balance. Such solutions correct the blood composition in case of dehydration caused by diarrhoea, cerebral edema, toxicosis, etc. They include saline injections of 0.9% and 10% sodium chloride solutions, Ringer's and Ringer-Locke's solutions, Petrov's fluid, 4.5-8.4% sodium bicarbonate solutions, 0.3%-0.6% potassium chloride solution, etc.

4. Drugs for parenteral feeding. They are used to provide energy resources to the body, deliver nutrients to organs and tissues, especially after surgery, in coma, when the patient cannot consume food naturally, etc. The representatives of this group are 40% glucose solution, casein hydrolysate, aminopeptide, amy-blood, fibrinosol, lipostabil, lipidin, lipofundin, introlipid, aminophosphatide, etc.

5. Solutions with oxygen transfer function. They are intended to restore the respiratory function of the blood, they include perfluorinated compounds. This group of infusion drugs is in the stage of invention and development.

6. Solutions of complex action, or polyfunctional. These drugs have a wide range of action and can combine several of the above functions.

In addition to the general requirements for solutions for injection (apirogecticity, sterility, stability, absence of mechanical inclusions), plasma replacement products also have specific requirements. When injected into the bloodstream, infusion solutions must fulfil their functional purpose and be completely excreted from the body without accumulating. They should not damage tissues or disrupt the functions of individual organs. Due to the large volumes administered, blood replacement products should not be toxic, cause sensitisation of the body after three repeated injections, irritate the vascular wall and cause embolism. their physical and chemical properties should be

stable. Many infusion solutions must be isotonic, isoionic, isohydric. their viscosity should correspond to the viscosity of blood plasma.

Isotonicity is the ability of solutions to have an osmotic pressure equal to the osmotic pressure of body fluids (blood plasma, lacrimal fluid, lymph, etc.).

Isoionicity is the property of injectable solutions to contain certain ions in the ratio and amounts typical of blood serum. Therefore, infusion solutions contain K+, Ca2+, Mg2+, Na+ C1, SO, Rota, etc. ions. Today, plasma replacement solutions are manufactured with up to 40 trace elements that play an important physiological role.

An important requirement for injectable solutions is their stability during a certain storage time. Drug stability is the ability of a medicinal substance to retain its physicochemical properties and pharmacological activity during the time specified in the specifications.

Some medicinal substances are unstable during production or storage, do not withstand heat sterilisation, etc. and may undergo various chemical transformations in solution. This involves chemical reactions such as hydrolysis, redox and photochemical processes, isomerisation, etc. Various reactions are initiated by light, air oxygen, elevated temperature during sterilisation, changes in the pH of the solution, chemical impurities in the feedstock and the release of catalysts due to glass leaching.

The stability of injectable solutions primarily depends on the quality of the starting solvents and medicinal substances, the class and grade of glass in ampoules and vials, the presence of oxygen in water and solutions, the pH of solutions, the temperature and time of sterilisation, the presence of heavy metal ions, the conditions of production and storage of drugs, etc.

The mechanism of the redox process is revealed in the skewed theory of A. N. Bach and I. O. Engler and the theory of branched chains by N. N. Semenov.

Solutions are stabilised by physical and chemical methods. Physical methods include: separation of the ampoule drug substance and solvent, selection of ampoules made of chemically resistant material, coating the inner surface of ampoules with special films, replacing glass with polymer, and observing the principle of gas protection.

Chemical methods are based on the addition of stabilisers or antioxidants. Stabilisers can slow down or eliminate undesirable chemical reactions, create a certain pH value for solutions, increase the solubility of drugs or keep them suspended. The choice of stabiliser primarily depends on the nature of the drug substance.

Despite the diversity and extreme complexity of the processes occurring in solutions, medicinal substances requiring stabilisation can be divided into three groups:

1) Solutions of salts formed by weak bases and strong

acids (salts of alkaloids, salts of nitrogenous and synthetic nitrogenous

bases, etc,)

2) Solutions of salts formed by strong bases and weak

acids (sodium thiosulfate, theophylline, sodium caffeine benzoate, etc.),

3) Solutions of lightly oxidising substances (ascorbic acid, etc.)

To stabilise substances of the first group, a 0.1 M solution of hydrochloric acid is used, for substances of the second group - a 0.1 M solution of sodium hydroxide or sodium bicarbonate.

Direct and indirect antioxidants are used to stabilise solutions of easily oxidised substances.

Direct antioxidants have a higher ability to oxidise by binding oxygen, thereby preventing undesirable processes in solutions. Indirect antioxidants or negative catalysts are substances that form complex compounds with heavy metal ions that inhibit redox processes.

The possibility of oxidation of medicinal substances decreases with a decrease in the oxygen concentration in the solvent and above the solution. Therefore, the solvents used for the preparation of injectable solutions should be freed from oxygen by boiling, saturating with carbon dioxide or nitrogen, and other methods. In the industrial production of injectable solutions, the initial binding of oxygen in the solvent is irrational, so at the post-distillation technological stages of the production of solutions in ampoules, its saturation occurs again. Therefore, it is more advisable to remove it immediately before filling the ampoules. One of the ways to remove oxygen and stabilise some injectable solutions is through gas protection.

Another method of stabilising easily oxidised substances is to use high molecular weight or surfactants (propylene glycol, low molecular weight polyethylene oxide, etc.). The use of preservatives also helps to increase the stability of many drugs in ampoules.

Solutions of a number of unstable substances cannot acquire the required stability when using any one form of stabilisation. In this case, it is necessary to use a combination of stabilising factors of combined protection.

In each specific case, the use of stabilising agents requires careful consideration when introducing them into injectable solutions.

Among the diverse range of medicinal products used by modern scientific medicine, ophthalmic dosage forms occupy a special place, and their production is the subject of a separate section of pharmaceutical technology. This is due to both the unique features of the human eye (peculiar structure and properties) and the specific mechanisms of absorption, distribution and interaction of medicinal substances with various tissues and fluids of the eye.

The vulnerability of ocular tissues, a large number of diseases of the human eye (eyelid and eye socket abscesses, anioma, blepharitis, glaucoma, trachoma, cataracts and a number of other diseases) have necessitated the development and continuous improvement of medicines used in ophthalmology practice.

Equally important is the task of creating simple, convenient, aesthetic, informative and cost-effective packaging of ophthalmic medicines that will allow them to be stored in a sterile and chemically unchanged state for a long time, and ensure quick and easy administration at the time of use.

Tasks for the topic.

Answer the questions:

1. The concept of stability of drugs. The basic principle of stabilisation.
2. Factors affecting the stability of injectable solutions.
3. Theories of redox processes by A.N. Bach and I.O. Engler.
4. The theory of branched chains by N. N. Semenov.
5. Chemical methods of stabilisation.
6. Stabilisers used in the production of injectable solutions.

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

8. Physical methods of stabilisation.

9. Gas protection of injectable solutions.

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

11. Characteristics of a group of substances that require chemical stabilisation.

12. Mechanisms of action of stabilisers:

12.1. Stabilisation of solutions of salts of weak bases and strong acids.

12.2. Stabilisation of solutions of salts of strong bases and weak acids.

12.3. Stabilisation of glucose solutions for injection.

13.Stabilisation of solutions of lightly oxidising substances.

13.1. Mechanisms of action of direct antioxidants.

13.2. Mechanisms of action of indirect antioxidants.

13.3. Use of intravenous antioxidants to stabilise injectable solutions.

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

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

16. The use of preservatives.

17. Technological methods of stabilisation of ampoule solutions.

Tasks on the topic:

Task 1. Preparation of a solution of novocaine 0.25% or 0.5% for injection in 2 ml ampoules

(solutio novocaini 0.25% aut 0.5% pro injectionibus)

Composition: (df x, article 468)

Novocaine 2.5 or 5.0 g (FS 42-2709-90)

Hydrochloric acid solution 0.1 n to pH 3.8 - 4.5 (GOST 3118-77)

Water for injection up to 1 litre (FS 42-2620-89)

Description: Transparent colourless liquid. The pH of the solution, the content of

novocaine in 1 ml of solution, respectively, should be 0.00235 - 0.00265 g or 0.00485 - 0.00515 g.

Preparation. The technological process begins with opening, washing and drying 10 ampoules of neutral glass. The internal washing of the ampoules is carried out using laboratory installations of vacuum or syringe washing. The vials are dried in an oven at 180°C. According to the working prescription, weigh out the required amount of analgin and dissolve it in a 50 ml volumetric flask in a small amount (20-25 ml) of water for injection with stirring. After dissolving the novocaine, the solution is brought to the mark with water for injection, first acidified with a calculated amount of sterile hydrochloric acid solution. The solution is thoroughly mixed.

After bringing to the standard concentration, the solution is filtered through a sterile glass filter No. 3 and the ampoules are filled by syringe method according to the filling standards.

The ampoules are sealed by heating or capillary pulling, and then sterilised with saturated water vapour at 120°C (0.1 MPa) for 8 minutes.

The quality control of the solution in ampoules is carried out according to the following technological parameters: determination of the filling rate of ampoules, determination of the pH of the solution, determination of the tightness of ampoules, control for mechanical inclusions, determination of the transparency of the solution.

After obtaining satisfactory analysis results, the finished product is labelled and packaged.

Task 2. Preparation of sodium solution

Caffeine benzoate 10% or 20% for injection in 2 ml ampoules (solutio coffeini-natrii benzoatis 10% aut 20% pro injection1bus)

Composition: (gf x, art.174)

Sodium caffeine benzoate 100.0 g or 200.0 g

Sodium hydroxide solution 0.1 n 4 ml

Water for injection up to 1 litre

Description: Colourless, transparent liquid, pH of the solution should be 6.8 - 8.5.

The content of sodium caffeine benzoate in 1 ml of solution should be 0.097 -

0.103 or 0.194 - 0.206 g.

Preparation. The technological process begins with opening, washing and drying 10 ampoules of neutral glass. The internal washing of the ampoules is carried out using laboratory vacuum or syringe washers. Ampoules are dried in an oven at 180°C.

According to the working prescription, the required amount of caffeine benzoate is weighed out, dissolved in a sterile 50 ml volumetric flask in half the amount of water for injection, to which the calculated amount of sterile 0.1 n sodium hydroxide solution is added. Dissolution is carried out with stirring and gentle heating in a water bath. The volume of the solution is brought to the mark with water for injection and mixed thoroughly.

After bringing to the standard concentration, the solution is filtered through a sterile glass filter No. 3 and the ampoules are filled by syringe method according to the filling standards.

The ampoules are sealed by heating or capillary pulling, and then sterilised with saturated water vapour at 120°C (0.11 MPa) for 8 minutes.

The quality control of the solution in ampoules is carried out according to the following technological parameters: determination of the filling rate of ampoules, determination of the pH of the solution, determination of the tightness of ampoules, control for mechanical inclusions, determination of the transparency of the solution.

Upon receipt of satisfactory analysis results, the finished product is labelled and packaged.

Task 3. Preparation of the solution

Novocainamide 10% for injection in 1 or 2 ml ampoules (solutio novocainamidi10% pro injectionibus)

Composition: (gf x art. 465)

Novocainamide 100.0 g

Sodium metabisulfite 5.0 g

Water for injection up to 1 litre

Description: Transparent colourless liquid. The solution pH is 3.8-5.0.

The content of novocainamide in 1 ml of solution should be 0.097-0.103 g.

Write down the preparation.

Task 4. Preparation of a solution of ascorbic acid 5% for injection in 5 ml ampoules (solut1o acidi ascorb1nici 5% pro injectionibus)

Composition: (SPhf X art.7)

Ascorbic acid 50.0 g (phs 42-2668-89)

Sodium bicarbonate 23.85 g (SPhf X p. 430 or GOST 4201-79)

Sodium sulfite anhydrous 2.0 g (GOST 11683-76)

Water for injection, saturated with

with carbon dioxide up to 1 litre (FS 42-2620-89)

Description: Transparent, colourless or yellowish solution. pH 6.0 - 7.0.

The content of ascorbic acid in 1 ml of solution should be 0.0475 - 0.0525 g.

Topic: «Industrial production of eye, ear and nasal dosage forms»

The purpose of aseptic production is to maintain the sterility of a product made from components that have been previously sterilised by one of the methods described above. This is achieved by using the conditions and equipment described above and designed to prevent microbial contamination.

The following stages of the manufacturing process may be carried out under aseptic conditions: container filling and sealing, mixing of ingredients followed by aseptic filling and sealing.

Before each batch of any medicinal product sterilised by filtration or manufactured under aseptic conditions is released, sterility tests must be carried out on an appropriate number of samples.

In addition to the general requirements for eye, ear and nasal dosage forms, such as apirogue, sterility, stability, absence of mechanical inclusions, they also have specific requirements. They should NOT damage tissues and should NOT impair the functions of vision, ear, and respiratory tract. These drugs should NOT be toxic and not cause sensitisation of the body with repeated use, not irritate the vascular wall and NOT cause embolism. their physical and chemical properties should be stable. Many preparations for the eyes, nose and ear must be isotonic, isoionic, isohydric.

Isotonicity is the ability of a solution to have an osmotic pressure equal to the osmotic pressure of body fluids (blood plasma, lacrimal fluid, lymph, etc.).

Isoionicity is the property of injectable solutions to contain certain ions in the ratio and amounts typical of blood serum. Therefore, infusion solutions contain K+, Ca2+, Mg2+, Na+C1, SO, and other ions. Plasma replacement solutions containing up to 40 trace elements, which play an important physiological role, are now being manufactured.

An important requirement for eye, ear and nasal dosage forms is their stability during a certain storage time. Drug stability is the ability of a medicinal substance to preserve its physicochemical properties and pharmacological activity for the time specified in the specifications.

Among the diverse range of medicinal products used in modern scientific medicine, ophthalmic dosage forms occupy a special place, and their production is the subject of

a separate section of pharmaceutical technology. This is due to both the unique features of the human organ of vision (peculiar structure and properties) and the specific mechanisms of absorption, distribution and interaction of medicinal substances with various tissues and fluids of the eye.

The vulnerability of ocular tissues, a large number of diseases of the human eye (eyelid and eye socket abscesses, anioma, blepharitis, glaucoma, trachoma, cataracts and a number of other diseases) have necessitated the development and continuous improvement of medicines used in ophthalmology practice.

No less important is the task of creating simple, convenient, aesthetic, informative and cost-effective packaging for ophthalmic medicines that will allow them to be stored in a sterile and chemically unchanged state for a long time, and ensure quick and easy administration at the time of use.

Ophthalmic medicinal products are produced in liquid (drops, other injectable solutions, lotions), soft (ointments, suspensions, emulsions), solid (inserts, powders, trituration tablets, pencils) and other dosage forms.

These dosage forms are subject to the same requirements as injectable solutions. They must be free from mechanical and microbial contamination, have an accurate concentration of active ingredients, be isotonic, sterile and stable, and in some cases have prolonged action and buffering properties.

Ophthalmic medicinal products are manufactured under aseptic conditions, due to the fact that they are applied to the conjunctiva of the diseased eye. Normally, the tear fluid contains lysozyme, which has the ability to lysate microorganisms that have entered the conjunctiva, but in case of eye diseases, the content of lysozyme (muromidase) in the tear fluid decreases, and the eye becomes insufficiently protected from the effects of microorganisms. In view of this, the conditions of the manufacturing process and all preparatory operations should be the same as those for sterile dosage forms.

Among ophthalmic dosage forms, eye drops and ointments have the largest share.

Eye drops are the simplest form of administration of active substances, prevention and treatment of many eye diseases.

Water is used as a solvent for eye drops for other medicinal products. Injections, sterile fatty oils (peach, almond, etc.) are used as solvents for eye drops.

Stability is a prerequisite for the industrial production of eye drops, as mass production requires a fairly long shelf life of eye drops. Preservatives, pH regulators, buffer systems, and antioxidants are used to stabilise eye drops.

Hypertonic and hypotonic aqueous solutions during instillation cause discomfort and are poorly tolerated by patients, so eye drops require isotonicity. In addition to isotonicity, the pH value of the solutions should be within 3.5-8.5.

The bioavailability of ophthalmic pharmaceuticals largely depends on the time of contact of the active substance with the tissues in the prosthesis of the eye. Increasing the time of action (prolongation) of active substances reduces the dose and frequency of instillations, and often avoids side effects.

Promising solvents for prolonged-acting eye drops, which increase the bioavailability of drugs, are methyl cellulose solutions, 25% PEG-400 solution, 0.1-0.3% solutions of microbial polysaccharide - aubazidan.

The choice of the method of thermal sterilisation of eye drops depends on the degree of stability of the active substances in the solutions during heating. Most often, sterilisation is carried out by steam under the advantage of solutions of thermolabile substances - by tindalisation or sterile filtration.

A dropper tube is most commonly used for packaging eye drops.

Ointments are intended for lubrication of the skin and eyelid margins or for putting the ointment behind the lower eyelid into the conjunctiva of the eye sac.

The technology of manufacturing ophthalmic ointments follows the stages and operations typical for the production of conventional ointments. However, there are some peculiarities. The active ingredients, which are not soluble in the ointment base, are crushed and sieved through a sieve with a mesh diameter of 0.1 mm. The ointment base should NOT have foreign inclusions and impurities, be neutral, sterile and should be easily distributed on the mucous membrane of the eye. The pH of the ointment should match the pH of the tear fluid, otherwise lacrimation and rapid washing out of the active substance occur.

CLASSIFICATION OF OPHTHALMIC DOSAGE FORMS AND REQUIREMENTS FOR THEM

According to the State Pharmacopoeia of Ukraine, ophthalmic medicinal products are sterile liquid or solid preparations intended for application to the eyeball and/or conjunctiva or for injection into the conjunctival sac. Eye medicinal products are classified as follows:

- eye drops;
- eye lotions;
- ophthalmic soft medicinal products b;
- eye inserts.

In addition, they also include:

- ophthalmic injections:

a) subconjunctival injections, which are injected into the conjunctival sac, from where the medicinal substance diffuses through the sclera into the eyes;

b) retrobulbar, which are injected behind the eyeball;

- eye sprays;
- eyelid ointments intended for use on the outer surface of the eyelid;
- contact lens processing liquids - sterile, moisturising and disinfecting aqueous solutions for storage, cleaning and facilitating the application of contact lenses or contact glasses of ophthalmic devices used for eye examinations.

Today, the requirements for products used in ophthalmic practice have increased significantly. Modern pharmaceutical codes, specifications of different countries, the State Pharmacopoeia of Ukraine do not make a significant difference between medicines for the treatment of eye diseases and paranormal drugs. Both should be free from mechanical and microbial contamination as much as possible.

Medicinal products for the eyes must be: sterile, stable, isotonic (osmolar or osmolality), contain the exact dosage of the medicinal substance, and not have mechanical contaminants visible to the naked eye, some must have a prolonged effect, and be easy to use.

The role of aseptic conditions in the manufacture of ophthalmic medicinal products that are not subject to heat treatment (sterilisation), as well as those containing thermolabile medicinal substances (sprays, emulsions, suspensions, etc.), is particularly important. When they are heated, the processes of crystallisation, flocculation and coalescence are dramatically enhanced. Compliance with the rules of asepsis is the only way to ensure the proper quality of such medicines.

In practice, this is achieved by dissolving thermolabile substances under aseptic conditions in pre-sterilised solvents or in a base for preparation in sterile dishes, adding preservatives and stabilisers as necessary. To ensure sterility, some solutions are filtered through filters capable of retaining microorganisms. Filling and sealing of primary containers should also be carried out under aseptic conditions. These manipulations are carried out in special blocks, modules, boxes, where the degree of cleanliness is equal to class A or B.

Ophthalmic medicinal products containing thermostable substances are prepared in class C or D production facilities with mandatory sterilisation (thermal, gas or radiation).

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

The requirements for sustained-release medicinal products are that the optimal level of the drug substance in them should be maintained for a specified period of time, its concentration should not undergo significant fluctuations as it is released from the dosage form, and the methods used to obtain the prolongation effect should be economical and not have a negative impact on the body. Among the methods of prolongation are: the use of narrow solvents, the addition of biosoluble polymeric substances to the composition, and the development of new dosage forms with a controlled release rate of active substances.

To increase the duration of action of medicinal substances in eye drops, they tried to replace water with various oils: sterile fish oil, refined sunflower oil, but these solvents have not become widespread for various reasons. Recently, bio-soluble

polymeric materials of synthetic origin have been proposed to replace water, the use of which for the deposit of medicinal substances eliminates the harmful effects of polymeric products on the body. At the same time, the study of the biodegradation of these polymers in the body and in simulated environments is a necessary step towards improving old materials and creating new ones that can be destroyed by environmental factors.

An alternative form of prolonged-release ophthalmic products is ocular inserts.

Ocular dosage forms (ODFs) include liquid (drops, lotions), soft (ointments, suspensions, emulsions), solid (films, powders, trituration tablets, pencils) and other forms. In ophthalmological practice, they are used with various medicinal substances for preventive, therapeutic and diagnostic purposes.

Medicinal products for the eyes must contain an accurate dosage of the drug substance and be stable, sterile, and free from mechanical contaminants visible to the naked eye, and some of them must be isotonic and have a prolonged effect.

The need to manufacture them under aseptic conditions is due to the fact that they are applied to the conjunctiva of the diseased eye. Normally, the tear fluid contains lysozyme, which has the ability to lysate microorganisms that have entered the conjunctiva. However, in case of eye diseases, the content of lysozyme (myromidase) in the tear fluid decreases and the eyes are not sufficiently protected from the effects of microorganisms. In this regard, the conditions for the manufacturing process of ODFs and all preparatory operations should be the same as for the production of other sterile dosage forms.

Factory-made ophthalmic medicinal products are manufactured in the form of drops, ointments and films according to the nomenclature of commonly encountered extemporaneous prescriptions.

Eye drops (Guttae ophthalmicae) are aqueous and oil solutions or the finest suspensions of medicinal substances.

Solvents for eye drops include water for injection, sterile fatty oils (peach, almond, etc.).

Stability is a prerequisite for the industrial production of eye drops, so multi-batch production requires that the shelf life of the eye drops be sufficiently long.

To stabilise eye drops, preservatives, substances that regulate the pH of the medium, buffer systems, and antioxidants are used.

Some unstable drugs may be available as dry substance or triturated tablets in vials that are dissolved in water for injection or another sterile solvent before use.

Hypertonic and hypotonic aqueous solutions cause discomfort and are poorly tolerated by patients when instilled in the eye, so eye drops require isotonization. In addition to isotonicity, the pH of the solutions should be within the pH range of 4.5-9.0.

The bioavailability of ODFs largely depends on the time of contact of the drug substance with the tissues in the pre-corneal region of the eye. Increasing the duration of action (prolongation) of medicinal substances allows to reduce the dose and frequency of drug administration, often avoiding side effects.

Natural oils and synthetic polymers are used in eye drops to prolong the action of medicinal substances. Promising solvents for the preparation of long-acting eye drops that increase the bioavailability of drugs are methyl cellulose, 25% PEG-400 solution, 0.1-0.3% solutions of microbial polysaccharide - aubazidan.

After dissolution and stabilisation of the drug substance, the solution is filtered through a sterile filter.

The choice of the method of thermal sterilisation of eye drops is determined by the degree of stability of the drug substances in the solutions when heated. Most often, sterilisation is carried out by pressurised steam; for solutions of thermolabile substances, the method of tindalisation or sterile filtration is used.

Eye ointments (Unguentae ophthalmica) are used to lubricate the skin and eyelid margins or to place the ointment under the lower eyelid in the conjunctival sac.

The technology for the production of eye ointments follows the stages and operations typical for the production of conventional ointments. However, there are some peculiarities.

Medicinal substances insoluble in the ointment base are crushed and sieved through a sieve with a mesh diameter of 0.1 mm. The ointment base should NOT have foreign

inclusions and impurities, be neutral, sterile and easily distributed on the mucous membrane of the eye. The pH of the ointment should correspond to the pH of the tear fluid, otherwise lacrimation and rapid washing out of the drug substance occurs.

Eye films (Membranulae ophthalmicae) are mechanically strong and hard oval-shaped plates with smooth edges and flat surfaces, 6-9 mm long, 3-4.5 mm wide, 0.35 mm thick, with an average weight of 0.015 g, prepared from biosoluble non-toxic polymers with medicinal substances for insertion into the conjunctival cavity of the eye.

In ophthalmology, ophthalmic medicated films (OMFs) are used to replace frequent instillations of aqueous eye drops and prolong the effect of medicinal substances by extending the contact time.

The solubility of eye films with various medicinal substances is determined by the composition of the base and can be 35-90 minutes. Aqueous solutions of MC, PVA, polyacrylamide derivatives are used as film-forming agents.

The following physical and chemical properties are controlled in the production of OMFs: gloss, integrity, surface roughness, elasticity, strength and adhesion.

OMFs are packaged in plastic cases or blisters made of PVC film and aluminium foil. Packages are placed in cardboard boxes of 20-100 pieces and sterilised with gamma rays with an integrated radiation dose of 20 kGy or ethylene oxide.

Thus, OMFs have made it possible to expand the use of antiglaucoma and antiviral agents, simplify the treatment methodology, and increase therapeutic efficacy compared to drops and ointments.

Tasks for the topic:

Answer the question:

1. What groups and on what grounds are ocular PTs classified?
2. What are the requirements of the SFC for ocular PT equipment?
3. What is the purpose and methods of isotonisation of ocular radiopharmaceuticals?
4. What is the isohydricity of infusion solutions and what are the most common ways to achieve it?
5. What is the importance of isoionicity and viscosity of infusion solutions?

6. What are the main stages in the process of producing ophthalmic solutions?

7. Describe concentrates, powders and lyophilised dosage forms for intravenous infusion.

8. What groups and on what grounds are classified ophthalmic drugs?

9. What are the requirements of the SFSU to ophthalmic medicinal products?

10. What excipients are used for their production?

11. What is the peculiarity of the production of eye drops using the Bottlepack technology?

12. What parameters are used to control the quality of ophthalmic medicines?

Topic: «Production of tinctures. Alcoholometry»

Tinctures (Tincturae) are coloured liquid alcohol or water-alcohol extracts from medicinal plant material obtained without heating and removal of the extractant.

Spirometry is a set of methods used to determine the amount of alcohol (anhydrous alcohol, ethyl alcohol) in various alcoholic liquids of practical or technical importance, for example, in mash, alcohol, vodka, wine, beer, liqueurs, etc. similar liquids, the main constituents of which are alcohol and water.

Methods of preparation

The following methods are used to prepare tinctures: - maceration and its varieties;

- percolation;
- dissolution of thick and dry extracts.

maceration

Previously, the method of maceration, or infusion, (from the Latin maceratio - soaking) was widely used to produce tinctures. Nowadays, its use is gradually decreasing, because it is difficult to achieve complete extraction of medicinal substances from plant material using this method.

Maceration is carried out as follows. The crushed raw material with the prescribed amount of extractant is loaded into the maceration tank and infused at a temperature of 15-20 °C, stirring occasionally. If no time is specifically specified, the infusion is carried out for 7 days. After that, the extract is drained, the residue is squeezed out, the squeezed out extract is washed with a small amount of extractant, squeezed out again, the squeezed out extract is added to the initially drained extract, after which the combined extract is brought to the required volume with the extractant.

This method is inefficient - it is slow and the raw material is not completely depleted. To intensify the extraction of the material from methane, the process is carried out using fractional maceration (remaceration), maceration with forced circulation of the extractant, vortex extraction (turbo extraction), ultrasound, etc.

Remaceration, or crushed maceration with separation of the extractant or raw material and extractant. The total amount of extractant is divided into 3-4 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. Such an extraction process allows for a more complete depletion of the raw material with less time, as a high concentration difference in the raw material and extractant is constantly maintained.

Vortex extraction, or turbo extraction, is based on vortex, very intense mixing of the raw material and extractant while grinding the raw material. The turbine stirrer rotates at a speed of 8000-13,000 rpm. The extraction time is reduced to 10 min, and the tinctures are standard.

Ultrasonic extraction. To intensify the maceration process, the use of ultrasonic vibrations is effective. This accelerates the extraction and achieves a complete extraction of the active ingredients. The ultrasonic source is placed into the processed medium or attached to the body of the maceration tank in a place filled with extractant and raw material. The greatest effect of ultrasound is achieved when the cell of the material to be extracted is well impregnated with the sonicated extractant. The resulting ultrasonic waves create alternating pressure, cavitation and a "sonic wind". As a result, the material impregnation and dissolution of the cell contents is accelerated, the flow velocity of the raw material particles increases, and turbulent and vortex flows occur in the extractant boundary layer. Molecular diffusion inside the material cells and in the diffusion layer changes to convective diffusion, which leads to intensification of mass transfer. Cavitation causes cell destruction. This accelerates the extraction process by washing the extractive substances out of the destroyed cells and tissue. With sonication, the extraction can be achieved within a few minutes.

Other types of maceration dynamisation include: grinding the raw material in an extractant medium, for example, in a ball mill; remaceration, accompanied by pressing on hydraulic presses or rollers. In the latter case, the process is repeated until equilibrium concentrations are reached. The method reduces the loss of active ingredients and

extractant, as a small amount of extract remains in the meal. The finished tincture contains a high amount of extractive substances.

Percolation - (from the Latin for "filtering through ..."), i.e. filtering the extractant through the plant material in order to extract substances soluble in the extractant. The process is carried out in percolators and includes three successive stages: soaking of the raw material, infusion, and percolation. Soaking can be combined with infusion, but if the raw material is capable of swelling strongly, the soaking stage must be carried out in a separate container. The raw material is poured with half or equal amount of extractant, relative to the weight of the raw material, and left in a closed container for 4-6 hours to swell. The swollen raw material is loaded into the percolator on a false bottom with an optimum density, covered with filter material, pressed with a perforated disc and filled with extractant to displace air as much as possible. The layer of extractant above the raw material should be about 20-40 mm. The infusion lasts for 24 hours (rarely 48 hours), after which the actual percolation is performed. The actual percolation is the continuous passage of the extractant through the layer of raw material and the collection of percolate. In this case, the percolate is drained and the extractant is simultaneously fed from above at a rate not exceeding 1/24 or 1/48 (for large-scale production) of the percolator volume used per 1:00 (see Study Problem 4). At this speed, percolate is collected in an amount equal to the required volume of tincture. After that, the extractant is recovered from the spent raw material, and the percolate is sent to the purification stage. The percolation is considered to be carried out correctly if, simultaneously with the consumption of the calculated amount of extractant, complete extraction of active substances is achieved, which is established by the colourlessness of the percolate or by means of appropriate qualitative reactions. The spent raw material (meal) is recovered, i.e. the extractant is extracted to be returned to production. Purification of extracts. The resulting extracts are cloudy liquids containing a significant amount of suspended particles.

Modern extraction preparations from medicinal plant materials can be divided into three groups according to the technology of their production:

- total (galenic) preparations;

- Newly galenic (maximally purified) preparations;

- preparations of individual substances.

Galenic preparations should be considered as a specific group of medicinal products that, together with chemical-pharmaceutical and other preparations, are part of medicines. They are called Galenic by the name of the famous Roman physician and pharmacist Claudius Galen, who lived in 131-201 AD. The term "galenic drugs" appeared in the XIII century.

The extracts from raw materials used in the production of galenic preparations (tinctures, extracts, etc.) are not chemically individual substances, but rather complex complexes that often act differently from a single chemically pure substance. That is why the therapeutic effect of galenic preparations is due to the entire complex of biologically active substances, enhancing, weakening or modifying the effect of the main substances.

In the 60s of the XIX century, new galenic preparations, called new-galenic preparations, appeared. They are extracts from medicinal plants, fully or partially freed from concomitant substances, and are therefore also called maximally purified preparations (MPPs). These are also total preparations, but with a narrow spectrum of action on the body and with their own characteristics. For example, deep purification increases their stability, eliminates the side effects of a number of related substances (resins, tannins, etc.), and allows them to be recommended for parenteral use.

The industrial production of single-substance medicines was organised in the former USSR in the mid-20th century. While relatively recently their production was considered difficult to access, advances in chemistry, physics, drug technology and pharmacology have made it possible to isolate them, conduct comprehensive research and analyse them. Preparations of individual alkaloids, cardiac glycosides, etc. became widespread.

Extraction processes are the basis for the production of extractive drugs. In pharmacy, they are widely used to produce drugs from medicinal plant materials (tinctures, liquid, thick and dry extracts, concentrates, maximally purified extracts, i.e.,

new-gallenic drugs, extracts from fresh plants, etc.) and from animal raw materials (hormones, enzymes, drugs of non-specific action - pantocrine, vitohepat, etc.).

Extraction in the solid-liquid system and in the liquid-liquid system, or liquid-liquid extraction, are distinguished. The most popular extraction in pharmaceutical production is the solid-liquid extraction, where the solid is the medicinal plant or animal raw material and the liquid is the extractant. Liquid extraction is used for purification of extracts in the production of highly purified drugs and preparations of individual substances from medicinal plant materials.

In everyday work, it is important for a pharmacist to know the differences between extracts from different manufacturers. The efficacy and safety of such preparations depend on many factors. Firstly, the quality of the plant material, which in turn depends on

- the part of the medicinal plant used to make the extract - root, leaves, flowers, fruits, etc;

- the method of growing the medicinal plant - wild or cultivated;

- growing conditions - climate, soil quality, humidity;

- time of harvesting of plant material;

- the method of drying or storing the plant material, as active substances are often very sensitive to sunlight and humidity.

Second, the extraction process is crucial in the manufacture of phytopharmaceuticals. The quality of the extract is influenced by the type and concentration of the extractant, the ratio of raw materials to extractant, and the extraction method - soaking, straining, etc.

To improve the quality of extracts, the following methods are used:

- selection of source material;

- transition from wild collection of raw materials to cultivation;

- special methods of standardisation of extracts - mixing extracts of different series and different origins, as well as those obtained from wild collection and those obtained in the process of cultivation.

Thirdly, different batches of extracts used for the preparation of a medicinal product may differ significantly in the content of active substances, so the method of mixing different batches of extracts is used to standardise the content of active substances in the extract.

Since different manufacturers use different production methods, extracts from different manufacturers are not the same, i.e. an extract is different from another. It is not possible to apply the scientific data for a particular extract to extracts from another manufacturer. Therefore, pharmacists and pharmacists need to pay attention to the fact that only those extracts whose quality and efficacy have been proven in clinical trials can be recommended in their daily work. Extracts from raw materials used in the production of galenic preparations (tinctures, extracts, etc.) are not chemically individual substances, but rather complex complexes that often act differently from a single chemically pure substance. That is why the therapeutic effect of galenic preparations is caused by the entire complex of biologically active substances, enhancing, weakening or modifying the effect of the main substances.

Tinctures are transparent, coloured liquid alcohol-introductive extracts from the LRS obtained without heating and removal of the extractant. Tinctures are widely used in medical practice as stand-alone preparations for internal and external use, and they can also be included in drops, ointments, plasters, etc. In the production of tinctures, a mass-volume ratio between raw materials and the finished product is used. Typically, from 1 part by weight of a non-potent drug substance, 5 parts by volume of the finished product are obtained, i.e. in a ratio of 1:5. From one part of a potent substance, 10 parts of tincture are obtained, i.e. 1:10. Exceptions are bitter tinctures, tinctures of calendula, hawthorn, arnica, which are prepared in a ratio of 1:10, mint tinctures - 1:20, sophora tinctures - 1:2. The process of preparing tinctures consists of the following stages: preparation of the raw material and extractant, extraction, purification, standardisation, packaging, packing and labelling. The preparation of raw materials includes grinding and sieving of the plant material. According to the requirements of the NTC, the plant material must have a certain particle size before extraction, and then it is sieved. The preparation of the extractant is reduced to calculating the required amount and diluting

the distillate or strengthening the previously obtained recuperates according to the "cross" rule or formulas: X = V or X = V (b + a + c)

Where: V is the volume of ethanol of the required concentration; b is the required concentration in volume percentage; a is the actual concentration in volume percentage; c is the volume concentration of weak ethanol used for dilution. Most tinctures are produced using 70% ethanol, less often 40% (tinctures of belladonna, barberry, St. John's wort, cinquefoil, etc.) and extremely rarely other concentrations: 90% (tinctures of mint, capsicum), 95% (tincture of lemongrass). When calculating the amount of extractant required to obtain the required volume of tincture, the volume of alcohol absorbed and retained by the medicinal raw material is taken into account. The total amount of extractant of a given concentration to produce a tincture is calculated by the formula: V = V1 + RK, (4) where V1 is the volume of tincture (finished product), l or ml; R is the amount of plant material, kg or g; K is the absorption coefficient of the extractant by the raw material, which is 2-3 for herbs and leaves; 1.3-1.5 for bark, roots, rhizomes. Preparation of extracts. Tinctures are obtained by dissolving thick or dry extracts, but more often by the extraction method. Dissolution of thick or dry extracts. This method is used to obtain tinctures when using poisonous raw materials or to speed up production.

The method involves the simple dissolution of a calculated amount of dry or thick extract in alcohol of the required concentration in a stirred reactor. The resulting solutions are filtered. This method is used to produce breast elixir, etc. Extracts in the production of tinctures are obtained by the following methods: maceration, maceration using turbo-extraction and circulation of the extractant, fine maceration, percolation. Maceration (from the Latin for soaking).

In pharmaceutical practice, several methods of maceration are used, differing in extraction time, ratio of extractant to raw material, sequence of operation, etc. Maceration from the International Pharmacopoeia. The crushed raw material and ¾ of the extractant are placed in a sealed vessel and insisted for 5 days. The mixture is periodically stirred. The extract is drained, the meal is squeezed out and washed with a clean extractant. To wash the raw material, take enough extractant to obtain a given

amount of tincture. Maceration (classic version). The crushed raw material with the prescribed amount of extractant is loaded into the maceration tank and insisted at a temperature of 15-200C, stirring occasionally. If no special terms are specified, the infusion is carried out for 7 days.

After infusion, the extract is drained off, the residue is squeezed out and washed with a small amount of extractant, and squeezed out again. The squeezed out extract is added to the first drained extract, after which the combined extract is brought to the required volume with the extractant. The described maceration is rarely used nowadays. New forms of maceration with maximum dynamisation of all types of diffusion are used. One of these forms is maceration using turbo extraction or vortex extraction. The method is based on the vortex mixing of raw materials and extractant with simultaneous grinding of raw materials. The turbine stirrer rotates at a speed of 8000-13000 rpm. The extraction time is reduced to 10 min, and the tincture is standard.

Maceration with extractant circulation can be carried out in any container having a false bottom and a bottom fitting for draining the hood. During the infusion process, the extract is circulated to the top of the container by a pump until it is completely saturated with the active ingredients, i.e. until it reaches equilibrium. This reduces the infusion time by several times. Another type of dynamic maceration, when a significant acceleration of free diffusion in the extractant washing the raw material is achieved by adjusting the hydrodynamic conditions, is the use of vibration and pulsation of the mixture of crushed raw material and extractant, achieved by means of electromagnetic and other vibrators. Intensification of the maceration process with simultaneous grinding of the raw material in the extractant medium using high-speed agitators, in a ball mill, using a RPA (rotary pulsation apparatus) allows to speed up the process, so that a large number of cells are opened simultaneously with intensive mixing during grinding of the raw material. At the same time, the extraction process is supplemented by the process of washing out the extractive substances from the destroyed cells. The extracts are quickly saturated, but they contain many small particles of plant material, which will greatly complicate further purification. Fine maceration or remaceration involves the re-

extraction of the original plant material in separate, variable portions of fresh extractant. The process most often takes place in percolators (extractors, diffusers).

An extractor is a vertical cylindrical apparatus with a body and a steam jacket. A perforated disc, or false bottom, is placed in the lower part of the body, on which the filter material is placed. To facilitate the unloading of the spent raw material (meal), the bottom cover is equipped with a counterweight. Through the top cover, the crushed dry plant material is loaded, the filter material and perforated disc are placed on top as a load. Then the raw material is poured with the extractant to the "mirror", 30-40 mm thick (in the laboratory, 10-20 mm) and left to infuse for 24 hours. After a day, the extract is completely drained, and the raw material is again poured with fresh extract to the "mirror" and after infusion for 1.5 hours, a second plum is obtained.

Similarly, the third and fourth plums are obtained after 1.5 hours each. All plums are combined. Their number should be equal to the required volume of tincture. The extractant is recovered from the spent raw material, and the combined plums are transferred for purification.

Percolation - (from the Latin for "filtering through ..."), i.e., filtering an extractant through plant material in order to extract substances soluble in extractants. The process is carried out in percolators and includes three successive stages: soaking of the raw material, infusion, and percolation. Soaking can be combined with infusion, but if the raw material is capable of swelling strongly, the soaking stage must be carried out in a separate container. The raw material is poured with half or equal amount of extractant, relative to the weight of the raw material, and left in a closed container for 4-6 hours to swell. The swollen raw material is loaded into the percolator on a false bottom with an optimum density, covered with filter material, pressed with a perforated disc and filled with extractant to displace air as much as possible. The layer of extractant above the raw material should be about 20-40 mm. The infusion lasts for 24 hours (rarely 48 hours), after which the actual percolation is performed. The actual percolation is the continuous passage of the extractant through the layer of raw material and the collection of percolate. In this case, the percolate is drained and the extractant is simultaneously fed from above at a rate not exceeding 1/24 or 1/48 (for large-scale production) of the

percolator volume used per 1:00 (see Study Problem 4). At this speed, percolate is collected in an amount equal to the required volume of tincture. After that, the extractant is recovered from the spent raw material, and the percolate is sent to the purification stage. The percolation is considered to be carried out correctly if, simultaneously with the consumption of the calculated amount of extractant, complete extraction of active substances is achieved, which is established by the colourlessness of the percolate or by means of appropriate qualitative reactions. The spent raw material (meal) is recovered, i.e. the extractant is extracted to be returned to production. Purification of extracts. The resulting extracts are cloudy liquids containing a significant amount of suspended particles.

Purification of the extracts is carried out by settling at a temperature not exceeding 100°C until a clear liquid is obtained. After settling for at least 2 days, the extracts are filtered by decantation. Standardisation, packing, packaging, labelling. Tinctures must comply with the requirements of the NTM. They determine: the content of active or extractive substances (by dry residue), alcohol content or density, and heavy metals. If necessary, the finished tinctures are brought up to standard by adding a pure extractant or tinctures with a different content of active ingredients, having previously performed calculations according to formulas 2-3 (see back 5 and 7). The finished tincture complying with the requirements of the NTC is bottled, sealed and labelled on semi-automatic and automatic lines in various glass containers. Store the tinctures in well-sealed glass containers in a cool (150C) place protected from light.

Tasks for the topic:

Answer the question:

1. Characteristics and classification of tinctures.
2. Preparation of raw materials and extractant for the extraction process.
3. Methods of obtaining tinctures.
4. Preparation of tinctures by extraction. The essence of the extraction process.
5. Calculation of the amount of raw materials and extractant for the preparation of tinctures.

6. The sequence of stages in percolation. Equipment used.

7. Preparation of tinctures by dissolving thick and dry extracts.

8. Methods of purification of tinctures.

9. Factors affecting the completeness and speed of extraction of BAS.

10. The device of maceration tanks and percolators.

11. Methods of intensification of maceration.

12. Determination of alcohol content in tinctures.

13. Difference between methods for determining the concentration of alcohol in pharmaceuticals and induction-alcohol solutions.

14. Quality control of tinctures.

15. Packing, packaging and labelling of tinctures.

Tasks:

1. How much raw material and extractant is needed to obtain 150 ml of valerian tincture? (The absorption coefficient is 1.3).

2. What volume of 95% ethanol is required to prepare 150 ml of valerian tincture? How to prepare the extractant?

3. What amount of raw materials and extractant is required to prepare 350 ml of belladonna tincture?

4. Calculate the rate of percolation in drops per minute, if the diameter of the percolator is 5 ci, the height of the layer of loaded plant material is 11 cm, and 1 ml of percolate contains 40 drops.

5. Requirements for the results of work, including design: to give the basic concepts and rules of the pharmaceutical enterprise and safety rules, the concept of good practice, technological flow charts, to make a material balance.

6. Control materials for the final stage of the class: tasks, assignments, tests, etc. (if necessary):

Topic: «Production of thick and dry extracts. Intensification of extraction processes»

Extracts are concentrated extracts from dried plant or animal materials.

They can be classified depending on the consistency into liquid extracts (Extracta fluida), thick extracts (Extracta spissa) and dry extracts (Extracta sicea); on the extractant used: water (Extracta aquosa), alcohol (Extracta spirituosa), ether (Extracta aetherea), oil (Ex4racta oleosa) and those obtained with the help of liquefied gases. In addition, there are standardised extracts (Extracta standartisata) or extract concentrates.

Liquid extracts are only alcohol-based; others can be alcoholic, aqueous, etheric, etc.

Liquid extracts

Liquid extracts are liquid concentrated aqueous-alcoholic extracts from medicinal plant material (MPM) obtained in a 1:1 ratio. At pharmaceutical enterprises, liquid extracts are prepared by weight (1 kg of raw material is used to produce 1 kg of liquid extract).

Liquid extracts are widely used in the pharmaceutical industry because they have the following advantages: 1) the same ratio between the active substances contained in the raw material and the finished product; 2) ease of measurement in pharmacies with vials and pipettes; 3) the possibility of obtaining liquid extracts containing volatile substances (essential oils) without evaporation.

The negative characteristics of liquid extracts include: 1) their saturation with concomitant substances extracted from plant material; 2) the appearance of precipitates at slight temperature drops or partial loss of alcohol; 3) the need for hermetic closure and storage at 15-20 °C; 4) they contain large volumes of extractant and are poorly transportable.

Methods of preparation

Liquid extracts are obtained by percolation, repercolation (in various variants), fractional maceration of various modifications, and dissolution of thick and dry extracts.

Percolation in the production of liquid extracts at the stages of swelling and infusion does not differ from percolation in the production of tinctures. At the stage of percolation

itself, the process is carried out in the same way and at the same speed; the only difference is in the collection of the finished extracts. For liquid extracts, the extracts are divided into two portions. The first portion in the amount of 85 % by weight of the raw material is collected in a separate container. Then percolation is carried out in another container until the raw material is completely depleted. This produces 5-8 times more weak extracts (depending on the weight of the raw material loaded into the percolator), which are called "leavings". The leavings are evaporated under vacuum at a temperature of 50-60 °C' up to 15% relative to the weight of the raw material loaded into the percolator. After cooling, the condensed residue is dissolved in the first portion of the extract. The resulting extracts are obtained in a 1:1 ratio.

Repercolation, i.e. repeated (multiple) percolation, which allows to maximise the solubility of the extractant and obtain concentrated extracts when the raw material is completely depleted. In all cases, the process is carried out in a battery of percolators (from 3 to 10), which work in conjunction. In the battery, the finished product is drained from the percolator, which always has fresh raw materials, and fresh extractant is fed into the percolator, where the raw materials are most depleted. The extracts from the first percolator are used to process the raw material in the next percolator, and so on throughout the battery - the next raw material is extracted with extracts obtained from the previous percolators. In this way, a countercurrent flow of raw material and extractant is carried out from the first to the last percolator in the battery. As the feedstock is depleted, the position of the head and tail percolators changes.

There are various variants of repercolation with the division of raw materials into equal and unequal parts, with a complete and incomplete cycle, which allow to obtain concentrated extracts without further evaporation.

The repercolation with the division of the raw material into equal parts with an incomplete cycle is carried out in a battery of percolators.

The first portion of the raw material to be loaded is pre-soaked with an equal or half volume of extractant relative to the weight of the raw material. After swelling for 4-6 hours, the material is placed in percolator I and infused for 24 hours with twice the volume of extractant relative to the weight of the raw material. After the specified time,

percolation is carried out until the raw material is completely depleted with the separation of extracts into the first portion in the amount of 80 % of the raw material weight, which is considered to be the finished product; the second portion (less concentrated extracts) - in an amount equal to the raw material weight and intended for soaking the raw material for percolator II; the third portion - batch 2 in an amount double the weight of the raw material and intended for infusion of the raw material in percolator III; the fourth portion - batch 3 in an amount almost 6 times the weight of the raw material and intended for extraction (percolation) of the raw material in percolator II. Percolator III produces 100 % of the finished product relative to the weight of the raw material in the percolator and collects the billets for processing the raw material in the next percolator. The last percolator produces IOO% of the finished product and tempering, which is used to process the next batch of similar raw materials. All portions of the finished product obtained from each percolator are combined.

Extracts - (from the Latin extractum - extract, extraction) are concentrated extracts from the LRS. They can be classified according to the consistency (liquid, thick and dry) or the extractant used.

Liquid extracts are liquid concentrated water-alcohol extracts from the LRS obtained in a 1:1 ratio. At pharmaceutical enterprises, liquid extracts are prepared by weight (1 kg of raw material is used to obtain 1 kg of liquid extract). If the extracts contain active substances that are quantified, then instead of bringing them to a standard volume (or mass), they are brought to the concentration of active substances as in the original raw material.

In the production of liquid extracts, 50-70% ethanol is usually used as an extractant, less often other concentrations.

Liquid extracts are used independently in the form of drops or as part of complex liquid drugs.

The production process of liquid extracts includes the following stages:

- preparation of the LF and extractant;
- extraction of the LF;
- extraction purification;

- standardisation; packing; packaging and labelling.

Preparation of the LQA and extractants is carried out in the same way as for tinctures. The calculation of the required amount of extractant is carried out

by the formula: $V = P\,n + P\,k$ (6)

where n is the number of extractant volumes required to completely deplete the raw material (usually 5 to 10 extractant volumes are required and depends on the properties of the raw material), other notations are the same as in formula (4). If the extractor for liquid extracts is not evaporated to the required volume, then n = 1 is accepted.

The extraction of LRS is carried out by the methods of fractional maceration in various modifications, exhaustive percolation, various types of repercolation, and countercurrent extraction.

The variant of transient fractional maceration does not allow for effective extraction even during the first infusion, so during a 2-hour extraction of dry raw materials, equilibrium is not reached, and therefore, the full extraction capacity of the extractant is not used, and the extracts are not sufficiently saturated. The last, 3rd percolator produces spent raw materials (meal) containing quite a lot of BAS, so the raw materials are processed with rather saturated extracts from the 1st and 2nd percolators. For this reason, this variant of fractional maceration is used in laboratory conditions or for small-scale production, when a small amount of the finished product is obtained.

Percolation in the production of liquid extracts at the stages of soaking and infusion of raw materials is no different from percolation in the production of tinctures. At the stage of percolation itself, the process is carried out similarly and at the same speed as for tinctures. The difference lies in the collection of the finished extracts. For liquid extracts, the extracts are divided into two portions. The first portion in the amount of 85% by weight of the raw material is collected in a separate container, and percolation is carried out in another container until the raw material is completely depleted. In this case, 5-8 times more weak extracts are obtained (relative to the weight of the raw material loaded into the percolator), which are called "tempering". This "tempering" is evaporated under vacuum at a temperature of 50-60°C to 15% by weight of the raw material loaded into the percolator. After cooling, this condensed residue is dissolved in

the first extraction portion. The result is a 1:1 ratio of extracts to raw material. After purification, in case of poor quality, dilute with ethanol of the appropriate concentration to the standard content of active ingredients or volume.

Repercollection, i.e. repeated (multiple) percolation, allows to maximise the solubility of the extractant and obtain concentrated extracts when the raw material is completely depleted. The process is carried out in several percolators (from 3 to 10), which work in conjunction, the so-called percolator battery. The number of percolators in a battery depends on the properties of the raw material: the harder the raw material to be extracted, the greater the number of percolators. The extractant supply to the percolator battery can be carried out according to the principle of direct flow and countercurrent.

There are various variants of repercolation with the distribution of raw materials into equal and unequal parts, with a complete and incomplete cycle, for raw materials with large and small bulk density.

Repercussion with the division of raw materials into equal parts with a complete cycle is carried out in a battery of percolators. The raw material divided into equal parts is loaded into the percolators. In the first percolator, the raw material is soaked for swelling, which takes 4-6 hours, after which the extractant is fed to the percolator to the "mirror" and insisted for 24 h. Then it is percolated into a separate container, obtaining 80% of the finished product (G.P.1-80%) in relation to the mass of raw material in this percolator. Percolation is continued until the raw material is completely exhausted in another container - "batch 1" is obtained. "Batch 1" is soaked, infused and percolated in the Pth percolator, from which the finished product (G.P.2-100%) is obtained in an amount equal to 100% of the weight of the raw material in the percolator and "batch 2". Batch 2 is carried out by soaking, infusion and percolation of raw materials in the 111th percolator from which (G.P.3-100%) finished product 3 is obtained in an amount equal to 100% of the weight of raw materials in the percolator and "batch 3". The process is carried out in each subsequent percolator, if there are more than 3 of them. The output of the last percolator is evaporated to 20% of the finished product drained from the 1st

percolator. This yields 300 kg of liquid extract per 300 kg of raw material: 80 + 100 + 100 + 20 = 300 litres (kg), i.e. a 1:1 ratio.

Repercolation with the division of raw materials into equal parts with an unfinished cycle is carried out in the same way as in the previous case. The difference is that the "releases" from the last percolator are not evaporated, but transferred to a portion of fresh raw materials in the 1st percolator. This option is used when there is a large amount of raw material and it is processed for a long time. In this case, the quality of the finished product is higher, because there is no evaporation and, consequently, no inactivation of biologically active substances.

Repercussion according to Bosina and Chulkov [Textbook, Vol. 2, pp. 96-102].

Repercussion with the division of raw materials into unequal parts according to the US and German pharmacopoeias. According to the US Pharmacopoeia, the starting material is taken as 100% and loaded into the percolators in a ratio of 5: 3: 2. Work begins with the largest portion of the raw material and is treated with a pure extractant. The percolate is collected in two steps: finished product 1 in the amount of 20% of the total amount of raw materials and the waste product, which is used for swelling, infusion and percolation in the Pth percolator. From the 2nd percolator, the finished product 2 is obtained in the amount of 30% of the total amount of raw materials and the batch 2 used for the 3rd percolator. From the 3rd percolator, 50% of the finished product is collected in relation to the mass of raw materials. In total, 20 + 30 + 50 = 100% of the finished product per 100% of the raw material, i.e. 1: 1.

In accordance with the German Pharmacopoeia, all dry raw materials are loaded into three percolators in a ratio of 5: 3.25: 1.75 and the process is similar to that described above for the US Pharmacopoeia. Repercussion with the division of raw materials into unequal parts according to the US and German pharmacopoeias can be used for small-scale production when obtaining a small amount of product, so in these modifications of repercussion, the raw materials in the 2nd and 3rd percolators are not completely depleted.

Extraction purification. The extracts obtained by any of the methods described above are settled for at least 2 days at a temperature not exceeding 10°C until a clear

liquid is obtained. Settling may sometimes be carried out in the presence of adsorbents, which contributes to better purification and greater stability during storage and transportation. The settled clear portion of the extraction is filtered from accidentally caught impurities and lastly, the remaining extract with sediment is filtered. The filtered extracts are mixed thoroughly and standardised.

Standardisation, packing, packaging. Determine the content of active substances according to the methods specified in private articles, the alcohol content (GF XI, batch 2, p. 26), or density (GF XI, batch 1, p. 24), dry residue (GF XI, batch 2, p. 161), and heavy metals (GF XI, batch 1, p. 161). Liquid extracts that comply with the requirements of the NTC are bottled, capped and labelled on semi-automatic and automatic lines into glass containers of various capacities.

They are stored in packaging that ensures stability during the specified shelf life and, if necessary, in a cool, dark place. Precipitation may occur during storage.

Oil extracts or medicinal oils (Oleo medicata) are extracts from LRS obtained using vegetable or mineral oils. Medicinal oils were quite common in the nomenclature of galenic preparations of the past centuries. They were obtained from alkaloid-containing (belladonna, belladonna, dope, hemlock), essential oils (wormwood, chamomile, sweet clover, poplar buds) and some other plants (arnica, walnut, St. John's wort) by infusing finely ground raw materials in olive or sesame oil heated to 60-70°C. The extracts obtained in this way are typical extracts with the only difference being that vegetable oils are used as an extractant, and therefore the complex of extracted substances will be lipophilic in nature.

Medical oils are currently produced according to two main schemes:

1. Vegetable oil is used as an extractant and then an oil extract is obtained;

2. Volatile solvents (ethanol 70%, methylene chloride, dichloroethane, chloroform, ether, liquefied gases: carbon dioxide, refrigerant-12, etc.) are used as an extractant and then a concentrate of lipophilic complexes is obtained, which is blended (brought to standard) with vegetable oil (often sunflower).

Currently, in medical practice, oil extracts from bellflower leaves (bellflower oil), dope leaves (dope oil), St. John's wort, eucalyptus leaves (chlorophyllipte), rosehip mya-

cota oil (Extractum Rosae oleosum), carotolin (Carotolinum), rosehip seed oil (Oleum Rosae), sea buckthorn oil (Oleum Hippophae) are used. A new herbal medicine, aromelin, obtained by extraction with liquefied gases (chladone-12) from the squeezed fruits of chokeberry, was approved for medical use. Aromelin has anti-inflammatory, wound-healing, and anti-burn effects that are 3-10 times greater than those of sea buckthorn oil.

In the case of oil extraction, the technological process of obtaining medical oils includes

- Preparation of the LFO and extractant;

- extraction of the LFO;

- extraction purification;

- standardisation, packaging and labelling of the finished product. Preparation of the LFO and extractants. LFOs are crushed to a fine particle size, and oils are heated to 60-75°C. LRW is extracted with heated oil at a temperature of 50-65°C by maceration or countercurrent extraction in a battery of percolators. The resulting extract is sent for purification. Purification from oil extracts is carried out by filtration through print filters. After that, the purified extracts are sent to the standardisation stage. Standardisation of oil extracts is carried out by the content of active ingredients and acid number (free acid content). The standardised finished product is packed in dry glass containers and well wrapped. Store in a cool, dark place.

When extracting with volatile solvents, the technological process of producing medical oils includes

- Preparation of the LRS and extractant;

- extraction of the volatile oils;

- removal of the extractant - obtaining a concentrate;

- blending and standardisation;

- packing, packaging of the finished product. Preparation of the LRW is carried out in the same way as for oil extraction. LPG extraction is performed by circulating extraction, countercurrent extraction in a battery of percolators or extraction with liquefied gases.

Circulating extraction is performed using methylene chloride, dichloroethane, chloroform, ether or other volatile solvent with a constant boiling point.

In the production of white oil using improved technology, the method of countercurrent extraction in a battery of percolators with a mixture of 70% ethanol and 10% ammonia solution is used.

Extraction with liquefied gases is carried out according to the general scheme shown: raw materials with a moisture content of no more than 7%, crushed to a particle size of 0.1-0.2 mm, are loaded into extractors, which are then hermetically sealed. Liquefied gas under pressure (55-65 atm for carbon dioxide and 4.5-5.5 atm for refrigerant-12) from the assembly enters the lower part of the extractors through the lower valves with the upper valves open, which are closed after the extractant forms a mirror over the raw material. The supply of the extractant from below allows the air to be forced out of the raw material and thus prevents the formation of stagnant zones, where extraction is extremely slow.

Depending on the type of raw material, the extraction can be carried out in different ways by transferring the extractant from the 1st, 2nd and 3rd extractors, or in parallel. The infusion time also depends on the properties of the raw material and the extractant. According to the technology proposed by the SSTCL, when extracting with chladone-12, the infusion lasts 3:00 at a temperature of 18-25 °C under a pressure of 4.5-5.5 atm and a ratio of raw material to solvent of 1:5. The extracts are fed into the evaporator to remove the extractant. The pressure in the evaporator is much lower than in the extractors, so the extractant is converted to gas and enters the condenser, where it is cooled, condensed and enters the collector with a level indicator. The extractant is fed back to the raw material from the collector. The finished product - lipophilic concentrate - is discharged from the evaporator through the bottom valve.

The advantage of this method is that the solvent is in a closed loop and can be used repeatedly. At the end of the extraction process, the extractant is drained from the extractors into the evaporator, and the extractors are depressurised to remove the extractant from the meal. The meal is discharged into the discharge hoppers through the discharge bottoms.

The SICLR conducted research on the use of liquefied chlorofluorinated gases (chladones) such as methane, ethane, propane and butane as extractants from LRW. Under normal conditions, these gases are gases; under overpressure, they are colourless, highly mobile liquids with a viscosity significantly lower than that of organic solvents. Refrigerants are chemically indifferent to the extracted surfactants and the construction materials of the apparatus. They are non-toxic, do not form explosive mixtures with air, and are fire and explosion-proof.

The analysis of the extraction results showed that the studied chladones extract essential oils, coumarin derivatives, furanochromones, carotenoids, tocopherols, sesquiterpenes, terpenoids, sterols, some iridoids, chlorophylls, alkaloids and a number of other natural compounds. The yield of extracted substances during the treatment of the same type of raw material with different chladones is not the same. The most selective solvent with respect to essential oils was CZ18 (c-C4F8), which practically does not extract fatty oils. The extracts obtained with the help of methane series chladones [chladone-I (CCIzR); chladone-12- (SSURz); chladone-22 (CHCIF2)] contained a mixture of essential and fatty oils, carotenoids, terpenoids and other natural substances. The extracts, semi-soluble with chladone C318 and chladone-114- (C2CI2P4), do not contain chlorophyll, which distinguishes these extractants from methane chladones. It has been established that chladones have a selective ability with respect to native substances. Thus, by subjecting LRS to sequential treatment with different chladones, it is possible to obtain separate groups of BAS. It was also found that chladones do not extract water-soluble substances (polysaccharides, proteins, phenolic compounds, etc.). Therefore, it is advisable to use the meal after treatment with chladones to obtain other compounds extracted with polar solvents. Sequential treatment of raw materials with chladones and then with more polar solvents (water, water-alcohol mixtures, alcohols, acetone, etc.) will allow for the comprehensive use of valuable plant material.

Removal of the extractant. In circulating extraction, the extractant is distilled from the concentrate under vacuum, sometimes water is added to remove the extractant residue and reduce the distillation temperature. In the case of liquefied gas extraction,

the latter is removed from the concentrate, as mentioned above, by reducing the pressure. As a result, the evaporator produces a concentrate that is blended and standardised.

Blending and standardisation of concentrates. The lipophilic complex product obtained after extraction with volatile extractants is blended with sunflower oil in calculated quantities to meet the requirements of the NTD. Blending is not performed in the production of rosehip oil.

Adoniside. Production of adoniside in pharmacy. To increase the yield of medicinal substances from Montenegrin herb, F. D. Zilberg proposed to modify the production of adonylene. The preparation obtained by her method, she called adoniside; it is a clear liquid slightly yellowish in colour, which has a bitter taste. For the production of 1 ton of adoniside spend: Aluminium oxide hydrate 0.625 kg cut herb Goricetum - 75 LEED 383.7 Ethyl alcohol in terms of 100% 270 l Chloroform medical (GOST 5996-51) 171 kg Technological process. Production of adoniside is divided into the following stages. Grinding. Dry herb of Montenegrin spring grass is crushed by means of "excelsior". adoniside Preparation of extractor. Chloroform, 96° alcohol, and distillation (if any) are poured into a mixer-measurer in such proportions that the mixture contains 95 volume parts of chloroform and 5 volume parts of alcohol. The resulting liquid was subsequently named by F. D. Silberg as a universal extractant, because it extracts relatively well all cardiac glucosides from plant material. At the same time ballast substances pass into this mixture in negligible quantities. Extraction. The crushed herb Montenegrin is loaded through the upper hatch into the extractor 1. In the same pour universal extractor - so much that the entire herb was covered with it. The mixture is infused at a temperature of 45-50 ° C. The obtained extraction from the extractor through pipelines 2 or 3 goes to the evaporator (distillation cube) 4. The evaporator is heated with blind steam (through a steam jacket). The distilled vapours pass through the pipeline 6 to the cooler 7, and from there to the collector 8 and to the extractor 1. In addition, the vapours extracted from the boiler can be distilled directly into the extractor via pipelines 5 and 6, if desired. This method of extraction is commonly referred to as circulation extraction. According to this method, the extraction proceeds until the plant raw material is completely exhausted. After that, the extractant flow into the extractor is

stopped. The remaining extraction is discharged through pipeline 3 into the evaporator. The extractant absorbed in the herb is expelled by sharp or muffled steam. The extractor vapour, having passed the cooler 7, is collected in the collector 8. The condensate stands and water is separated from it. After that, through the bottom hatch unload the spent plant material, load the extractor with new material, fill it with universal extractor and insist on the previous method. Evaporation. The rest of the obtained extraction is evaporated in the same evaporator or better - in a separate vacuum-apparatus approximately to the weight of the plant material taken for extraction. In this case, proteins, carbohydrates, tannids and saponins are not transferred to the alcohol-chloroform extraction from the herb, but cardiac glucosides, chlorophyll, resin-like substances, fats, oils and organic acids are extracted. During evaporation, because of the large amount of chloroform and alcohol remaining in the extract, some of the dissolved substances precipitate out and some remain in solution. In order to finally isolate the water-soluble substances, an almost equal quantity of distilled water is added to the cube residue. The distillation is continued, preferably under vacuum, until the alcohol and chloroform are completely removed. As a consequence, all water insoluble substances (resins, fat-like substances, oils, chlorophyll, etc.) are precipitated. In this case, the distillation, consisting of chloroform and other impurities, to avoid volatilisation of chloroform (a poisonous substance) is collected in a separate receiver - a settling tank with a tightly closing lid. Settling and filtering. Aqueous solution of glucosides is pumped into the settling tank. After some time, the liquid is drained from the sediment, passed first through calico and paper, and then through a vacuum filter, in which two sheets of filter paper are placed and poured on them a layer of aluminium oxide (the last operation serves to remove ballast from the concentrated aqueous solution of glucosides, and aluminium oxide adsorbs glucosides only in a very small amount). Before filtering, the finely ground aluminium oxide hydrate is lightly calcined. This calcination is finished when water vapour is no longer emitted from the surface of the powder. After cooling, the aluminium oxide is immediately used for adsorption of ballast substances or poured into jars with lapped corks.

Packaging, labelling. The product complying with the requirements of NTDs is packed

in dark stock, tightly sealed and labelled. Store in a cool, dark place.

Tasks on the topic of the lesson:

Answer the questions:

1. Characteristics and classification of tinctures.

2. Preparation of raw materials and extractant for extraction.

3. Preparation of tinctures by extraction. The essence of the extraction process.

4. Arrangement of maceration tanks and percolators.

5. Methods of intensification of tincture production.

6. Determination of alcohol content in tinctures.

7. Calculation of the amount of raw materials and extractant for the production of tinctures.

8. Factors affecting the completeness and rate of extraction of active substances.

9. Stages of the method of maceration and remaceration (bismaceration).

10. Sequence of stages during percolation. Equipment used.

11. Methods of purification of tinctures.

12. Standardisation. Quality control of tinctures.

13. Storage. Packing, packaging and labelling of tinctures.

14. Methods of obtaining extracts in the production of medicinal oils that ensure the completeness of extraction of BAS from Medicinal plant raw materials (MPRM)?

Tasks:

1. Be able to make calculations of raw materials and extractant, and draw up a working list.

2. To load the maceration tank and percolator with LRW and extractant.

3. To obtain tinctures by various extraction methods.

4. Determine the ethanol content by the boiling point of the tincture and distillation method.

5. Draw up a material balance sheet and a technological scheme for the production of the resulting tincture.

Task 1. Preparation and study of St. John's wort oil extract (St. John's wort oil) (Extractum Hyperici oleosum. Oleum Hyperici)

Task 2. How much raw material and extractant should be taken to prepare 425 litres of liquid extract by the accelerated fractional maceration method of countercurrent type? In what quantities should pure extractant be fed into the 1st percolator at each loading? K = 2,5.

Topic: «Production of drugs under pressure»

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

Active substances are the main part of a medicinal product under pressure, and all other components are excipients used to deliver the active ingredients in the required form.

Solvents - used to dissolve active ingredients and ensure, with the help of a propellant, the distribution of a small amount of a drug solution in a large volume of air.

Auxiliary substances - this group includes emulsifiers, surfactants, solubilisers, preservatives, lubricants, etc. They are designed to ensure proper aerosol quality, create the required release form of aerosol packaging and make aerosol use more efficient.

Pressurised pharmaceuticals are preparations in which active and excipients are pressurised by a displacing gas (propellant) in an aerosol can hermetically sealed with a valve. Aerosolised medicines are produced in the form of liquid and solid particles, pellets and films dispersed in a gas medium. They are intended for inhalation, application to the skin, insertion into the body cavity, etc.

There are several classifications of pressurised drugs:

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

2) Depending on the particle size of the dispersed phase, they are divided into spray (particle diameter up to 50 microns, propellant concentration up to 80%), shower (particle diameter up to 200 microns, propellant concentration 30-70%) and foam (particle diameter over 200 microns, propellant concentration up to 30%).

3) Depending on the application, aerosols can be medical and pharmaceutical.

The production of pressurised medicinal products in the form of solutions consists of several stages: preparation of a solution of the active ingredient (concentrate), its removal from insoluble impurities, packaging in containers, sealing, filling with

propellant, testing for strength and tightness, standardisation, and packaging for further transportation.

An aerosol is a medicinal product that is under gas pressure in special containers and contains one or more active ingredients. Propellants provide the pressure necessary for the medicinal product to escape from the container. Pressurised medicinal products are a solution, emulsion or suspension; they are intended for topical application to the skin, mucous membranes or for inhalation. In addition to medicinal substances, they may contain excipients such as emulsifiers, solvents, and sliding agents that protect the valve from clogging. Medicinal aerosols are divided into pharmaceutical and medical aerosols.

A pharmaceutical aerosol is a finished dosage form consisting of a canister, a valve and spray system, and contents of various consistencies that can be released from the canister with the help of a propellant. An aerosol contains medicinal and excipients and, inevitably, one or more propellants.

A medical aerosol is an aerosol of one or more medicinal products in the form of liquid or solid particles produced by means of special stationary devices intended for inhalation in a medical facility.

Pharmaceutical aerosols are classified into the following groups according to their intended use: inhalation, otolaryngological, dermatological, dental, proctological, gynaecological, ophthalmological, special purpose (diagnostic, dressing, haemostatic, etc.). The great popularity of therapeutic aerosols is explained by a number of advantages that distinguish them from other dosage forms:

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

- atomisation produces particles of approximately the same size, which makes it possible to adjust their size; this is especially important for the treatment of bronchial asthma and respiratory diseases;

- various medicinal substances can be dosed using special valves;

- the balloon is fully sealed, which protects the substances from fluctuations in atmospheric conditions, drying out, contamination, etc,

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

- medicinal substances from aerosols are rapidly absorbed and can be used for emergency care;

- the economic advantage is high efficiency of action combined with reduced consumption of active ingredients;

- the ability to apply medicinal substances directly to the affected areas;

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

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

A large number of different chemicals are used to create aerosols. They can be divided into five main groups: active ingredients, solvents, fragrances, excipients and propellants.

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

Organic solvents and water are widely used to prepare various aerosol formulations, which serve to obtain a solution of the active ingredient and ensure that a small amount of it is distributed in a large volume of air with the help of a propellant. To impart a pleasant and mask an unpleasant odour, the aerosol may contain fragrant substances. The type of fragrance (flavouring) should correspond to the nature of the product for which it is intended. Benzaldehyde, various essences, essential oils, etc. can be used as fragrances.

The group of auxiliary substances includes surface-active substances (emulsifiers, solubilisers), preservatives, consistency substances, etc. They are designed to ensure proper aerosol quality, create the required form of package discharge and make the drug more efficient. Diffusing or swelling gases, which create pressure inside the can, are important for dispensing an aerosol product. These gases are called propellants.

Propellants are classified according to their saturated vapour pressure, their aggregate state under normal conditions and their chemical nature.

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

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

1. Liquefied gases:

a) organofluorine compounds (fluorine and fluorocarbons, or otherwise known as CFCs);

b) paraffin hydrocarbons (propane, butane, isobutane);

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

2. Compressed (non-liquefied) gases. These include nitrogen, nitrous oxide, carbon dioxide, etc.

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

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

Aerosol packaging consists of a can, a valve and the contents. A can containing a solution, suspension or emulsion of a medicinal product and a propellant is hermetically sealed with a valve with a spray head.

A siphon tube is immersed in the contents of the cylinder, designed to deliver the medicine to the opening in the valve stem. The valve allows you to adjust the dose of the medicine. A layer of compressed gaseous propellant is located above the contents of the balloon, which presses on the contents and the walls of the balloon and facilitates the release of the drug.

When the valve head is pressed vertically or tilted slightly sideways (depending on the valve design), a conical jet or ribbon-like mass is discharged from the opening in the head. Depending on the contents of the cylinder, the jet may resemble mist (drug solutions), smoke or dust (suspensions). The ribbon-like mass may be a rich foam or a "worm" squeezed out of the pipe (emulsions, ointments, creams).

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

According to the principle of dispensing the contents of the cylinder, valves are divided into metering and multiple continuous action. They are used for liquid and viscous systems, for suspensions, foams, etc.

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

The capacity of the packaging can vary from 3 ml to 3 litres, except for glass, which is limited to 300 ml.

Metal cylinders are most often made of aluminium, and their inner surface is coated with protective varnishes. For these purposes, various polymeric materials, anti-corrosion varnishes or copolymers are used.

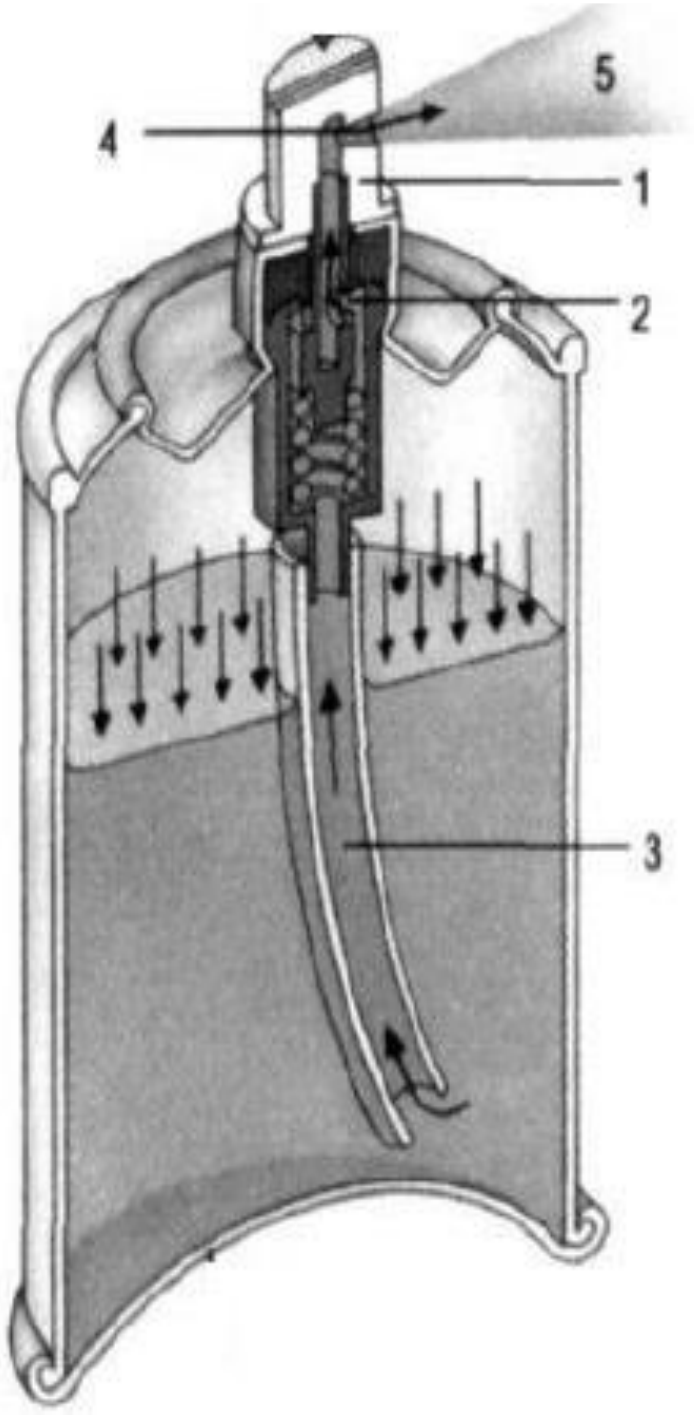

Figure 1. The structure of an aerosol can:

1 - valve head; 2 - valve; 3 - siphon tube; 4 - nozzle; 5 - sprayed substance.

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

Depending on the degree of miscibility of the main formulation components with the propellant, aerosols are divided into aerosol solutions, aerosol emulsions, aerosol suspensions and combined systems.

The production of aerosols includes the manufacture of cans, valve and spray systems, preparation of propellants or their mixtures, concentrates, filling of aerosol cans and quality control.

The production of aluminium monoblock cylinders is carried out by moulding them from flat billets on impact presses, and the cylinder neck is formed on special multi-spindle cone-forming machines. This process involves 12-14 or more operations, depending on the diameter of the cylinder.

Glass cylinders are made from neutral borosilicate glass NS-1 or NS-2 on automatic high-performance ejection molding machines. The production process involves double annealing in horizontal furnaces with a maximum temperature of 640-650°C to eliminate or reduce residual internal glass stress.

After moulding, the glass cans are coated with a polyethylene or polyvinyl chloride protective coating.

Plastic aerosol cans are manufactured by vacuum moulding (monoblock) or injection moulding on moulding or injection machines.

Valve and spray systems are manufactured at plastic processing plants.

A standard valve and spray system has the following elements:

- A spray nozzle is used to actuate the valve and spray the medicine. It can be of various designs and configurations, depending on the aggregate state of the medicine and the route of administration.
- The stem is used to open and close the valve. The stem cavity is part of the expansion chamber.
- The collar seals the connection between the stem and the opening in the valve bowl (capsule) and is also a nipple that closes or opens the opening in the stem.
- The body is the place where all the parts are assembled, and its cavity is part of the expansion chamber.
- The siphon tube is used to convey the contents from the bottom of the cylinder to the valve.
- A gasket seals the valve's attachment points on the cylinder.
- The cup (or capsule) is used to assemble all valve parts and attach it to the cylinder.

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

- Standard valves - used to evacuate products of the perfumery and cosmetics, chemical, pharmaceutical, food industries, leather goods, etc;
- Universal valves - spray the contents at any angle and are used to evacuate products of the chemical and perfumery and cosmetic industries;
- Reversible valves - spray the contents only in the inverted position and are used mainly for the evacuation of products of the pharmaceutical industry.

Принцип дії стандартного аерозольного клапана полягає в наступному: клапан приводиться в дію натисканням на розпилювальну головку вертикально вниз. Разом з головкою рухається вниз шток, стискаючи пружину. Отвір у штоку потрапляє, з-під гумової прокладки в порожнину кишені, заповненої продуктом. У цей отвір прямує продукт і через порожнину штока поступає в головку для розпилювання. При звільненні головки пружина піднімає шток вгору і дія клапана припиняється.

На сьогодні визначилися 4 альтернативні напрями створення нешкідливих агентів-витиснювачів (пропелентів), розроблено нові методи розпилювання, вдосконалюються наявні конструкції аерозольних упаковок:

- упаковки з сировини, ЩО не МІСТЯТЬ фенолу: насичені парафінові вуглеводні метанового ряду (пропан, бутан, ізобу тан) і стиснені гази (азот, закис азоту, двоокис вуглецю та ін.);
- балони, в яких пропелент відокремлений від продукту і не виділяється у навколишнє середовище (рис. 2);
- упаковки з механічним розпилювачем помпового типу;
- стискувані полімерні й інші балони.

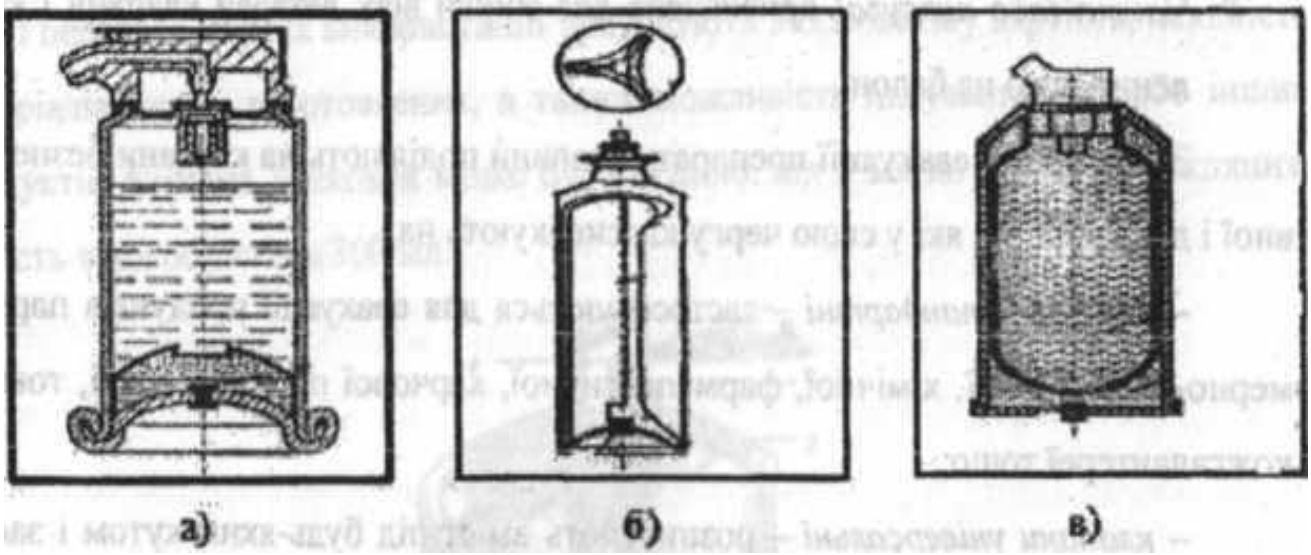

Figure 2. Two-chamber aerosol packs:

a - aerosol package with a piston;

b - aerosol packaging with a liner;

c - aerosol packaging with an inner pouch.

The aerosol production technology consists of the following stages (see the aerosol production flowchart):

1. preparation of production;
2. preparation of raw materials and solvent;
3. preparation of cylinders for filling;
4. preparation and purification of aerosol concentrate;
5. packaging of the concentrate in cans;
6. sealing of aerosol cans;
7. filling aerosol cans with propellant;
8. checking the cylinders for strength and tightness;
9. quality control of preparations under pressure;
10. packaging, labelling of finished products.

Standardisation:

- organoleptic control (appearance, control for mechanical inclusions);
- physical and chemical control (internal pressure of the cylinder, tightness, determination of the percentage yield of the container contents, determination of the

average weight of the drug in one dose (for dosing valves), determination of the dispersion of aerosol particles, the norm of filling the cylinder);

- chemical control (qualitative and quantitative analysis of active substances);

- biological control

Preparation and transportation of propellant mixtures.

The most complex and specific operations for aerosol packaging companies are the preparation of liquefied propellant mixtures and their supply to the filling line. In Russia, chemical companies have organised the production of only one mixture, chladones 11 and 12, in a 50:50 ratio. If the recipe calls for a different ratio of refrigerants or other mixtures, they are prepared in different ways at special sites.

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

1) transfer of propellants from the container in which they are stored by means of overpressure created in the container either by nitrogen or by heated vapours of the refrigerants themselves;

2) pumping by pumps.

Concentrate solutions are prepared in the same way as conventional drug solutions in reactors with a heat exchanger and stirrer. The solutions are freed from impurities by settling, filtration or centrifugation.

If concentrate solutions are prepared using viscous solvents (fatty oils), the dissolution is carried out under heating, and purification is carried out under pressure. If volatile solvents (ethyl alcohol) are used, the substances are dissolved in covered reactors and filtered under pressure. The systems may include stabilisers and preservatives. The standardisation of concentrate solutions is based on the percentage of active ingredients or the density of the solution.

The decisive factor in the technology of pressurised medicinal products in the form of solutions is the pressure inside the container, the control of which can serve as a quantitative characteristic of certain physical and chemical properties: the completeness of the content delivery, dispersion, and solubility of the propellant in the concentrate. The greater the ability of the concentrate to dissolve the propellant, the lower the pressure in the container.

Testing of medicinal products under pressure at the plants is carried out by the Quality Department in accordance with the specifications for the product. It should be noted that the quality of this group of drugs depends on many factors and requires a special form of control, as it is impossible to make changes to the composition of the drug after the container is sealed.

Standardisation of pressurised medicinal products includes several types of control: organoleptic, physicochemical, chemical, microbiological and biological control (in case of presence of cardiac glycosides, etc.).

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

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

Containers have their own specific features during transportation compared to the current rules for other dosage forms. The storage conditions indicated on the packaging and in the technical documentation should be observed (avoid shock, direct sunlight and high temperature).

Medicinal products under pressure are packed in sturdy wooden boxes if the product is flammable; for less hazardous products, cardboard transport containers are allowed.

Tasks on the topic:

Task 1. Determine the average mass of one dose given by an aerosol if the mass of the can with a spray is 35.05 g, and after 15 clicks - 30.15 g. Explain the reasons why the stem of the metering valve may not provide a portioned release of the contents of the cylinder when pressed.

Task 2. Draw up a working prescription for obtaining 600 packs of Ingalipt, if the Cross, at the stage of preparation of the aerosol concentrate and its packaging is 1.025, and at the stage of filling the cylinders with propellant is 1.012.

Tests KROK-2:

1. A pharmaceutical company is launching a new product. Which section of the industrial technological regulations describes the appearance and physical and chemical properties of the finished product:

A Characteristics of the final product

B. Description of the technological process

C. Characteristics of raw materials and intermediate products

D Characteristics of auxiliary raw materials and materials

E. Information materials

2. Which section of the regulation describes the sanitary preparation of production facilities:

A. Description of the stages of the technological process and industrial sanitation

B. Safety, fire safety and industrial sanitation

C. Safe operation of production and environmental protection

D Information materials

E. General characteristics of the production

3. Specify the analytical regulatory document that establishes requirements for the composition of the drug and its manufacturing process:

A. Technological regulations, pharmacopoeial article

B. Technical regulations

C. State standard (GOST)

D Industry standard (OST)

E. Technical specifications

4. The industrial and technical department is developing technical regulations. Several pieces of equipment have been replaced in production. Which section of the technical regulations should be urgently amended.

A. Hardware diagram

B. Section on labour protection

C. Table of MPCs

D Emergency response plan

E. List of instructions

5. A pharmaceutical company produces different finished medicinal products according to technological regulations. During what period is the industrial regulation valid:

A 5 years

B. 3 years

C. 8 years

D. 1 year

E. 6 months

6. A regulatory document that sets out the requirements for specific products and services and regulates the relationship between a supplier and a consumer. Which document meets this definition:

A. Technical specifications;

B. Standard;

C. Technical regulations;

D Technological regulations;

E. Methodological instructions.

7. What do not regulate the rules of the GMR:

A. requirements for bioavailability of the drug;

B. pharmaceutical terminology;

C. requirements for buildings and production facilities;

D. requirements for personnel;

E. the need for validation.

8. A consumption factor is:

A. The ratio of the mass of the initial components to the mass of the finished product.

B. The amount of a substance used to produce a given amount of a drug.

C. The ratio of the mass of the finished product to the mass of the starting materials.

D The ratio of the mass of material losses to the mass of the starting materials.

E. The sum of the masses of losses and starting materials.

9. Validation is a concept related to GMP and means:

A. That the system works as intended.

B. The profitability of the enterprise.

C. Control over the work of the enterprise's quality control department.

D Product sterility.

E. Quality control of medicinal products.

10. GMP rules regulate:

A. All answers are correct.

B. Pharmaceutical technology.

C. Requirements for buildings and premises of pharmaceutical production.

D Requirements for personnel.

E. The need for validation.

11. The need for validation:

A. Conducting preclinical trials of pharmaceuticals.

B. Organisation of the production of medicinal products.

C. Conducting clinical trials.

D Rules of retail trade.

E. Rules of wholesale trade.

12. GMP regulations govern:

A. Conducting clinical trials

B. Organisation of production of medicinal products.

C. Conducting preclinical studies of pharmaceuticals.

D Rules of retail trade.

E. Rules of wholesale trade.

13. Material balance is:

A. The ratio between the amount of input materials, finished goods, production waste and material losses.

B. The amount of material losses.

C. The ratio between the amount of finished product and waste.

D Description of the technological process.

E. The ratio of the amount of energy input to the technological process and released after its completion.

14. Choose a machine for medium grinding of plant material:

A. Grass and root cutter

B. Vibration mill

C. Drum mill

D Rod mill

E. Jet mill

15. Different equipment is used in the manufacture of solutions at pharmaceutical enterprises. What devices are used for mechanical mixing of liquids?

A. Vane and turbine mixers.

B. Liquid whistles.

C. Pulsators.

D Reactors.

E. Bubblers.

16. When choosing grinding equipment, consider the physical and chemical properties of the material. Determine the grinding method for fibrous material with a cellular

structure.

A. Cutting, abrasion

B. Impact, splitting, abrasion

C. Crushing, impact

D Crushing, abrasion

E. Impact

17. Different equipment is used in the production of solutions at pharmaceutical enterprises. What devices are used for mechanical mixing of liquids?

A. Paddle mixers

B. Compressors

C. Pulsators

D Liquid whistles

E. Pumps

18. A pharmaceutical company uses different types of dryers. Which of the following are contact dryers?

A. Roller dryers

B. Belt dryers

C. Air-circulating

D Pneumatic

E. Spraying

19. Different types of dryers are used in the manufacture of phyto- and organopreparations. Which dryer is most appropriate for drying thermolabile substances?

A. Freeze dryer

B. Roller dryer

C. Belt dryer

D Drying cabinet

E. Drum

20. A variety of equipment is used to filter solutions. What filters are used for filtration under vacuum:

A. Nootch filters

B. Print filters

C. Frame press filters

D Bag filters

E. Centrifuges

21. What should be the correct clothing package when working in a cleanroom according to GMP guidelines?

A. Coveralls, helmet, mask, shoe covers, gloves

B. Pantsuit, mask, shoe covers

C. Coveralls, mask, shoe covers, gloves

D. Pantsuit, headgear, gloves, shoe covers

E. Pantsuit, helmet, shoe covers

22. For the production of sterile products under GMP factory conditions, WHO classifies clean areas according to the requirements for air characteristics into the following cleanliness classes:

A. A, B, C, D

B. A, B, C, D, E

C. I, II and III

D. I and II

E. A and B

23. A pharmaceutical company produces tablets. Which device is used to determine their cracking strength:

A. The HNDHFI device

B. Device VP-12A

D. Freeabiliser

C. The device "swinging basket"

E. Model 545P-AK-3 device

24. Which normative-technical document establishes requirements for the quality of a medicinal product or medicinal plant material, approved for a limited period of time.

A. Temporary pharmacopoeial article (TPA)

B. Pharmacopoeial article (PA)

C. Technological industrial regulations (TIR)

D. Industry standard (OSTU)

E. State standard (GOST)

25. A regulatory document that sets out requirements for specific products and services and regulates the relationship between a supplier and a consumer. Which document meets this definition?

A. Technical specifications;

B. Methodological instructions.

C. Technical regulations;

D. Standard;

E. Technological regulations;

26. Which glass grade belongs to the first class?

A. USP-1

B. AB-1 (boron-free glass)

C. NS-2 (neutral glass-2)

D. NS-2 A (neutral-2A glass)

E. MTB (medical container colourless)

27. Indicate what type of glass can be used to make ampoules for tocopherol solution?

A. AB-1

B. NS-3

C. NS-1

D. HT-1

E. SNS-1

28. Which glass grade belongs to the second class?

A. AB-1 (boron-free glass)

B. USP-1

C. NS-1 (neutral-1 glass)

D. NS-3 (neutral glass-3)

E. SNS-1 (neutral light-sensitive glass)

29. What brand of glass is not used for the manufacture of ampoules:

A. MTB (medical container colourless)

B. AB-1 (boron-free glass)

C. NS-1 (neutral glass-1)

D. NS-3 (neutral glass-3)

E. SNS-1 (neutral light-sensitive glass)

30. In the production of ampoules, to change the properties of glass, various components are introduced into its composition. For what purpose is boron oxide added to the glass.

A. To increase the chemical resistance of glass

B. To reduce the melting point of ampoule glass

C. To give the glass the desired colour

D. To increase the mechanical strength of the glass

E. To increase the thermal stability of the glass

31.When assessing the quality of ampoules, chemical resistance is determined. Specify the methods for determining this indicator:

A. With the help of various acid-base indicators, using a pH meter, weight methods

B. Visual, weight methods

C. Polarisation-optical

D. Autoclaving method followed by titration with hydrochloric acid solution

E. Method of exposure of glass samples to sodium carbonate and sodium bicarbonate solution

32. Specify the device for determining the residual stress in ampoule glass:

A. Polariscope-polarimeter

B. Densimeter

C. pH meter

D. Photoelectrocolourimeter

E. Spectrophotometer

33. The following method is used to determine the residual stress in ampoule glass:

A. Polarisation-optical

B. Methylene blue solution

C. With the help of a pycnometer

D. Using a "drum wiper"

E. Using a Soxhlet apparatus

34. How does residual stress in the glass affect the quality of ampoules?

A. Reduced mechanical stability

B. Increases mechanical resistance

C. Chemical resistance increases

D. Increases the size of the ampoule

E. The colour of the ampoule changes

35. In an ampoule shop, it is necessary to remove residual voltage before using ampoules. What operation is performed for this purpose?

A. Annealing the ampoules
B. Drying in tunnel ovens
C. Washing with desalinated water
D. Cutting of capillaries
E. Softening of glass with gas burners

36. Which parameter is used to calibrate glass wires at glassworks:
A. By the outer diameter
B. By the inner diameter
C. By wall thickness
D. By length
E. By mass

37. The technological stage "Preparation of ampoules for filling" includes the operations of drying and sterilisation of ampoules. Select the equipment and facilities for this operation:
A. Tunnel dryer, drying cabinets, laminar flow drying cabinets of heated air
B. Laminar flow heated air dryers, Krupin chamber, ultrasonicator
C. Steam sterilisers type AP-7 and AP-18, Resepin apparatus
D. Ultrasonic unit, tunnel dryer, drying cabinets
E. Krupin's chamber, ultrasonic device, Rezepin apparatus, laminar flow dryers of heated air

38. In the production of ampoules, glass with the required heat resistance is selected. Indicate what this property of ampoule glass ensures that the ampoules meet the requirements of regulatory and technical documentation:
A. Withstanding sharp temperature fluctuations
B. Easy cutting of capillaries
C. High-quality sealing of ampoules
D. Withstanding the load during production and transport

E. Ability to protect photosensitive substances

39. What percentage of the ampoules taken for the test of the "heat resistance" indicator should be intact:

A. 98%

B. 75%

C. 30%

D. 50%

E. 95%

40. When testing the thermal stability of 100 vials from one batch, 20 vials cracked. Was the glass used in their manufacture heat-resistant?

A. No, there should be 98 whole ones

B. No, it should be 95

C. No, it should be 90

D. Yes, there should be 80 integers

E. Yes, there should be 75 integers

41. In the production of ampoules, glass is selected with the required fusibility. What is this property of ampoule glass?

A. High-quality and fast sealing of ampoules

B. Easy cutting of capillaries

C. Withstanding the load during production and transport

D. Withstanding sharp temperature fluctuations

E. Ability to protect photosensitive solutions

42. In the manufacture of ampoules for injectable solutions, different grades of glass are used. Indicate which grade of glass can be used to make ampoules for solutions that are sensitive to light:

A. SNS-1

B. NS-1

C. NS-3

D. AB-1

E. HT-1

43. What type of glass should be used in the manufacture of ampoules for a solution of cyanocobalamin 0.01%?

A. Light-protective neutral (SNS-1)

B. Boron-free (AB-1)

C. Neutral (NS-2)

D. Neutral (NS-1)

E. Neutral (NS-2A)

44. The ampoule shop of the enterprise produces solutions for injections. From the list below, select the brands of ampoule glass used in the production of an injectable solution of novocaine:

A. NS-3, NS-1, USP-1

B. NS-1, NS-2, NS-3

C. NS-1, NS-2A, NS-3

D. OS-1, USP-1, NS-2

E. HT-1, SS-1, AB-1

45. Which solutions for parenteral administration of the listed substances are subjected to special purification in the absence of a "for injection" grade?

A. Magnesium sulfate, calcium chloride, glucose

B. Gelatin, novocaine, sodium sulfite

C. Sodium nitrite, ergotal, calcium chloride

D. Hexamethylene tetramine, novocaine

E. Ascorbic acid, analgin

46. At a pharmaceutical company, demineralised water is obtained by using membrane separation methods. Choose the method in which the water passes through a semipermeable membrane under the influence of external pressure:

A. Reverse osmosis
B. Electrodialysis
C. Evaporation through a membrane
D. Dialysis
E. Sorption

47. Specify the requirements for water for injection that make it significantly different from purified water:

A. Absence of pyrogens
B. Absence of heavy metals
C. Absence of sulphates, chlorides
D. Absence of nitrites and nitrates
E. Absence of reducing agents

48. Indicate what impurities are removed from calcium gluconate in the absence of a "for injection" grade.

A. From impurities of calcium oxalate
B. From impurities of iron salts
C. From impurities of manganese and iron salts
D. From impurities of calcium sulphate and iron
E. From dyes and pyrogenic substances

49. For what purpose is activated carbon used in the manufacture of injectable solutions:

A. To purify some injectable solutions
B. To create a buffer system
C. As an antioxidant
D. To increase the chemical resistance of ampoule glass

E. To relieve residual stress in ampoules

50. To remove impurities from an injectable glucose solution, a special purification is performed using the following substances:

A. Adsorption of impurities on activated carbon

B. Addition of calcium hydroxide followed by filtration

C. Addition of hydrochloric acid followed by adsorption on activated carbon

D. Pretreatment with activated carbon followed by stabilisation with hydrochloric acid

E. Addition of iron oxide followed by adsorption of impurities on activated carbon

51. At a pharmaceutical enterprise, one of the methods of sterilisation of thermolabile substances is the method of tindalisation. Indicate the essence of this method:

A. Three times heating of the solution to 40-60°C with breaks for a day for thermostatting

B. Autoclaving at a temperature of 119-121°C and a pressure of 1.01.1 atm

C. Sterilisation at 100°C by flowing steam

D. Dry heat sterilisation at 180-200°C for a long time

E. Sterilisation by high and ultra-high frequency current

52. The ampoule shop of the enterprise produces glucose solution. Indicate what impurities are removed from the glucose in the absence of a "for injection" grade:

A. From pyrogenic substances and dyes

B. From sulphates and iron

C. From manganese and iron

D. From pyrogenic and protein substances

E. From impurities of protein nature and dyes

53. Specify the methods of controlling solutions for parenteral administration for mechanical inclusions:

A. Visual and optical
B. Limulus test
C. Amperometric methods
D. Gravimetric methods
E. NMR and UV spectroscopy

54. One of the steps in the process of preparing solutions for injection is filtering the solutions. What filters are used for sterile filtration?
A. Candle filters
B. Print filters
C. Fungus filter
D. Nootch filters
E. HNDHFI filter

55. A pharmaceutical company produces a solution of eufiline for injection. Specify the features of the preparation of this solution:
A. Purification by sterile filtration
B. Purification of the solution from colouring and pyrogenic substances
C. Dissolution of the drug substance by heating
D. Preparation of a higher concentration solution
E. Adding a stabiliser

56. Indicate the best way to dry sterile powders for injection:
A. In freeze dryers
B. In chamber vacuum dryers
C. In spray dryers
D. In fluidised bed dryers
E. In chamber air circulation dryers

57. Name the main operations at the amplification stage:

A. Filling ampoules with solution, sealing ampoules, quality assessment
B. Washing ampoules, filling ampoules with solution, sealing ampoules
C. Ampoule washing, drying and sterilisation, quality assessment
D. Filling, washing, sterilisation
E. Sealing, sterilisation, packaging.

58. Which solutions for parenteral administration of the following substances are subjected to special purification in the absence of a "for injection" grade?
A. Magnesium sulfate, calcium chloride, glucose
B. Gelatin, novocaine, sodium sulfite
C. Sodium nitrite, ergotal, calcium chloride
D. Hexamethylene tetramine, novocaine
E. Ascorbic acid, analgin

59. Which solvent is not used in the production of injectable solutions:
A. Mineral oils
B. Mineral oils
C. Water
D. Glycerin
E. Ethyl oleate

60. Which oil is not used for the preparation of injectable solutions:
A. Petroleum jelly
B. Peach oil
C. Olive oil
D. Sunflower
E. Corn

61. The ampoule shop of an enterprise produces calcium gluconate solution for injection. Indicate what impurities are removed from the calcium gluconate in the absence of the

"for injection" grade.

A. From impurities of calcium oxalate

B. From impurities of iron salts

C. From impurities of manganese and iron salts

D. From impurities of calcium sulphate and iron

E. From dyes and pyrogenic substances

62. The ampoule shop produces solutions for injection. Specify the stabiliser for 1% morphine hydrochloride solution for injection.

A. Hydrochloric acid solution 0.1 n

B. Sodium chloride solution 0.1 n

C. Aminopropylene glycol

D. Rongalite

E. Sodium metabisulfite

63. For stabilisation of 5%, 10%, 20% solutions of novocaine, which are made in industrial conditions, use:

A. Hydrochloric acid 0.1 n

B. Antioxidants in combination with hydrochloric acid

C. Alkalis

D. Buffer solutions

E. Weibel stabiliser

64. Which stabiliser should be used to stabilise glucose solutions:

A. Weibel stabiliser

B. Kurschmann's stabiliser

C. Stabiliser 0.1M NaOH

D. Stabiliser 0.1M HCl

E. Carboxymethyl cellulose

65. The ampoule shop of the enterprise produces solutions for injection. Indicate the composition of Weibel's reagent, which is used in the production of injectable glucose solutions:

A. Hydrochloric acid, sodium chloride, water
B. Water, hydrochloric acid, sodium hydroxide
C. Hydrochloric acid, sodium bromide, water
D. Hydrochloric acid, sodium nitrite
E. Hydrochloric acid, calcium chloride, water

66. In what amount is added Weibel stabiliser to parenteral solutions.

A. 5%
B. 13%
C. 15%
D. 7%
E. 1%

67. The ampoule shop produces solutions for injection. Indicate to which group of solutions the solution of ascorbic acid for injection belongs:

A. Solutions that are easily oxidised
B. Solutions of substances that require special purification
C. Solutions of substances that are not subject to heat sterilisation
D. Solutions of salts formed by weak bases and strong acids
E. Solutions of salts formed by strong bases and weak acids

68. The ampoule shop of an enterprise produces a solution of caffeine-benzoate for injection. Which stabiliser is added to stabilise the solution:

A. 0.1 M sodium hydroxide solution
B. Sodium metabisulfite
C. 0.1 M hydrochloric acid solution
D. 0.1 M solution of hydrochloric acid and sodium chloride

E. Sodium bicarbonate and sodium sulfite

69. A pharmaceutical company produces a solution of magnesium sulfate for injection. Specify the features of the preparation of this solution:

A. Preparation of the solution, purification from impurities of manganese and iron salts

B. Preparation of the solution without heat sterilisation

C. Preparation of a higher concentration solution and purification from calcium sulphate and iron impurities

D. Dissolution of the drug substance by heating and purification from impurities of calcium oxalate

E. Purification of the solution from dyes and pyrogenic substances

70. To remove impurities from an injectable glucose solution, special purification is performed using the following substances:

A. Adsorption of impurities on activated carbon

B. Addition of calcium hydroxide followed by filtration

C. Addition of hydrochloric acid followed by adsorption on activated carbon

D. Pretreatment with activated carbon followed by stabilisation with hydrochloric acid

E. Addition of iron oxide followed by adsorption of impurities on activated carbon

71. Solutions for the injection of salts of weak acids and strong bases require stabilisation. Indicate which stabilisers are used for these solutions:

A. 0.1 M sodium hydroxide solution

B. 0.1 M hydrochloric acid solution

C. Trilon B

D. Ascorbic acid

E. Butyloxytoluene

72. The ampoule shop of the enterprise produces oil solutions for injection. What solvent

is used in the production of a 20% injectable solution of camphor in oil:

A. Peach oil

B. Olive oil

C. Polyethylene glycol 400

D. Vaseline oil

E. Benzyl benzoate

73. The ampoule shop of the enterprise produces an oil solution of camphor for injection. Indicate the volume of the oil solution to be prepared to fill 200 1 ml ampoules.

A. 230 ml

B. 220 ml

C. 210 ml

D. 200 ml

E. 240 ml

74. The ampoule shop of the enterprise produces a solution of glucose. Indicate from what impurities glucose is purified in the absence of the "for injection" grade:

A. From pyrogenic substances and dyes

B. From sulphates and iron

C. From manganese and iron

D. From pyrogenic and protein substances

E. From impurities of protein nature and dyes

75. Specify the methods of controlling solutions for parenteral administration for mechanical inclusions:

A. Visual and optical

B. Limulus test

C. Amperometric methods

D. Gravimetric methods

E. NMR and UV spectroscopy

76. Benzyl alcohol is used in solutions for parenteral administration as:

A. Antimicrobial preservative

B. Antioxidant

C. Buffer solution

D. A pH regulator

E. Isotonicity regulator

77. One of the steps in the process of preparing solutions for injection is filtering the solutions.Which filters are used for sterile filtration?

A. Candle filters

B. Print filters

C. Fungus filter

D. Nootch filters

E. HNDHFI filter

78. A solution for injection is being prepared in the ampoule shop. Indicate to which group of solutions eufilin for injection belongs:

A. Solutions that are not subject to heat sterilisation

B. Salt solutions formed by weak bases and strong acids

C. Solutions of substances that require special purification

D. Solutions of salts formed by strong bases and weak acids

E. Solutions that are easily oxidised

79. A pharmaceutical company produces a solution of eufiline for injection. Indicate the peculiarities of preparation of this solution:

A. Purification by sterile filtration

B. Purification of the solution from colouring and pyrogenic substances

C. Dissolution of the drug substance by heating

D. Preparation of a higher concentration solution

E. Adding a stabiliser

80. When calculating the isotonic concentration of solutions for injection, the value of plasma depression is used. Specify its value:

A. 0,52

B. 0,34

C. 0,10

D. 0,45

E. 0,90

81. Indicate the best way to dry sterile powders for injection:

A. In freeze dryers

B. In chamber vacuum dryers

C. In spray dryers

D. In fluidised bed dryers

E. In chamber air circulation dryers

82. Name the main operations at the amplification stage:

A. Filling ampoules with solution, sealing ampoules, quality assessment

B. Washing ampoules, filling ampoules with solution, sealing ampoules

C. Ampoule washing, drying and sterilisation, quality assessment

D. Washing of ampoules, drying, filling of ampoules with solution, sealing of ampoules, quality assessment

E. Filling ampoules with solution, sterilisation, washing, quality assessment

83. In the ampoule shop, ampoules are filled to a volume greater than the nominal volume. For what purpose is this done:

A. To ensure the correct dose when filling the syringe

B. To allow a portion of the solution to be taken for analysis

C. To remove air bubbles from the solution

D. To account for production losses

E. To ensure the stability of the solution

84. Which of the following methods of filling ampoules prevents contamination of capillaries with thick and viscous solutions:

A. Syringe

B. Vacuum

C. Turbovacuum

D. Vapour condensation

E. Filling in an inert gas environment

85. A pharmaceutical company produces solutions for injection. Which method can be used to fill the ampoules with an oil solution:

A. Syringe method

B. Vacuum

C. Vapour condensation

D. Turbovacuum

E. Ultrasonic

86. The ampoule shop of an enterprise produces a 5% tocopherol acetate oil solution for injection. Indicate which method of filling ampoules is rational to use when filling ampoules with this solution.

A. Vapour condensation

B. Vacuum

C. Syringe

D. Syringe and vacuum

E. Syringe and vapour condensation

87. For which injectable solutions is amplification carried out in an inert gas environment (nitrogen, argon, carbon dioxide)?

A. Substances that are easily oxidised
B. Essential oils
C. Powders
D. Hydrolytically unstable substances
E. Light-sensitive substances

88. Which group of infusion solutions includes polyvinylpyrrolidone, polyvinyl alcohol, hemodesis, neohemodesis, polydes:
A. Detoxification solutions
B. Hemodynamic, anti-shock fluids
C. Regulators of water and salt balance
D. Preparations for parenteral nutrition
E. Solutions with the function of oxygen transfer

89. What is a feature of the technology of calcium gluconate solution?
A. Dissolution in hot water
B. Preparation under aseptic conditions without further sterilisation
C. Pre-sterilisation of the powder
D. Filling the vial with 2/3 of the solution
E. Stabilisation with a solution of 0.1 M hydrochloric acid

90. In the ampoule shop solutions for injection are made. Indicate to which group of solutions the solution of ascorbic acid for injection belongs:
A. Solutions that are easily oxidised
B. Solutions of salts formed by strong bases and weak acids
C. Solutions of substances that are not subject to heat sterilisation
D. Solutions of salts formed by weak bases and strong acids
E. Solutions of substances that require special cleaning

91. A pharmacist has prepared an injectable solution with a readily oxidising substance

that needs to be stabilised with an antioxidant. Identify this substance:

A. Ascorbic acid

B. Dimedrol

C. Sodium chloride

D. Urotropin

E. Calcium gluconate

92. A pharmacist has prepared an injectable solution of ascorbic acid. Specify the substance necessary to stabilise the solution:

A. Sodium sulfite

B. Sodium citrate

C. Sodium acetate

D. Sodium chloride

E. Sodium bromide

93. What is a feature of the technology of calcium gluconate solution?

A. Dissolution in hot water

B. Stabilisation with a solution of 0.1 M hydrochloric acid

C. Prepare under aseptic conditions without further sterilisation

D. Pre-sterilisation of the powder

E. Filling the vial with 2/3 of the solution

94. Which grade of glass belongs to the first class?

A. USP-1

B. AB-1 (boron-free glass)

C. NS-2 (neutral glass-2)

D. NS-2 A (neutral-2A glass)

E. MTB (medical container colourless)

95. Indicate what type of glass can be used to make ampoules for tocopherol solution?

A. AB-1

B. NS-3

C. NS-1

D. HT-1

E. SNS-1

96. Which glass grade belongs to the second class?

A. AB-1 (boron-free glass)

B. USP-1

C. NS-1 (neutral-1 glass)

D. NS-3 (neutral glass-3)

E. SNS-1 (neutral light-sensitive glass)

97. What brand of glass is not used for the manufacture of ampoules:

A. MTB (medical container colourless)

B. AB-1 (boron-free glass)

C. NS-1 (neutral glass-1)

D. NS-3 (neutral glass-3)

E. SNS-1 (neutral light-sensitive glass)

98. In the production of ampoules, various components are added to the glass to change its properties. What is the purpose of adding boron oxide to glass?

A. To increase the chemical resistance of glass

B. To reduce the melting point of ampoule glass

C. To give the glass the desired colour

D. To increase the mechanical strength of the glass

E. To increase the thermal stability of the glass

99. When assessing the quality of ampoules, chemical resistance is determined. Specify the methods for determining this indicator:

A. With the help of various acid-base indicators, using a pH meter, weight methods

B. Visual, weight methods

C. Polarisation-optical

D. Autoclaving method followed by titration with hydrochloric acid solution

E. Method of exposure of glass samples to sodium carbonate and sodium bicarbonate solution

100. Specify the device for determining the residual stress in ampoule glass:

A. Polariscope-polarimeter

B. Densimeter

C. pH meter

D. Photoelectrocolourimeter

E. Spectrophotometer

101. To determine the residual voltage in an ampoule glass, use the method:

A. Polarisation-optical

B. Methylene blue solution

C. With the help of a pycnometer

D. Using a "drum wiper"

E. Using a Soxhlet apparatus

102. What is the effect of residual stress in the glass on the quality of ampoules?

A. Reduced mechanical stability

B. Increases mechanical resistance

C. Chemical resistance increases

D. Increases the size of the ampoule

E. The colour of the ampoule changes

103. In an ampoule shop, it is necessary to remove residual voltage before using ampoules. What operation is carried out for this purpose:

A. Annealing the ampoules

B. Drying in tunnel ovens

C. Washing with desalinated water

D. Cutting of capillaries

E. Softening the glass with gas burners

104. Which parameter is used to calibrate glass wires at glassworks:

A. By the outer diameter

B. By the inner diameter

C. By wall thickness

D. By length

E. By mass

105. The technological stage "Preparation of ampoules for filling" includes the operations of drying and sterilisation of ampoules. Select the equipment and facilities for this operation:

A. Tunnel dryer, drying cabinets, laminar flow drying cabinets of heated air

B. Laminar flow heated air dryers, Krupin chamber, ultrasonicator

C. Steam sterilisers type AP-7 and AP-18, Resepin apparatus

D. Ultrasonic unit, tunnel dryer, drying cabinets

E. Krupin's chamber, ultrasonic device, Rezepin apparatus, laminar flow dryers of heated air

106. In the production of ampoules, glass with the required heat resistance is selected. Indicate what this property of ampoule glass provides so that the ampoules meet the requirements of regulatory and technical documentation:

A. Withstanding sharp temperature fluctuations

B. Easy cutting of capillaries

C. High-quality sealing of ampoules

D. Withstanding the load during production and transport

E. Ability to protect photosensitive substances

107. What percentage of the ampoules taken for the test of "heat resistance" should be intact:

A. 98%

B. 75%

C. 30%

D. 50%

E. 95%

108. When testing the thermal stability of 100 ampoules from one batch, 20 ampoules cracked. Was the glass used in their manufacture heat-resistant?

A. No, there should be 98 whole ones

B. No, it should be 95

C. No, it should be 90

D. Yes, there should be 80 integers

E. Yes, there should be 75 integers

109. In the production of ampoules, glass is selected with the required fusibility. What is this property of ampoule glass?

A. High-quality and high-speed sealing of ampoules

B. Easy cutting of capillaries

C. Withstanding the load during production and transportation

D. Withstanding sharp temperature fluctuations

E. Ability to protect photosensitive solutions

110. In the production of ampoules for injectable solutions, glass of different grades is used. Indicate what type of glass can be used to make ampoules for solutions that are sensitive to light:

A. SNS-1

B. NS-1

C. NS-3

D. AB-1

E. HT-1

111. What type of glass should be used to make ampoules for cyanocobalamin 0.01% solution?

A. Light-protective neutral (SNS-1)

B. Boron-free (AB-1)

C. Neutral (NS-2)

D. Neutral (NS-1)

E. Neutral (NS-2A)

112. The ampoule shop of the enterprise produces solutions for injections. From the list below, select the brands of ampoule glass used in the production of an injectable solution of novocaine:

A. NS-3, NS-1, USP-1

B. NS-1, NS-2, NS-3

C. NS-1, NS-2A, NS-3

D. OS-1, USP-1, NS-2

E. HT-1, SS-1, AB-1

113. Which solutions for parenteral administration of the listed substances are subject to special purification in the absence of a "for injection" grade?

A. Magnesium sulfate, calcium chloride, glucose

B. Gelatin, novocaine, sodium sulfite

C. Sodium nitrite, ergotal, calcium chloride

D. Hexamethylene tetramine, novocaine

D. Ascorbic acid, analgin

114. At a pharmaceutical company, demineralised water is obtained by using membrane

separation methods. Choose the method in which the water passes through a semipermeable membrane under the influence of external pressure:

A. Reverse osmosis

B. Electrodialysis

C. Evaporation through a membrane

D. Dialysis

E. Sorption

115. Specify the requirements for water for injection that differ significantly from purified water:

A. Absence of pyrogens

B. Absence of heavy metals

C. Absence of sulphates, chlorides

D. Absence of nitrites and nitrates

E. Absence of reducing agents

116. Which solvent is not used in the production of injectable solutions:

A. Mineral oils

B. Fatty oils

C. Water

D. Glycerine

E. Ethyl oleate

117. Which oil is not used for the preparation of injectable solutions:

A. Petroleum jelly

B. Peach oil

C. Olive oil

D. Sunflower

E. Corn

118. The ampoule shop of the enterprise produces a solution of calcium gluconate for injection. Indicate what impurities are removed from calcium gluconate in the absence of the "for injection" grade.

A. From impurities of calcium oxalate

B. From impurities of iron salts

C. From impurities of manganese and iron salts

D. From impurities of calcium sulphate and iron

E. From dyes and pyrogenic substances

119. The ampoule shop produces solutions for injection. Specify the stabiliser for 1% morphine hydrochloride solution for injection.

A. Hydrochloric acid solution 0.1 n

B. Sodium chloride solution 0.1 n

C. Aminopropylene glycol

D. Rongalite

E. Sodium metabisulfite

120. For stabilisation of 5%, 10%, 20% solutions of novocaine, which are made in industrial conditions, use:

A. Hydrochloric acid 0.1 n

B. Antioxidants in combination with hydrochloric acid

C. Alkalis

D. Buffer solutions

E. Weibel stabiliser

121. Which stabiliser should be used to stabilise glucose solutions:

A. Weibel stabiliser

B. Kurschmann's stabiliser

C. Stabiliser 0.1M NaOH

D. Stabiliser 0.1M HCl

E. Carboxymethyl cellulose

122. The ampoule shop of the enterprise produces solutions for injection. Indicate the composition of Weibel's reagent, which is used in the production of injectable glucose solutions:

A. Hydrochloric acid, sodium chloride, water
B. Water, hydrochloric acid, sodium hydroxide
C. Hydrochloric acid, sodium bromide, water
D. Hydrochloric acid, sodium nitrite
E. Hydrochloric acid, calcium chloride, water

123. In what amount is added Weibel stabiliser to parenteral solutions.

A. 5%
B. 13%
C. 15%
D. 7%
E. 1%

124. The ampoule shop produces solutions for injection. Indicate to which group of solutions the solution of ascorbic acid for injection belongs:

A. Solutions that are easily oxidised
B. Solutions of substances that require special purification
C. Solutions of substances that are not subject to heat sterilisation
D. Solutions of salts formed by weak bases and strong acids
E. Solutions of salts formed by strong bases and weak acids

125. For what purpose is activated carbon used in the manufacture of injectable solutions:

A. To purify some injectable solutions
B. To create a buffer system

C. As an antioxidant

D. To increase the chemical resistance of ampoule glass

E. To relieve residual stress in ampoules

126. A pharmaceutical company produces a solution of magnesium sulfate for injection. Specify the features of the preparation of this solution:

A. Preparation of the solution, purification from manganese and iron salts

B. Preparation of the solution without heat sterilisation

C. Preparation of a higher concentration solution and purification from calcium sulphate and iron impurities

D. Dissolution of the drug substance by heating and purification from impurities of calcium oxalate

E. Purification of the solution from dyes and pyrogenic substances

127. To remove impurities from the injectable glucose solution, special purification is performed using the following substances:

A. Adsorption of impurities on activated carbon

B. Addition of calcium hydroxide followed by filtration

C. Addition of hydrochloric acid followed by adsorption on activated carbon

D. Pretreatment with activated carbon followed by stabilisation with hydrochloric acid

E. Addition of iron oxide followed by adsorption of impurities on activated carbon

128. At a pharmaceutical enterprise, one of the methods of sterilisation of thermolabile substances is the method of tindalisation. Indicate the essence of this method:

A. Heating the solution three times to 40-60°C with breaks for a day for thermostatting

B. Autoclaving at a temperature of 119-121°C and a pressure of 1.01.1 atm

C. Sterilisation at 100°C by flowing steam

D. Dry heat sterilisation at 180-200°C for a long time

E. High and ultra-high frequency current sterilisation

129. Solutions for injection of salts of weak acids and strong bases require stabilisation. Indicate which stabilisers are used for these solutions:

A. 0.1 M sodium hydroxide solution

B. 0.1 M hydrochloric acid solution

C. Trilon B

D. Ascorbic acid

E. Butyloxytoluene

130. The ampoule shop of an enterprise produces a solution of caffeine-benzoate for injection. Which stabiliser is added to stabilise the solution:

A. 0.1 M sodium hydroxide solution

B. Sodium metabisulfite

C. 0.1 M hydrochloric acid solution

D. 0.1 M solution of hydrochloric acid and sodium chloride

E. Sodium bicarbonate and sodium sulfite

131. The ampoule shop of the enterprise produces oil solutions for injection. What solvent is used in the production of a 20% injectable solution of camphor in oil:

A. Peach oil

B. Olive oil

C. Polyethylene glycol 400

D. Vaseline oil

E. Benzyl benzoate

132. The ampoule shop of the enterprise produces an oil solution of camphor for injection. Indicate the volume of the oil solution to be prepared to fill 200 1 ml ampoules.

A. 230 ml

B. 220 ml

C. 210 ml

D. 200 ml

E. 240 ml

134. The ampoule shop of the enterprise produces a solution of glucose. Indicate from what impurities glucose is purified in the absence of the "for injection" grade:

A. From pyrogenic substances and dyes

B. From sulphates and iron

C. From manganese and iron

D. From pyrogenic and protein substances

E. From impurities of protein nature and dyes

135. Specify the methods of controlling solutions for parenteral administration for mechanical inclusions:

A. Visual and optical

B. Limulus test

C. Amperometric methods

D. Gravimetric methods

E. NMR and UV spectroscopy

136. Benzyl alcohol is used in solutions for parenteral administration as:

A. Antimicrobial preservative

B. Antioxidant

C. Buffer solution

D. A pH regulator

E. Isotonicity regulator

137. One of the steps in the manufacturing process of solutions for injection is the filtration of the solutions.Which filters are used for sterile filtration?

A. Candle filters

B. Print filters

C. Fungus filter

D. Nootch filters

E. HNDHFI filter

138. A solution for injection is prepared in the ampoule shop. Indicate to which group of solutions eufilin for injection belongs:

A. Solutions that are not subject to heat sterilisation

B. Salt solutions formed by weak bases and strong acids

C. Solutions of substances that require special purification

D. Solutions of salts formed by strong bases and weak acids

E. Solutions that are easily oxidised

139. A pharmaceutical company produces a solution of eufilin for injection. Indicate the peculiarities of preparation of this solution:

A. Purification by sterile filtration

B. Purification of the solution from colouring and pyrogenic substances

C. Dissolution of the drug substance by heating

D. Preparation of a higher concentration solution

E. Adding a stabiliser

140. When calculating the isotonic concentration of solutions for injection, the value of plasma depression is used. State its value:

A. 0,52

B. 0,34

C. 0,10

D. 0,45

E. 0,90

141. State the best method for drying sterile injectable powders:

A. In freeze dryers

B. In chamber vacuum dryers

C. In spray dryers

D. In fluidised bed dryers

E. In chamber air circulation dryers

142. Name the main operations at the amplification stage:

A. Filling ampoules with solution, sealing ampoules, quality assessment

B. Washing ampoules, filling ampoules with solution, sealing ampoules

C. Ampoule washing, drying and sterilisation, quality assessment

D. Washing of ampoules, drying, filling of ampoules with solution, sealing of ampoules, quality assessment

E. Filling ampoules with solution, sterilisation, washing, quality assessment

143. In the ampoule shop, ampoules are filled to a volume greater than the nominal volume. For what purpose is this done:

A. To ensure the correct dose when filling the syringe

B. To allow a portion of the solution to be taken for analysis

C. To remove air bubbles from the solution

D. To account for production losses

E. To ensure the stability of the solution

144. Which of the following methods of filling ampoules prevents contamination of capillaries with thick and viscous solutions:

A. Syringe

B. Vacuum

C. Turbovacuum

D. Vapour condensation

E. Filling in an inert gas environment

145. A pharmaceutical company produces solutions for injection. Which method can be used to fill the ampoules with an oil solution:

A. Syringe method
B. Vacuum
C. Vapour condensation
D. Turbovacuum
E. Ultrasonic

146. The ampoule shop of the enterprise produces a 5% oil solution of tocopherol acetate for injection. Indicate which method of filling ampoules is rational to use when filling ampoules with this solution.

A. Vapour condensation
B. Vacuum
C. Syringe
D. Syringe and vacuum
E. Syringe and vapour condensation

147. For which injectable solutions is amplification carried out in an inert gas environment (nitrogen, argon, carbon dioxide)?

A. Substances that are easily oxidised
B. Essential oils
C. Powders
D. Hydrolytically unstable substances
E. Light-sensitive substances

148. What infusion solutions are introduced into the body in the need to correct the blood composition in dehydration caused by diarrhoea, cerebral edema, toxicosis:

A. Regulators of water-salt balance and acid-base balance
B. Hemodynamic antishock drugs
C. Detoxification solutions

D. Preparations for parenteral nutrition

E. Solutions with the function of oxygen transfer

149. Which group of infusion solutions includes polyvinylpyrrolidone, polyvinyl alcohol, hemodesis, neohemodesis, polydes:

A. Detoxification solutions

B. Hemodynamic, anti-shock fluids

C. Regulators of water and salt balance

D. Preparations for parenteral nutrition

E. Solutions with the function of oxygen transfer

150. What is a feature of the technology of calcium gluconate solution?

A. Dissolution in hot water

B. Preparation under aseptic conditions without further sterilisation

C. Pre-sterilisation of the powder

D. Filling the vial with 2/3 of the solution

E. Stabilisation with a solution of 0.1 M hydrochloric acid

151. In the ampoule shop solutions for injection are made. Indicate to which group of solutions the solution of ascorbic acid for injection belongs:

A. Solutions that are easily oxidised

B. Solutions of salts formed by strong bases and weak acids

C. Solutions of substances that are not subject to heat sterilisation

D. Solutions of salts formed by weak bases and strong acids

E. Solutions of substances that require special cleaning

152. A pharmacist has prepared an injectable solution with a readily oxidising substance that needs to be stabilised with an antioxidant. Identify this substance:

A. Ascorbic acid

B. Dimedrol

C. Sodium chloride

D. Urotropin

E. Calcium gluconate

153. A pharmacist has prepared an injectable solution of ascorbic acid. Specify the substance necessary to stabilise the solution:

A. Sodium sulfite

B. Sodium citrate

C. Sodium acetate

D. Sodium chloride

E. Sodium bromide

157. What is a feature of the technology of calcium gluconate solution?

A. Dissolution in hot water

B. Stabilisation with a solution of 0.1 M hydrochloric acid

C. Prepare under aseptic conditions without further sterilisation

D. Pre-sterilisation of the powder

E. Filling the vial with 2/3 of the solution

158. Which of the following industrial ophthalmic dosage forms are called minims:

A. Eye lotions

B. Extended-release ophthalmic dosage forms

C. Solutions for washing eye lenses

D. Gelatinous oval discs for single use

E. Ocular dosage forms and single-use products

159. Depending on the solubility, ocular inserts are divided into:

A. emulsion, fat-soluble, combined

B. Biosoluble, tear-soluble, mixed

C. Single-acting, insoluble, biosoluble

D. Water-soluble, fat-soluble, combined

E. Water-soluble, insoluble, combined

160. A pharmaceutical company produces single-use ophthalmic dosage forms - lamellas. Which of the following substances is used for their preparation?

A. agar

B. collagen

C. methyl cellulose

D. elastin

E. chitosan

161. For the manufacture of eye films as biosoluble polymers, the following film-forming substances are used:

A. Phenol-formaldehyde and perchlorovinyl resins

B. Collagen, acetyl starch, methylcellulose vine, acrylic acid derivatives

C. Oil and epoxy resins, casein

D. Amber, rosin, copal and others

E. Urea and melamine-formaldehyde resins

162. A pharmaceutical company produces eye medicinal films from a bio-soluble polymer. Indicate which of the following substances are used for their preparation:

A. Collagen

B. Methylcellulose, Na-carboxymethylcellulose

C. Polyvinylpyrrolidone, polyvinyl alcohol

D. Starch, dextran

E. Gelatin, gelatoses

163. Which excipient is NOT used to control the viscosity of eye drops?

A. hydroxypropyl methyl cellulose

B. magnesium silicate

C. polyvinyl alcohol

D. polyvinylpyrrolidone

E. methyl cellulose

164. A pharmaceutical company produces a suspension of steroid hormones for ophthalmology. Indicate which excipients are used to stabilise the dispersed phase.

A. Methyl cellulose

B. Tween 80

C. Spen -80

D. proxanol

E. PEG-400 and 0.1% sodium chloride solution

165. A pharmaceutical company produces eye medicines in tubes-droppers. Specify the method of their sterilisation:

A. radiation

B. dry heat sterilisation

C. autoclaving

D. Nitration

E. filtration

166. A pharmaceutical company produces single-use eye dosage forms - lamellas. Which of the following substances is used for their preparation?

A. Gelatin

B. Collagen

C. Methyl cellulose

D. Agar

E. Chitosan

167. A pharmaceutical company manufactures eye medicines in dropper tubes. Specify the method of their sterilisation:

A. Gas

B. Dry heat

C. Autoclaving

D. Radiation

E. Filtration

168. The pharmacist prepared a massage cream of the following composition:

Beeswax 12.0 Almond oil 68.5 Spermaceti 12.0

Anhydrous lanolin 7.5 Lavender essential oil 3 drops.

Indicate the type of cream:

A. Fatty

B. Fat-free

C. emulsion

D. Suspension

E. Combined

169. Medicinal substances are introduced into an ointment depending on their properties. How should the pharmacist introduce dimedrol into a petroleum jelly-lanolin base:

A. Pre-dissolve in a minimum amount of water

B. Grind with glycerin

C. Grind with part of the molten base

D. Dissolve in the molten base

E. Grind with alcohol or ether

170. An ointment base of an alloy of petroleum jelly and lanolin is used to prepare eye ointments. Specify the method of its sterilisation

A. Dry heat

B. ethylene oxide

C. Flowing steam

D. Pasteurisation

E. Tindalisation

171. Oil-based eye drops are additionally controlled:

A. Acid and peroxide numbers

B. Microbiological purity

C. Transparency

D. Identity

E. Sterility

172. The company produces eye drops. For what purpose is sodium chloride added to the composition of eye drops?

A. To create an isotonic solution

B. To prevent the growth of microorganisms

C. Removal of pyrogens

D. Prevention of glass leaching

E. Elimination of hydrolysis

173. Solutions of protected colloids are used to prepare nasal drops. Which process step should be performed in the preparation of protargol solution?

A. Pour a thin layer of water onto a wide surface without stirring

B. Dissolve in purified water with shaking

C. Dissolve in purified water by heating

D. Dissolve in a small amount of glycerin

E. Dissolve with a small volume of purified water

174. A pharmaceutical company produces sterile aqueous solutions for wetting and rinsing the eyes and for impregnating materials that are applied to the eye. Name them:

A. Eye drops

B. Eye sprays

C. Eye drops

D. Eye ointments

E. Eye inserts.

175. Indicate the duration of infusion in the production of tinctures by maceration:

A. 7 days

B. 1-2 days

C. 24 hours

D. 3-4 hours

E. 14 days

176. Specify the methods of obtaining tinctures:

A. Maceration, percolation, dissolution of extracts

B. Dissolution of extracts

C. Percolation, dissolution of extracts

D. Distillation, maceration

E. Percolation, dissolution of plant material

177. In the manufacture of liquid dosage forms, the following liquid ingredients are dosed by volume:

A. Valerian tincture.

B. Dimexide.

C. Methyl salicylate

D. Polyethylene glycol-400

E. Perhydrol

178. While preparing an infusion of marshmallow root, the pharmacist made a mistake in the temperature of the water for the preparation of this extract and the final product turned out to be cloudy. What temperature is required for the extraction of this raw material?

A. Room temperature

B. 40

C. 100

D. 60

E. 80

179. Transparent liquid aqueous-alcoholic extracts from dried or fresh medicinal plant material, which are obtained without heating and removal of the extractant, are called:

A. Tinctures

B. Liquid extracts

C. Thick extracts

D. Extracts concentrates

E. Oil extracts

180. Which extraction method is a type of maceration?

A. Bismaceration

B. Percolation

C. Repercussion

D. Dynamisation

E. Countercurrent extraction

181. An alcoholic solution of boric acid is prepared in a chemical shop. What filters are used to filter this solution?

A. Printing filters

B. Nootch filters

C. Membrane filters

D. Bag filters

E. Paper filters

182. A pharmaceutical company produces camphor oil for external use. Indicate which oil is used as a solvent:

A. Sunflower oil
B. Peach oil
C. Vaseline
D. Olive oil
E. Lilac

183. Oil is used in the production of a number of dosage forms. The method of obtaining this oil is:
A. Pressing
B. Enfluorination
C. Distillation with water
D. Distillation with water vapour
E. Sublimation

184. In the manufacture of decoctions with a volume of 1000-3000 ml, the time of infusion in a boiling water bath is:

A. 40 minutes
B. 25 minutes
C. 30 minutes
D. 45 minutes
E. 15 minutes

185. A pharmacist is preparing an extraction ointment. State the component that should be used to make this type of ointment:
A. 64 parts sugar and 36 parts water
B. 73 parts sugar, 22 parts water, 5 parts 90% alcohol
C. 50 parts sugar and 50 parts water
D. 32 parts sugar, 33 parts water, 2 parts 90% alcohol
E. 45 parts sugar and 55 parts water

186. Galenic preparations include:

A. Tinctures

B. Granules

C. Capsules

D. Aerosols

E. Spansules

187. Twin-80 is introduced into emulsion systems. Indicate the role of tween-80 in emulsions:

A. Emulsifier

B. Antioxidant

C. Preservative

D. Flavouring agent

E. Solvent

188. A pharmacist has prepared a solution of colargol. Indicate the type of dispersion system:

A. Colloidal solution

B. True solution

C. Suspension

D. Emulsion

E. Aerosol

189. What mainly determines the choice of extractant in the preparation of individual substances:

A. Selectivity for active substances

B. Ability to eliminate hydrolysis

C. Heat resistance

D. Pharmacological indifference

E. Cost

190. The phytochemical shop of the enterprise produces tincture of calendula. Indicate what raw materials are used to make this preparation:

A. Flowers

B. Roots, rhizomes and grass

C. Grass

D. Leaves and essential oil

E. Roots

191. The enterprise manufactures galena preparations. Galen preparations include:

A. The sum of biologically active substances

B. Only individual active substance

C. Corrigents of smell

D. Corrigents of taste

E. Preservatives

192. Specify the potent medicinal plant material from which an infusion is prepared in a ratio of 1:400:

A. Foxglove leaves

B. Rhizomes with valerian roots

C. Althea root

D. Sage leaves

E. Stinging nettle herb

193. The phytochemical shop produces tinctures. This dosage form is:

A. Alcoholic extracts from medicinal plant raw materials obtained without heating and removing the extractant

B. Water extracts from medicinal plant raw materials

C. Water-ethanol extracts from medicinal plant raw materials containing 25% moisture

D. Oil extracts from medicinal plant raw materials

E. Extracts from medicinal plant raw materials obtained using ether or chloroform

194. Tinctures are made at a pharmaceutical enterprise. For the manufacture of an experimental series of the drug, it is necessary to specify the equipment used for grinding raw materials:

A. Grass cutters

B. Excelsior

C. Vibromlin

D. Dismembrator

E. Rolls

195. Which of the following extractants has a number of advantages, including affordability?

A. Water

B. Ethyl alcohol

C. Methyl alcohol

D. Chloride methylene

E. Ethyl ether

196. Specify which extractant is used at pharmaceutical enterprises for the manufacture of tinctures:

A. Ethyl alcohol

B. Acetone

C. Chloroform

D. Diethyl ether

E. Peach oil

197. A tincture with an inflated content of active substances was obtained in a phytochemical shop. To bring the tincture to the standard, it is necessary:

A. Dilute with the extractant to the standard

B. Consider an irreparable defect

C. Precipitate excess active substances

D. Leave unchanged

E. Filter through sorbents

198. The phytochemical shop of the pharmaceutical enterprise produces valerian tincture. Specify the technological features of the production of this drug:

A. It is prepared in 70% ethanol in a ratio of 1:5

B. Prepared in 70% ethanol in a ratio of 1:10

C. Prepared in 90% ethanol in a ratio of 1:5

D. Prepared in 90% ethanol in a ratio of 1:10

E. It is prepared in 95% ethanol in a ratio of 1:10

199. One of the methods of obtaining tinctures in factory conditions is that the total amount of extractant is divided into 3-4 parts and the raw materials are successively extracted with the first part of the extractant, then the second, third and fourth, draining the hood each time; the time of infusion depends on the properties of the plant material. What is the name of this method?

A. Remaceration

B. Maceration

C. Percolations

D. Vortex extraction

E. Maceration with forced circulation of the extractant

200. Specify the type of moisture that is tightly bound to the material, which is not completely removed during drying:

A. Crystallization

B. Free

C. Hygroscopic

D. Osmotic

E. Balanced

201. Extractive substances are released from plant raw materials due to:

A. Molecular and convective diffusion

B. Molecular and cellular diffusion

C. Convective and cellular diffusion

D. Coacervation

E. Adsorption and readsorption of the extractant by plant raw materials

202. In the manufacture of phytochemical preparations, extraction of extractive substances from plant raw materials takes place at the expense of:

A. Molecular and convective diffusion

B. Molecular and cellular diffusion

C. Convective and cellular diffusion

D. Coacervation

E. Absorption and adsorption of the extractant by plant raw materials

203. Specify the methods of obtaining tinctures:

A. Maceration, percolation, dissolution of extracts

B. Dissolving the extracts

C. Percolation, dissolution of extracts

D. Rectification, maceration

E. Percolation, dissolution of plant material

204. The phytochemical workshop of the enterprise produces tinctures by the maceration method. Specify the sequence of technological operations when obtaining tinctures by this method:

A. Infusing for 7 days with periodic mixing of the obtained extract, cleaning the extract, standardization, packaging

B. Soaking for swelling, infusing for 24-48 hours, obtaining hood, cleaning hood, standardization, packaging

C. Insisting for 24-48 hours, obtaining a hood, cleaning the hood, standardization, packaging

D. Insisting for 7 days, obtaining a hood, cleaning the hood, standardization, packaging

E. Soaking for swelling, infusing for 7 days, receiving hood, cleaning hood, standardization, packaging

205. Which of the methods of obtaining tinctures is ineffective and characterized by incomplete extraction of extractive substances:

A. Maceration

B. Repercolation with evaporation

C. Percolation

D. Repercolation with the distribution of raw materials into unequal parts

E. Extraction using ultrasound

206. Specify the duration of infusion in the production of tinctures by the maceration method:

A. 7 days

B. 1-2 days

C. 24 hours

D. 3-4 hours

E. 14 days

207. The phytochemical workshop of the enterprise is mastering the production of the drug from fresh plant raw materials. What extraction methods are used when obtaining preparations from fresh plant raw materials:

A. Maceration with 90% ethyl alcohol, bismaceration

B. Percolation, maceration with 70% ethyl alcohol

C. Repercolation, countercurrent extraction

D. Extraction in the liquid-liquid system, maceration

E. Vortex extraction, circulation extraction

208. Which extraction method is a type of maceration?

A. Bismaceration

B. Percolation

C. Repercolation

D. Dynamization

E. Countercurrent extraction

209. The phytochemical workshop of the enterprise produces tinctures by the percolation method. At what speed is percolation carried out:

A. 1/24 or 1/48 part of the working volume of the percolator per hour.

B. 1/50th of the working volume of the percolator in 30 minutes.

C. 1/20th of the working volume of the percolator per hour.

D. 1/40th of the working volume of the percolator per hour.

E. 1/10th of the working volume of the percolator in 30 minutes

210. The phytochemical workshop of the enterprise produces tinctures by the percolation method. What ratio of raw materials - extractant must be observed when soaking raw materials:

A. 1:1, 1:0,5

B. 0,5:1, 1:5

C. 1:5, 1:10

D. 1:2, 1:1

E. 0,5:2, 1 : 2

211. The phytochemical workshop of the enterprise produces tinctures by the percolation method. What amount of raw materials and extractant is needed to obtain 100 liters of nettle tincture, if K = 1.5:

A. 20 kg of raw materials, 130 liters of extractant

B. 10 kg of raw materials, 45 liters of extractant

C. 100 kg of raw material, 100 l of extractant

D. 50 kg of raw materials, 175 liters of extractant

E. 20 kg of raw materials, 150 liters of extractant

212. While preparing an infusion of althea root, the pharmacist made a mistake in the temperature of the water for preparing this extract, and the final product turned out to be cloudy. What temperature is needed for the water to extract this raw material?

A. Room temperature

B. 40 ºC

C. 100 ºC

D. 60 ºC

E. 80 ºC

213. What methods of hood cleaning are used in the production of tinctures:

A. Settling at a temperature of 8-10 °C, filtration

B. Extractive cleaning methods in the liquid-liquid system

C. Denaturation, filtration, sorption

D. Dialysis, advocacy

E. Solvent replacement, settling, filtration

214. One of the methods of purification of tinctures is settling. In the production process, it is necessary to determine at what temperature it is rational to use this method:

A. 10-15°C

B. Not higher than 10°C

C. 20°C

D. 18°C

E. 45°C

215. Different equipment is used to filter solutions. What filters are not used to filter alcohol solutions?

A. Nutch filters

B. Print filters

C. Frame filter presses

D. Bag filters

E. Filter funnels

216. What methods are used to determine alcohol in a tincture:

A. Distillation, by boiling point

B. Distillation, biological

C. Chemical, biological

D. By boiling point

E. With the help of an alcohol meter and a hydrometer

217. In what ratio are tinctures prepared from potent raw materials:

A. 1:10

B. 1:5

C. 1:25

D. 1:40

E. 1:100

218. The phytochemical workshop of the enterprise produces belladonna tincture. Specify in what ratio of raw materials and finished products the extractor is loaded:

A. 1:10

B. 1:1

C. 1:2

D. 1:20

E. 1:5

219. The phytochemical shop of the pharmaceutical enterprise produces valerian tincture from fresh raw materials. Specify the technological features of the production of this drug:

A. It is prepared in 70% ethanol in a ratio of 1:5

B. Prepared in 90% ethanol in a ratio of 1:5

C. It is prepared in 90% ethanol in a ratio of 1:10

D. It is prepared in 70% ethanol in a ratio of 1:10

E. It is prepared in 95% ethanol in a ratio of 1:10

220. Which quality indicator is not investigated during the analysis of tinctures:

A. Residual content of solvents

B. Density

C. Dry residue

D. Quantitative content of active substances

E. Heavy metals

221. The phytochemical workshop of the enterprise produces calendula tincture. Specify which raw materials are used to manufacture this drug:

A. Flowers

B. Roots, rhizomes and grass

C. Grass

D. Leaves and essential oil

E. Roots

222. When obtaining ethyl alcohol, the rectification process is used. Specify the principle of the process:

A. This is the separation of a mixture of intermixable liquids with different boiling points into separate fractions

B. This is distillation with inert gases

C. This is the washing of spent raw materials with 3-5 times the amount of ethanol

D. This is a technological technique for obtaining liquid extracts

E. This is deep vacuum distillation

223. Galenic preparations include:

A. Tinctures

B. Granules

C. Capsules

D. Aerosols

E. Spangles

224. Define the term "contact drying":

A. The drying process in phytochemical production when drying materials are heated with a heat carrier through an impermeable wall that conducts heat

B. The process of drying in phytochemical production by direct contact of materials to be dried with a hot gaseous coolant

C. Drying process in phytochemical production by contact heating or infrared heat generation

D. The process of drying in phytochemical production by means of contact introduction or generation of heat by high frequency currents

E. Drying process in phytochemical production by contact feeding or heat generation in a microwave field

225. The driving force of the diffusion process in the extraction of plant raw materials is:

A. The difference in concentrations of the active substance in the raw material and extractant

B. High temperature of the extractant

C. High polarity of the extractant

D. Brownian motion of particles

E. The presence of a film membrane

226. What phenomena do not take place in the process of extraction of plant raw materials?

A. Adsorption

B. Dialysis of the extractant inside the cell

C. Desorption

D. Dissolution of cell contents

E. Diffusion

227. In the production of maximally purified extraction preparations, specific methods of hood cleaning are used. Specify the method related to salting:

A. Effect of saturated solutions of strong electrolytes

B. The process of influencing the heating hood

C. Dialysis

D. Effect of UV radiation

E. Ultrasonic treatment

228. An extract from medicinal plant raw materials is obtained in the phytochemical shop. Specify the product characterized by the same ratio between the active substances contained in the raw material and the finished product:

A. Liquid extract

B. Tincture

C. Thick extract

D. Dry extract

E. Extract-concentrate

229. When making liquid extracts in accordance with the requirements of the pharmacopoeia, the raw materials and the extractant must be taken in the ratio:

A. 1:1

B. 1:3

C. 1:5

D. 1:10

E. 1:4

230. The phytochemical workshop of the enterprise produces liquid extracts. How many parts by volume of liquid extract are obtained from one weight part of medicinal plant raw materials:

A. 1.0

B. 0.5

C. 10.0

D. 5.0

E. 2.0

231. At a pharmaceutical enterprise, liquid extracts are produced by the percolation method. What is the first portion of percolate in relation to the mass of raw materials?

A. 85%

B. 80%

C. 90%

D. 75%

E. 60%

232. In the phytochemical workshop, one percolator is used to obtain a liquid extract. By what method is the process of obtaining the extract carried out:

A. Percolation

B. Repercolation with separation of raw materials into unequal parts according to the US Pharmacopoeia

C. By Bosin's method

D. Repercolation with a completed cycle

E. Chulkov's method

233. Which method of obtaining liquid extracts is accompanied by a further stage of evaporation of the extracts:

A. Repercolation with an unfinished cycle

B. Circulating extraction

C. Repercolation with a completed cycle

D. Chulkov repercolation

E. Repercolation with the distribution of raw materials into unequal parts

234. For the production of an extraction preparation, the phytochemical workshop selected: extractant - water; equipment - grinding rolls, a reactor with a steam "shirt", a filter. Specify the production of which extractive preparation is in question.

A. Liquid aloe extract

B. Thick licorice extract

C. Lantoside

D. Adoniside

E. Plantaglucid

235. Specify which extractant is used at pharmaceutical enterprises for the production of liquid extracts:

A. Ethyl alcohol

B. Acetone

C. Chloroform

D. Diethyl ether

E. Peach oil

236. At a pharmaceutical factory, a liquid extract of hawthorn is produced by the percolation method. Specify the amount of the first extraction when obtaining 200 liters of extract:

A. 170 l

B. 50 l

C. 70 l

D. 150 l

E. 200 l

237. Which of the extraction methods is the most accelerated:

A. Vortex extraction

B. Maceration

C. Percolation

D. Repercolation

E. Circulating extraction

238. A liquid extract of Eleutherococcus is produced at a pharmaceutical factory. What equipment should be used at the hood cleaning stage:

A. Settlers of periodic action, print-filters

B. Filters "Vladipor", "Millipore"

C. Sedimentators of continuous action, notch filters

D. Vacuum evaporator, "Khnihfi" filter

E. Centrifuges, notch filters

239. Specify the maximum moisture content in thick extracts according to the requirements of the Federal Ministry of Ukraine.

A. 30%

B. 20%

C. 10%

D. 5%

E. 75%

240. A pharmaceutical enterprise produces thick extracts. Specify the technological stage not provided for in their manufacture:

A. Drying

B. Extraction

C. Cleaning extracts

D. Evaporation

E. Standardization

241. What is the principle of operation of the Soxhlet apparatus when obtaining extracts:

A. Multiple circulation of the extractant through the raw material

B. Molecular diffusion of the extractant under static conditions

C. Using pseudo-liquefaction

D. Effect of ultrasonic cavitation

E. Countercurrent extraction

242. The main working parts of the vacuum-evaporative circulation apparatus "Symax" are:

A. Heating flask, "trunk", expansion flask, refrigerator, receiver

B. Spray nozzles, scraper shaft, body with heated walls, splash guard

C. Pump, nozzles, heat exchanger of the evaporation chamber, fan, separator, working container

D. Extractor, siphon tube, heating flask, refrigerator

E. Expansion flask, scraper shaft, fan, separator

243. The phytochemical workshop of the enterprise produces extracts by the circulation extraction method. Which extractant is not suitable for this method?

A. Ethyl alcohol

B. Ether

C. Chloroform

D. A mixture of chloroform and ether

E. Methylene chloride

244. What equipment is used for continuous countercurrent extraction with

simultaneous movement of raw materials and extractant?

A. Spring-blade extractor

B. Percolator with RPA

C. Soxhlet apparatus

D. Mixer

E. A battery of diffusers

245. In the production of thick extracts, the stage of thickening of the hood is carried out. Specify the equipment for thickening, which consists of a receiving flask, a heater, a refrigerator-condenser, a collecting flask:

A. Circulating vacuum-evaporator

B. Rotary direct current device

C. Foam evaporator

D. Evaporative cube

E. Steam-heated reactor

246. The phytochemical workshop of the enterprise produces a thick extract of male fern. Select the extractant and method of obtaining for the production of this product:

A. Diethyl ether, circulation method

B. 40% ethyl alcohol, TSANDI method

C. 0.25% ammonia solution, bismaceration

D. Chloroform water, percolation

E. Water, vortex extraction

247. Name the extract for the production of which diethyl ether is used:

A. Thick extract of male fern

B. Thick extract of the trefoil bean plant

C. Thick extract of belladonna leaves

D. Dandelion root thick extract

E. Adoniside

248. In the preparation of which thick extract, a Soxhlet-type apparatus is used:

A. Buckthorn extract is thick

B. Male fern extract is thick

C. Valerian extract is thick

D. Pepper mustard extract is thick

E. Licorice extract is thick

249. Why is settling carried out at a temperature of 8-10 °C during the purification of the primary extract?

A. At this temperature, ballast substances precipitate

B. To save production

C. For simultaneous cooling of the extract

D. To preserve the active substances

E. All answers are correct

250. Dandelion roots and bitter wormwood are extracted with water containing a preservative. What substance is used as a preservative:

A. 0.5% solution of chloroform in water

B. 0.25% solution of ammonia in water

C. 0.1 M solution of hydrochloric acid

D. 0.1% solution of Nipagin in water

E. 3% acetic acid

251. The phytochemical workshop of the enterprise produces a thick extract of wormwood. Select the extractant and the method of production for the production of this product:

A. Chloroform water; percolation

B. 0.25% ammonia solution; bismaceration

C. 70% ethyl alcohol; percolation or repercolation

D. 40% ethyl alcohol; the TSANDI method

E. Water; vortex extraction

252. Indicate for what purpose boiling water is used in the production of a thick extract of water legume:

A. In order to inactivate enzymes

B. To dissolve the glycoside meniactin

C. To disinfect the hood

D. To degrease vegetable raw materials

E. To illuminate the hood

253. The pharmaceutical enterprise produces a dry extract-concentrate of thermopsis, in which the concentration of active substances exceeds the norm. Specify the substance used to dilute the extract:

A. Lactose

B. Ethyl alcohol

C. Pectin

D. The water is purified

E. Sodium chloride

254. The phytochemical workshop of the enterprise produces dry extracts according to two technological schemes. From the equipment listed below, choose the one that is used at the drying stage when obtaining a dry extract, if the thickening stage is not provided:

A. Spray dryer, freeze dryer

B. Vacuum drying cabinet, belt dryer

C. Roll vacuum dryer, chamber dryer

D. Air fountain dryer, drum dryer

E. Infrared drying

255. Which vacuum-evaporating device provides natural circulation of the evaporating liquid:

A. Vacuum evaporation apparatus with a central circulation pipe

B. "Centriterm"

C. "Volcano"

D. Vacuum evaporator with countercurrent mixing condenser

E. Ball vacuum-evaporator

256. What is the basis of the operation of spring-blade, screw and disk extractors?

A. The principle of active counterflow of raw materials and extractant

B. The principle of active movement of the extractant

C. Use of carbon dioxide as an extractant

D. Circulation of the extractant

E. Dispersion of raw materials using electrical discharges

257. Extracts-concentrates are produced at a pharmaceutical enterprise. Indicate the ratio in which dry extracts-concentrates are prepared:

A. 1:1

B. 1:2

C. 1:5

D. 1:10

E. 1:1000

258. To obtain extracts-concentrates, use:

A. Ethanol 20-40%

B. Ethyl alcohol

C. The water is purified

D. Ethyl ether

E. Chloroform water

259. During the analysis of the dry extract-concentrate of thermopsis, an excessive content of active substances was established, the moisture content was 5%. How to act in this case:

A. Dilute to normal with lactose

B. Dilute with alcohol or water to normal

C. Dry under vacuum

D. Dry to normal, then add the estimated amount of lactose

E. Reject the series

260. In the manufacture of phytochemical preparations, extraction of extractive substances from plant raw materials takes place at the expense of:

A. Molecular and convective diffusion

B. Coacervation

C. Absorption and adsorption of the extractant by plant raw materials

D. Molecular and cellular diffusion

E. Convective and cellular diffusion

261. Which of the following indicators characterizes the quality of thick extracts?

A. Moisture content

B. Content of fillers

C. Alcohol content

D. Density

E. Transparency

262. What mainly determines the choice of extractant when obtaining individual substances?

A. Selectivity in relation to active substances

B. The ability to eliminate hydrolysis

C. Heat resistance

D. Pharmacological indifference

E. Cost

263. A pharmaceutical enterprise manufactures galenic preparations. Galen preparations include:

A. The sum of biologically active substances

B. Only individual active ingredient

C. Corrigents of smell

D. Corrigents of taste

E. Preservatives

267. The phytochemical workshop of the enterprise produces maximally purified extraction preparations. At the same time, specific methods of cleaning the hood are used. Select the method that applies to dialysis from the following definitions:

A. The property of biopolymer molecules not to pass through semipermeable membranes

B. The process of the effect of heating on the hood

C. The process of extraction from one liquid using another

D. Gas absorption process

E. The process of exposure to electrolyte

268. Specify the conditions under which the freeze-drying process takes place:

A. The hood is frozen, placed in a sublimation chamber, where a deep vacuum is created, the drying temperature is 20-30 oC

B. The hood is slightly evaporated at high temperatures, after which sublimation is carried out

C. Sublimation dryers are not used for the production of extraction preparations due to the use of ethyl alcohol as an extractant

D. The thickened extract in the form of a thin layer (0.5-0.8 cm) is placed on the sheets and dried at a temperature of 50-60 oC

E. The thickened extract in the form of a thin layer (0.5-0.8 cm) is placed on the sheets

and dried at a temperature of 50-60 oC and a pressure of 80-87 kPa

269. In the process of standardization of the production of thick extracts, the mass loss should not exceed:

A. 25-30%

B. 5%

C. 40%

D. 35%

E. 1%

270. In the production of aerosols, propellants are used. Indicate what role propellants play in aerosols:

A. They create pressure in the package

B. Solvents for medicinal substances

S. Stabilizers

D. Emulsifiers

E. dispersants

271. The aerosol workshop of the enterprise uses propellants of various groups in its work. Choose propellants belonging to the group of compressed gases:

A. Nitrogen, nitrous oxide, carbon dioxide

B. Refrigerants (freons)

B. Propane, butane, isobutane

D. Vinyl and methyl chloride

E. Methylene chloride, ethylene chloride

272. The aerosol workshop of the enterprise uses propellants of various groups in its work. Choose propellants that belong to the group of volatile organic solvents:

A. Methylene chloride, ethylene chloride

B. Refrigerants (freons)

C Propane, butane, isobutane

D. Vinyl and methyl chloride

E. Carbon dioxide

273. Aerosols include active components, solvents, propellants. Which of the substances listed below are used as propellants?

A. Freon 11, carbon monoxide, propane-butane

B. isopropyl myristate, neon, sulfur oxide

C Propylene glycol monostearate, argon, helium

D. Linetol, Myristic acid, benzocaine

E. Hydrogen sulfide, hydrogen, triethanolamine

274. The effectiveness of aerosol therapy is largely determined by the size of the particles of the dispersed phase. What depends on the size of the aerosol particles obtained when spraying the contents of the aerosol:

A. Outlet diameter, pressure of saturated fuel vapor

B. Grinding levels, container volumes

With the homogeneity of the system, the speed of spraying

D. calculation of percentage of solid phase content, filling temperature

E. fractional composition, method of filling the container

275. The workshop of a pharmaceutical enterprise that produces aerosol forms uses liquefied gases as a propellant. Which of the proposed substances belong to the group of liquefied gases?

A. Refrigerants or freons

B. Nitrogen

C Nitrous oxide

D. Methylene chloride

E. ethylene chloride

List of recommended literature

(basic, additional, electronic information resources):

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