MINISTRY OF HEALTH OF UKRAINE
ODESSA NATIONAL MEDICAL UNIVERSITY
DEPARTMENT OF PHARMACEUTICAL CHEMISTRY AND DRUGS TECHNOLOGY

APPROVE
Vice-rector for scientific and pedagogical work
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METHODOLOGICAL DEVELOPMENT OF A PRACTICAL LESSON

IN THE EDUCATIONAL DISCIPLINE «MANUFACTURING PHARMACEUTICAL PRACTICE IN DRUG TECHNOLOGY»

Faculty Pharmaceutical Course V

Educational discipline « Manufacturing pharmaceutical practice in drug technology»
(name of academic discipline)

Approved:

Meeting of the Department of pharmaceutical chemistry and drug technology

Odessa National Medical University

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Practical lesson № 1

Topic: General acquaintance with the pharmaceutical enterprise; internal regulations. Instruction on safety and labor protection rules.

Purpose: to study the organizational structure of the pharmaceutical enterprise, the characteristics of its shops and departments, the connection with the auxiliary shops (subdivisions) of the enterprise, the characteristics of workplaces (service areas), general requirements for premises and personnel, safety and sanitary rules at the enterprise; familiarization with instruction on the rules of safety and occupational health and safety; assimilation of the main terms used in the industrial production of medicinal products, familiarization with regulatory and methodical documentation, drawing up regulations.

Basic concepts: technological regulation, GMP, regulatory and technical documentation, excipient, production stage.

Equipment: production schemes, device samples.

Study time: 6 hours.

I. Organizational moment.

II. Control of reference knowledge

2.1. Requirements for students' theoretical readiness to perform practical classes (knowledge requirements, list of didactic units)

Requirements for theoretical knowledge:

Prospects for the development of pharmaceutical technology

Prospects for the development of pharmaceutical technology are closely linked to the influence of scientific and technological progress. On the basis of the latest scientific discoveries, fundamentally new, more advanced and productive technological processes are created, sharply increase labor productivity and improve the quality of finished products. Technologies have a significant impact on future economic indicators of production, require the development of low-operating, resource-saving and waste-free processes, their automation, maximum mechanization and computerization.

Thus, technology has received modern methods of finding optimal end results at the lowest cost, which is an example of how science is transformed into a direct productive force.

The development of pharmaceutical technology is determined by the requirements of modern pharmacotherapy, insists on the creation of such drugs that would be most effective from a therapeutic point of view with a minimum content of the drug substance and have no side effects. At the heart of solving problems - the provisions and principles of biopharmacy, based on the optimal selection of the composition and type of dosage form and the use of

optimal technological processes. This explains the widespread and deepening of biopharmaceutical research in many countries.

The primary problems of pharmaceutical technology include increasing the solubility of sparingly soluble substances in water and lipids; increasing the stability of homogeneous and heterogeneous drug systems; prolongation of the duration of action of drugs; creation of drugs of the directed action with the set pharmacokinetic properties.

It is worth noting the need to study and use in pharmaceutical technology the latest advances in colloid chemistry and chemical technology: new methods of dispersion, advances in physicochemical mechanics, colloid chemistry and polymer chemistry, the use of nonstoichiometric compounds, microencapsulation, new methods of drying, extraction and more another.

Terms of industrial production of drugs

Small-scale production is characterized by the fact that the production of the same product is systematically repeated (in a month, a quarter). The work is carried out according to plan, given the complexity of the manufactured drug in special rooms, where the equipment has a group location. For small-scale production of drugs is characterized by a large variety of products, multicomponent compositions, extensive use of pharmaceutical preparations. Finished products have a limited shelf life.

Large-scale production of drugs is characterized by high mechanization of technological processes, equipped with modern equipment, narrow specialization of production and a limited range of drugs that have a long shelf life.

Large-scale production differs in that the products of the same name are produced in constantly alternating batches or are continuous and are permanent. Machines and devices are located on a group basis.

The production process is calculated with great accuracy, and the products move continuously and sequentially at regular intervals, from one workplace to another. Finished products are also produced continuously and rhythmically.

Equipment for large-scale production of professional-digged and located in the course of the technological process. Automated lines can be used in mass production of drugs. Due to the complexity of the machines, high qualification of the workers servicing them is required. Full automation of the enterprise - the highest level of production.

Basic terms and concepts

To work successfully in the field of drug production, it is necessary to correctly use and understand the terms, which must accurately reflect the meaning and avoid misinterpretation. This section presents the semantic concepts of basic (basic) terms, most widely used in educational, reference and special literature, as well as in production activities (in the preparation of regulatory and technical documentation, etc.).

A medicinal product (drug substance) is a substance (mixture of substances) of synthetic or natural origin that has a certain biological activity and is approved for medical use, production and import for the purpose of diagnosis, prevention or treatment of humans or animals.

Very often, instead of the term "drug", "drug substance" or "drug substance" use the term synonymous with "active substance", which has the same definition and is used in the manufacture of finished drugs.

Active substances (substances, drugs) - biologically active substances that can change the state and functions of the body or have a preventive, diagnostic or therapeutic effect and are used for the production of finished drugs.

Excipient - a relatively chemically and biologically indifferent substance, approved for medical use in order to obtain a dosage form, to provide or preserve certain properties of drugs.

Medicinal (pharmaceutical) raw materials - medicines, medicinal plant raw materials, excipients permitted for medical use for the production of medicines or other pharmaceutical products or semi-finished products. In fact, the raw materials include all raw materials that come into production for processing in order to obtain a finished product or semi-finished product, except for packaging materials.

Dosage form - a form provided by a drug or medicinal plant raw material, convenient to use and provides the desired therapeutic effect.

Medicinal product (medicine, medicine) - a dosage form in packaged, packaged and labeled form in accordance with the requirements of regulatory and technical documentation, which has a certain shelf life and is convenient for medical use, transportation and storage.

Finished products - products that have passed all stages of the technological process, including packaging and labeling.

Finished drug (drug, medicine) - dosage form in the form and condition in which it is used.

Thus, using the drug and the excipient, after certain technological operations, you can get a dosage form (solution, ointment, tablets, etc.). The end product of the technological process is a drug.

Indicators of the level of production of the pharmaceutical drug are reflected in the technological regulations - the normative document that sets requirements for technological processes, technological equipment and premises associated with quality manufacturing in compliance with the conditions of labor protection and the environment.

Production instruction is a normative document that has the status of an enterprise standard, which regulates a certain part of the production process.

Process - a set of consecutive actions to create a product.

Technological process is a part of the production process that contains scientifically substantiated purposeful actions necessary to obtain the finished product. The technological process consists of separate, successive stages of production.

Production stage - a set of technological operations that lead to the production of an intermediate product (semi-finished product - the finished product), which is determined quantitatively and qualitatively. For example, the process of obtaining tablets includes the following production stages: mixing, granulation, compression. in turn, is a combination of a number of successive technological operations.

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

Technical means - a set of tools needed for the implementation of the technological process.

Cost rate - the maximum allowable amount of raw materials, semi-finished products required for the preparation of a unit of production.

Intermediate products - partially processed products obtained at any stage of the technological process, except the final stage, and intended for further processing before it becomes a finished product.

Processing-reprocessing at a certain stage of production of the whole series or part of a series of products of improper quality by carrying out one or more technological operations in order to obtain products that meet the requirements of regulatory documentation.

Intermediate - products obtained by the manufacturer from the supplier, which has undergone one or more stages of processing (supplier), necessary for the production of finished products (from the consumer). The intermediate for the supplier is the finished product.

Raw materials used in the production process are usually divided into the main raw material - is part of the finished product, and auxiliary raw materials are not part of the finished product, which is also called production waste.

Waste is a modified or substandard residue of raw materials, materials or semi-finished products, which without proper processing can not be used to prepare the finished product. Waste that can be reused to prepare the finished product is called returnable waste.

If production waste is of consumer value and can be further processed, it is called by-products. Production wastes that are not subject to further processing and do not represent consumer value are called waste. In modern production, it is desirable to turn all waste into by-products. In the process of production there are always material losses caused by spraying, evaporation, adhesion of material to the walls of the equipment. The above concepts related to the processing of pharmaceutical raw materials used in compiling the material balance.

Batch of finished drug - a set of units of the drug, which is made from the same series of raw materials, materials and intermediates in one process, including the same stage of sterilization.

The State Register of Medicinal Products is a normative document that contains information on medicinal products permitted for production and use in medical practice.

Quality of a medicinal product is a set of properties that give a medicinal product the ability to satisfy consumers in accordance with its purpose and meet the requirements established by law.

The quality of a medicinal product is regulated by a pharmacopoeial article - a normative document that defines the composition, packaging, shelf life and quality requirements of a medicinal product (medicinal substance or excipient) and has the status of a state standard.

Validation - assessment and documentary confirmation of compliance of the production process and product quality with the approved requirements.

Certificate - a written certificate (guarantee) that the quality of drugs (efficacy, safety) meets the established requirements of the specification, and the production process - the rules of good manufacturing practice (GMP).

Stability - the ability of a drug (drug) to retain its physicochemical and microbiological properties for some time since its release.

Shelf life - approved by the legislature, based on the results of special studies, the shelf life of the drug (drug), during which it retains its physicochemical, microbiological and therapeutic properties without changes or in the prescribed size, subject to storage conditions.

The semantic meaning of other terms is given in separate sections, when considering a particular material.

Regulatory and technical documentation in the industrial production of drugs

The industrial production of medicines is regulated by the relevant regulatory and technical documentation, approved in the prescribed manner.

The technical documentation should improve the quality and effectiveness of medicines, constantly improve on the basis of advances in science and technology and be revised in a timely manner to replace outdated indicators in accordance with the needs of health, population, national defense and exports.

In Ukraine, there are uniform requirements for the content, procedure for development, approval and approval of technical documentation of chemical-pharmaceutical products for medical purposes, as well as veterinary products and food additives produced by chemical-pharmaceutical enterprises and pharmaceutical factories.

Normative documentation is a document that establishes rules, general principles or characteristics relating to different activities or their results.

STD on drugs, medicinal plant raw materials and medical devices are divided into the following categories:

1. Technological and technical regulations.
2. State Pharmacopoeia.
3. Pharmacopoeial articles.
4. Temporary pharmacopoeial articles.
5. State standards.
6. Industry standards (OST), Industry standard of Ukraine.
7. Technical conditions.
8. Guiding normative document - instructions,
methodical instructions, etc.
9. Production and technological instructions.

Pharmacopoeial article - regulatory and technical document,

sets requirements for the drug, its packaging, conditions and shelf life and quality control methods. FS is approved for a drug or medicinal plant raw materials of mass production, approved by the Ministry of Health of Ukraine for medical use and industrial production.

Pharmacopoeial articles on drugs that have the greatest therapeutic value are widely used in medical practice and have high quality indicators, which are included in the State Pharmacopoeia. In addition to pharmacopoeial articles on drugs, GF contains general methods of physicochemical, chemical and biological analysis and information on the reagents used, indicators, as well as other materials that contain general requirements and standards for drugs. GF requirements for drugs are mandatory for all enterprises and institutions that manufacture, store, control and use them.

Thus, GF is a collection of mandatory national standards and regulations that regulate the quality of medicines.

Temporary pharmacopoeial article- normative - technical document approved for a limited period, which sets requirements for the quality of the drug or medicinal plant raw materials and has the character of a state standard. VFS for drugs and medicinal plant raw materials is approved for the first industrial (installation) series of new drugs recommended for medical use by the Pharmacological Committee of the Ministry of Health of Ukraine and scheduled for serial production. VFS is approved for a limited period, which is set depending on the degree of processing of the drug in production conditions - no more than 3 years.

A standard is a normative document that sets out for general and repeated use rules, requirements, general principles or characteristics relating to different activities or their results in order to achieve the optimal degree of regulation in a particular area.

State and industry standards (GOST, OST) are set for additional technical requirements and group characteristics required for the manufacture and supply of drugs (technical terms and designations, general technical documentation, technological standards, etc.). Osts are approved by the Ministry of Health of Ukraine or the Ministry of Medical and Microbiological Industry of Ukraine in agreement with the Ministry of Health of Ukraine.

Some types of raw materials, excipients, packaging and packaging are regulated by technical conditions (TU) or temporary technical conditions (VTU). Like the articles in the pharmacopoeia of TU and VTU are of the state standard.

Specifications are normative documents that set requirements for specific products, services and regulate the relationship between supplier and consumer of products.

All the work of pharmaceutical companies is characterized by strict regulation and production planning. The technological process of production of medicines is carried out on the basis of normative and technical documentation, presented in the form of two regulations - technological, related to the production of a specific product name, and technical, containing requirements for equipment and safe operation at this production site in this shop.

Technological regulations are a normative document, which sets out technological methods, technical means, norms and standards for the manufacture of a medicinal product.

Requirements of these regulations, which guarantee the quality of manufactured products, rational and safe conduct of technical processes, preservation of equipment, exclusion of the possibility of accidents and environmental pollution.

Thus, the effect of technological regulations extends to the production of a particular drug, subject to technical regulations.

The effect of the technical regulation covers the preparation of production (laboratory, research and industrial and industrial) premises and personnel for work; creation of necessary sanitary and hygienic conditions of production; compliance with the requirements related to labor protection, safety, fire safety, environmental protection; qualified efficient operation of equipment that guarantees the receipt of medicines in accordance with the requirements of the NTD.

Regulations for the production of chemical and pharmaceutical products are used as the main technological document:

- development of the developed chemical-pharmaceutical products for preclinical and clinical studies andproduction of new products;
- serial production of chemical and pharmaceutical products and intermediate products for it;

- preparation of production instructions for equipment safety, sanitation and firefighting measures;

- development and implementation of disposal measures industrial waste, disposal and treatment of industrial effluents and emissions into the atmosphere;

- establishment of technical and economic standards, including the number of consumption of raw materials and supplies;

- design of industrial production.

Depending on the stages of product development, the degree of development of technology of its production or the purposes of the work, the regulations are divided into the following categories:

- technological-temporary regulations;

- technological industrial regulations.

According to the temporary technological regulations

laboratory and research-industrial works, production of experimental batches of medicines for preclinical and clinical researches are carried out. They are a document for the right to obtain a permit for medical use of drugs and approval of a temporary pharmacopoeial article.

A special body of state quality control of medicines is the State Inspectorate for Quality Control of Medicines of the Ministry of Health of Ukraine.

The State Inspectorate for Quality Control of Medicinal Products is headed by the Chief State Inspector of Ukraine- Deputy Minister of Health of Ukraine, who is appointed and dismissed by the President of Ukraine.

State Laboratory for Quality Control of Medicines at the State Inspectorate for Quality Control of Medicines:

- conducts regular trials of drugs sold in Ukraine;

- in accordance with the requirements of regulatory documentation also carries out preliminary control of the first 5 industrial series of drugs, the production of which is mastered by the manufacturer; the conclusion of the laboratory on the quality of the drug precedes its sale to the consumer.

The Ministry of Health of Ukraine issues an order authorizing the production and use of a new drug in medical practice, issues a registration certificate to the manufacturer, and also enters the drug in the State Register of Medicines. Order of the Ministry of Health of Ukraine registration certificate - documents required for the issuance of a permit (license) for the production and wholesale of a medicinal product, as well as for its production.

The industrial production of medicines is regulated by the relevant *regulatory and technical documentation,* approved in accordance with the established procedure.

Normative documentation is a document that establishes rules, general principles or characteristics relating to different activities or its results.

NTD on drugs, medicinal plant raw materials and medical devices are divided into the following categories:

1. Technological and technical regulations.
2. State Pharmacopoeia (DF).
3. Analytical regulatory documentation.
4. State standards.

5. Industry standards, Industry standard of Ukraine.

6. Technical conditions.

7. Guiding normative document, instructions, methodical instructions, etc.

8. Production technological instructions.

Technological regulations ***are*** a normative document, which sets out technological methods, technical means, norms and standards for the manufacture of a medicinal product.

On the basis of technological regulations serial production of chemical - pharmaceutical products is carried out.

The technological process of drug production consists of separate, successive stages of production.

Stage of production - a set of technological operations that lead to the production of an intermediate product (at the final stage - the finished product). For example, the process of obtaining tablets includes the following production stages: mixing, granulation, compression. Each stage, in turn, is a combination of a series of successive technological operations.

Technological scheme of production should clearly (graphically in the form of a block diagram) reflect the sequence of work in this production with their division by stages and operations of the technological process, indicating the main material and energy communications (raw materials, steam, water, waste, sewage waters, emissions into the atmosphere).

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

The technological operation is depicted separately with the indication of belonging to a certain stage. Each stage and operation must be characterized by a name and denote them by an index consisting of a symbol and a serial number. The numbering of stages is carried out in the order of their execution in the course of technological process, beginning with receipt and preparation of raw materials and finishing with shipment of finished goods.

In the technological scheme use the following designations of stages:

stages of ancillary work

stages of the main technological process

stages of processing of used waste

stages of waste disposal

stages of neutralization of technological and ventilation emissions into the atmosphere

stages of packaging, labeling 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 include this stage of the main technological process.

Auxiliary works carried out in separate equipment for several stages of one or more productions are allocated to independent stages of auxiliary works (for example, preparation of purified water, solutions of acids or alkalis with the set concentration for all shop).

If the processing of waste or their disposal is carried out as independent work, they may not be included in the technological scheme of production. In this case, on the technological scheme, the arrow indicates where the waste for processing (disposal).

Analytical regulatory documentation - pharmacopoeial articles, documents on methods of analysis, as well as other analytical documentation that allows you to control the quality of the drug., is an integral part of registration documents – a et of materials for a drug, a specialized assessment 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 drug.

A standard is a normative document that sets out for general and repeated use rules, requirements, general principles or characteristics relating to different activities or their results in order to achieve the optimal degree of order in this area.

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

Technological regulations are a normative document, which sets out technological methods, technical means, norms and standards for the manufacture of a medicinal product.

The technical regulation is a normative document in which for the concrete complex of the technological equipment the conditions providing release of intermediate products or medicines of a separate dosage form of the set quality are stated.

Material balance – the ratio between the amount of raw materials, intermediates and intermediate products (C_1) used in production, and the amount of actually obtained finished products (C_2), by-products (C_3), waste or waste (C_4) and losses (C-), ie the ratio of theoretically possible and practically obtained yield of finished products.If there are no by-products of production, the equation of material balance is simplified:

$C_1 = C_{2+} C_6$.

Material losses in the production of drugs are of different origins, so they are divided into several groups:

-*mechanical,* which occur mostly in the absence or insufficient mechanization of the movement of materials during processing (liquid spillage, spraying, shaking, fighting, etc.);

- *physico-chemical,* observed in the case of the technological process without taking into account the physico-chemical properties of medicinal substances (incomplete extraction of active substances from medicinal plant raw materials, loss of volatile solvents during filtration, essential oil during evaporation, etc.);

-*chemical,* which are possible due to non-compliance or incorrect choice of parameters of chemical reactions (synthesis). Material balance is of great practical importance because it determines the degree of perfection of the technological process. The more complete it is, the more studied is the technology of this drug. The smaller the balance of various losses, the more correct the production process. Conversely, the greater the balance of material losses, the less perfect is the technology of this drug.

2.2. Questions (test tasks, tasks, clinical situations) to check basic knowledge on the subject of the lesson:

1. What is the degree of grinding of solids?

2. How to classify grinding machines and types of wood values depending on the degree of grinding of the product?

3. How to classify grinding machines?

4. Name the types of grass cutters (depending on the device), explain the principle of their operation.

5. Why is it necessary to grind plant material without residue?

6. In what ways is the grinding of the material achieved on cutters, rolls, dismembler, disintegrator, ball mill?

7. Explain the operating conditions of the ball mill.

8. List the mills used for ultra-fine details. What is the principle of their work?

9. How is useful work spent on grinding? What is the work of grinding and useless as those of can be reduced?

10. Explain the principle of mechanical separation of the material and indicate the types of FTA used in the pharmaceutical industry.

11. What factors affect the performance of FTA?

12. What mehanizova no screens explain how they was at bots.

13. How are hydraulic and air separation of materials and what equipment is used for their implementation?

14. Specify the types of mixers used for powder materials. What is the principle of their work?

15. What are medical fees?

16. Specify the stages of assembly technology.

17. How to grind medicinal plant raw materials that are part of the fees?

18. Name the official fee for Gf XI. What is its composition?

18. What are medicinal teas?

19. How to classify powders from grinding?

20. What are the stages of the technology of complex powders in water conditions?

21.Indicate the features of powders used in the form of powders.

21. How to pack powders in the factory?

22. Name the complex powders produced by the pharmaceutical industry. What is their composition?

III. Formation of professional skills and abilities:

3.1. Content of the task of practical work:

1. Basic terms of the industrial technology of drugs

2. Organizational structure of the pharmaceutical enterprise, characteristics of its shops and branches

3. GMP requirements for the organization of production and quality control of medicinal products

4. Normative documentation in the production of GLZ

5. Basic provisions of the technological regulations for the production of medicinal products

Educational tasks for practical work:

Task No. 1 Determine the category of NTD:

A) technological document of current serial production of goods.

B) a technological document that completes scientific research in laboratory conditions during the development of a technology for the production of a new type of product or a new technological method of production for mass-produced products.

Task No. 2 Determine the NTD, approved for a limited period, which establishes quality requirements for medicinal products or medicinal plant raw materials.

Task No. 3 Determine the functions of the technological control department at pharmaceutical enterprises.

Task No. 4 Determine the NTD, approved for a limited period, which establishes quality requirements for medicinal products or medicinal plant raw materials.

Task No. 5 Compile the organizational structure of regulatory documentation at the pharmaceutical enterprise.

3.2. requirements for work results, including to registration; According to the progress of the practical lesson, complete the individual task in your workbook.

3.3. requirements for work results, including registration; According to the recommendations (instructions) for the tasks.

2.4. control materials for the final stage of the lesson: problems, assignments, tests, etc.:

1. Organizational structure of the enterprise and connection schemes of its divisions.
2. The structure of regulatory and technical documentation at pharmaceutical enterprises.
3. Basic principles of the drug registration system.
4. The main parts of the registration dossier.
5. Specifications for raw materials, intermediate products, and finished products.
6. Quality control of medicines at a pharmaceutical enterprise.
7. The essence of the material balance.
8. How does the material balance of the series differ from the material balance of the stage?
9. What documents reflect the content of the technological regulation?
10. What are the main indicators of raw materials reflected in the certificate?

№	Question	Answer options	Explanation of the correct wever
1	Grinding equipment is classified by the way of grinding. What kind of machines does a roller crusher relate to?	A. Crushing B. Cutting C. Abrasive D. Impact E. Impact-centrifugal	Crushing action (gladkovalkovaja Rolling mill crusher, roller crusher with threaded grooved surface).
2	Production of tablets requires stage-to- stage quality control. What devices are used to determine the particle size distribution (fraction) of granules?	A. Standard set of sieves B. Various vibrosieves C. Friabilators D. Laboratory identifiers E. Microscope	Asieve or screener is an essential part of every pharmaceutical production process, particularly as product quality and integrity are so important. The use of a sieve gets rid of oversized contamination to ensure that ingredients and finished products are quality assured during production and before use or despatch.

3	Various types of dryers can be used for granule dehumidification. Specify the type of ”CLI-30” dryer:	A. Fluidized bed dryer B. Freeze dryer C. Infrared dryer D. Silica gel dryer E. Forced air dryer	Fluidized bed dryer (also called fluid bed dryer) is a kind of equipment used extensively in the pharmaceutical industries to reduce the moisture content of pharmaceutical powder and granules.
4	Dosage precision during tablet making mainly depends on the following technological property of tablet mass:	A. Flowability B. Relative density C. Compression ratio D. Compressibility E. Lyophilic property	Pharmaceutical tablets are manufactured through a series of batch steps finishing with compression into a form using a tablet press.
5	A pharmaceutical company produces warious medicines. Name the dosage form consisting of separate hard dry particles disintegrated to varying degree:	A. Powders B. Tablets C. Suspensions D. Emulsions E. Dried extract	Typically, a powder can be compacted or loosened into a vastly larger range of bulk densities than can a coarser granular material. When deposited by sprinkling, a powder may be very light and fluffy. When vibrated or compressed it may become very dense and even lose its ability to flow. The bulk density of coarse sand, on the other hand, does not vary over an appreciable range.
6	Preparation of multicomponent powders with phenylsalicylate and camphor is accompanied by generation of some fluid. What is the reason for their incompatibility?	A. Eutectic alloy formation B. Adsorption C. Crystallization water exudation D. Hygroscopic components E. Gases separation	As a result of the interaction between fenilsalitsilatom and camphor th form a is ARE eutectic alloy, in the form of Gust second maloruhom second fluid as a difficult to crystallize.

IV. Summing up

List of recommended literature:

Main:

- Промислова технологія лікарських засобів: базовий підручник для студ. вищ. навч.закладу (фармац. ф-тів) / Є. В. Гладух, О. А. Рубан, І. В. Сайко [та ін.] – Х. : НФаУ : Оригінал, 2016. – 632 с. : іл.
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Practical lesson № 2

Topic: Production of solid dosage forms according to GMP requirements (tablets, granules, dragees).

Purpose: learn how to use the state pharmacopoeia of Ukraine, normative technical documentation and reference literature to find the necessary information for preparing tablets, granules, dragees; to know the classification and characteristics of excipients used for the production of solid dosage forms; calculate the amount of medicinal and auxiliary substances for the preparation of tablets, taking into account the consumption factor; learn how to grind and sift solid medicinal and herbal raw materials; to be able to choose the optimal tableting technology; to be able to analyze and obtain tablets by direct pressing and

pressing with preliminary granulation; to be able to classify and propose the application of film, coated and pressed coatings on tablets; to analyze the quality of coated tablets; perform basic technological operations when receiving tablets, granules, dragees.

Basic concepts: consumption factor, granulation, pressing, granules, dragees, tablets, pressing, mixing.

Equipment: tablets, granules, dragees, schemes.

Study time: 8 hours.

I. Organizational moment.

II. Control of reference knowledge

2.1. Requirements for students' theoretical readiness to perform practical classes (knowledge requirements, list of didactic units)

Requirements for theoretical knowledge:

CHARACTERISTICS OF TABLETS

Tablets as a medicinal form have become widespread throughout the world. Today, tablet preparations make up more than three quarters of the total volume of finished medicines. The positive qualities of the tablets provide:

'— the proper level of mechanization at the main stages and operations, which ensures high productivity, cleanliness and hygiene of the production of these medicinal forms;

— accuracy of dosage of medicinal substances included in the tablet;

— the portability of tablets, which ensures the convenience of dispensing, storing and transporting them;

— long-term integrity of medicinal substances in a compressed state;

— for substances that are not stable enough

— the possibility of applying protective coatings;

— the possibility of masking unpleasant organoleptic properties (taste, smell, color), which is achieved by applying coatings;

— a combination of medicinal properties incompatible in terms of physico-chemical properties in other medicinal forms;

— localization of the action of the medicinal substance in a certain part of the gastrointestinal tract by applying membranes soluble in an acidic or alkaline medium;

— prolonging the effect of medicinal substances (by applying certain coatings, using special technology and composition of core tablets);

— regulation of sequential absorption of several medicinal substances from a tablet at specified time intervals (multilayer tablets);

-- prevention of errors when dispensing and taking medicines due to the application of appropriate inscriptions on the surface of the tablets.

However, tablets have some disadvantages:

— the effect of medicines in tablets develops relatively slowly;

— the tablet cannot be administered during vomiting and unconsciousness;

— during storage, tablets may become cemented, while the decomposition time increases;

— the composition of tablets may include excipients that have no therapeutic value, and sometimes cause some side effects (for example, talc irritates the mucous membrane of the stomach);

— certain drugs (for example, sodium or potassium bromide) form highly concentrated solutions in the dissolution zone, which can cause severe irritation of the mucous membranes (this defect is eliminated by dissolving the tablets in the appropriate amount of water);

— not all patients, especially children, can easily swallow pills.

CLASSIFICATION OF TABLETS

According to the method of production in industrial conditions, two classes of tablets are distinguished: 1. Pressed, which are obtained by pressing medicinal powders on tablet machines with different productivity. This method is the main one. 2. Formed or triturated tablets, which are obtained by forming a tablet mass. Trituration tablets contain small doses of medicinal substances and fillers: their weight can be up to 0.05 g. Tablets are also classified according to the structural feature: 1. By composition: simple (one-component) and complex (multi-component). 2. According to the structure of the building: frame, single-layer and multi-layer (at least two layers), with or without coating. Frame (or skeleton) tablets have an insoluble frame, the cavities of which are filled with a medicinal substance. A separate tablet is like a sponge impregnated with medicine. When taken, its frame does not dissolve, keeping its geometric shape, and the medicinal substance diffuses into the gastrointestinal tract. Single-layer tablets consist of a pressed mixture of drugs and auxiliary substances and are uniform throughout the entire volume of the dosage form. Medicinal substances are arranged in layers in multilayer tablets. The use of chemically incompatible substances causes their minimal interaction. 3. Tablet coating is classified into: coated, film and pressed. The forms of tablets produced by the chemical and pharmaceutical industry are very diverse: cylinders, spheres, cubes, triangles, quadrilaterals, etc. The most common is a flat-cylindrical shape with a chamfer and a biconvex shape that is convenient for swallowing. In addition, punches and dies for the production of tablets are simpler and very easy to install on tablet machines. Most of the existing filling and packaging machines are also adapted to work with flat-cylindrical and biconvex tablets. The flat-cylindrical form of tablets without a chamfer is not recommended for production, because during packaging

and transportation, the sharp edges of the tablets are destroyed, as a result of which the marketable appearance is lost. The size of the tablets varies from 3 to 25 mm in diameter. Tablets with a diameter of more than 25 mm are called briquettes. The most common are tablets with a diameter of 4 to 12 mm. Tablets with a diameter of more than 9 mm have one or two lines drawn perpendicularly and allow dividing the tablet into two or four parts and thus varying the dosage of the medicinal substance.

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

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

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

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

Injectabulettae — tablets made aseptically, are used to obtain injection solutions of medicinal substances. Solublettae are tablets used to prepare solutions for various pharmaceutical purposes.

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

Oral tablets can be classified as:

— on tablets without a shell;

— coated tablets;

— "effervescent" tablets;

— soluble tablets

— tablets are dispersed

— enteric-dissolving tablets;

— tablets with modified release;

— tablets for use in the oral cavity.

TECHNOLOGICAL PROCESS OF TABLETS MANUFACTURE DIRECT DRINKING

The method of direct pressing has some advantages. It achieves high productivity, significantly reduce production cycle time by eliminating some operations and stages, avoid using multiple items of equipment, reduce production space, reduce enero- and expenditures of labor. Direct pressing makes it possible to obtain tablets of moisto-, thermolibious and incompatible substances. At present, less than 20 names of tablets are obtained by this method. This is due to the fact that most medicinal substances do not have the properties that provide direct compression.

For today, tabletting without granulation is carried out:

1) with the addition of auxiliary substances that are polishyellow technological properties of the material;

2) the forced feeding of the tableted material from the loading hopper of the tablet machine to the matrix;

3) with a pre-directed crystallization of compressed substances

The size, strength of particles, compressibility, fluidity, moisture content and other properties of substances are of great importance for direct pressing. Coarse-dispersed powders with equiaxed particle shape and low porosity are characterized by the highest fluidity, such as lactose, phenylsalicylate, hexamethylenetetramine and other similar preparations included in this group. Therefore, such preparations can be compressed without prior granulation. Medicinal powders with a particle size of 0.5-1.0 mm, a natural slope angle of less than 42°, a bulk mass of more than 330 kg/m3, and a porosity of less than 37% have proven themselves to be the best. They consist of a sufficient number of isodiametric particles with approximately the same fractional composition and, as a rule, do not contain a large number of small fractions, they are united by the ability to pour out evenly from the funnel under the influence of their own weight, that is, the ability of arbitrary volumetric dosing, and also quite good compressibility However, the vast majority of medicinal substances are not capable of arbitrary dosing due to the significant (more than 70%) content of small fractions and the unevenness of the particle surface, which causes strong interparticle friction. In these cases, auxiliaries are added that improve fluidity properties and belong to the class of sliding auxiliaries. Tablets of vitamins, alkaloids, glucosides, acetylsalicylic acid, bromocamphor, phenolphthalein, sulfadimesine, phenobarbital, ephedrine hydrochloride, ascorbic acid, sodium bicarbonate, calcium lactate, streptocid, phenacetin and others are obtained by this method. Preliminary directional crystallization is one of the most complex methods of obtaining medicinal substances suitable for direct pressing.

This method is carried out by two methods:

1) recrystallization of the finished product in the required mode;

2) selection of certain conditions of crystallization of the synthesized product. Applying these methods, a crystalline medicinal substance with crystals of a fairly isodiametric (equiaxial) structure is obtained, which freely pours out of the funnel and, as a result, is easily amenable to arbitrary volumetric dosing, and this is an indispensable condition for direct pressing. This method is used to obtain tablets of acetylsalicylic and ascorbic acids.

To increase the compressibility of medicinal substances during direct pressing, dry adhesive substances are introduced into the composition of the powder mixture - most often microcrystalline cellulose (MCC) or polyethylene oxide (PEO). Due to its ability to absorb water and hydrate individual layers of tablets, MCC has a beneficial effect on the process of releasing medicinal substances. It is possible to make strong tablets from MCC, which, however, do not always disintegrate well- To improve the disintegration of MCC tablets, it

is recommended to add ultraamylopectin. For direct pressing, the use of modified starches is indicated. The latter enter into a chemical interaction with medicinal substances, significantly affecting their release and biological activity. Milk sugar is often used as a means of improving the flowability of powders, as well as granulated calcium sulfate, which has good fluidity and ensures the production of tablets with sufficient mechanical strength. Cyclodextrin is also used, which helps increase the mechanical strength of tablets and their disintegration. In direct tableting, maltose is recommended as a substance that ensures a uniform rate of falling asleep and has a slight hygroscopicity. The lactose mixture is also used.

The technology of making tablets consists in the fact that medicinal products are carefully mixed with the necessary amount of excipients and pressed on tablet machines. Disadvantages of this method are the possibility of delamination of the tablet mass, dosage changes during pressing with a small amount of active substances, and the use of high pressure. Some of these defects are reduced to a minimum during tableting by forced feeding of pressed substances into the matrix. Some constructive replacements of machine parts are carried out, i.e. vibration of the shoe, rotation of the matrix to a certain angle during the pressing process, installation of star-shaped mixers of various designs in the loading hopper, suction of material into the matrix hole using a vacuum that is created by itself, or a special combination with a vacuum line But, despite the successes achieved in the field of direct pressing, in the production of tablets, this method is used for a limited number of medicinal substances. Granulation In case of unsatisfactory technological properties of powdered masses, namely, poor compressibility and flowability, granulation must be carried out in advance to ensure the required quality of the tablets.

Granulation is a directed agglomeration of particles, that is, it is a process of transformation of a powdery material into grains of a certain size, which is necessary for:

1) improving the flowability of the tablet mixture,
2) improving compressibility,
3) preventing delamination,
4) ensuring dosing accuracy,
5) reducing dustiness of workers premises

The following granulation methods are used in the chemical and pharmaceutical industry:

- Granulation by pressing, or wet granulation.
- Dry granulation or briquetting.
- Granulation is structural.
- Granulation is mixed.

Pressing granulation, or wet granulation, includes the following stages:

1) mixing medicinal powders with auxiliary substances;

2) moistening the mixture of powders with solutions of gluing and binding substances to obtain a mass that forms a lump, but does not stick to the fingers;

3) obtaining wet granules, i.e. wiping the wet mass through perforated plates; drying of wet granules;

4) obtaining dry granules, for which the dry mass is rubbed through perforated plates to break up lumps and obtain homogeneous granules;

5) powdering of dry granules.

Wet granulation is currently the main type of granulation in the production of tablets, but it has a number of disadvantages: long-term effect of moisture on medicinal and auxiliary substances; deterioration of the ability to disintegrate (dissolution rate) of tablets;
- duration and complexity of the process;
- the need to use special equipment;
- energy intensity of the process.

2.2. Questions (test tasks, tasks, clinical situations) to check basic knowledge on the subject of the lesson:

1. Positive and negative aspects of tablets as a dosage form.
2. Influence of physico-chemical and technological properties of medicinal and auxiliary substances on the tableting process.
3. The principle of operation of tablet machines, granulators, dryers.
4. Characteristics of tablets as a dosage form. Types and groups of tablets. 5
. The essence, positive and negative aspects of direct pressing.
6. The main areas of production of tablets by direct pressing.
7. Stages of the technological process of obtaining tablets by direct pressing.
8. Purposes and main types of granulation in the production of tablets.
9. Wet granulation. Positive and negative aspects of this process.
10. Methods of structural granulation.
11. Cases of use of dry granulation (granulation by grinding).
12. Groups of auxiliary substances in the production of tablets.
13. Stages and equipment for the production of pre-granulated tablets.

Situational tasks.1) Compile the material balance at the stages of crushing and sieving 50 kg of boric acid using a ball mill. At the grinding stage, 2 kg of losses were obtained, and during sieving, 44 kg of pure fraction, 2 kg of waste and 1 kg of byproducts were obtained. Find output, technological losses, cost norms at each stage and general.

2) What is the degree of grinding if D = 10 mm, d = 0.12 mm?

3) Calculate the amount of starch for the production of 1,000 tablets of 0.5 g of norsulfasol with an average weight of 0.575, if the amount of talc in the finished tablets should be no more than 2%. 5. Calculate the number of liters of alcohol 96%, which must be taken to moisten 7.5 kg of a mixture of riboflavin with ascorbic acid, if the amount of moisturizer should be 40% of the weight of the drug.

4). At what number of revolutions of a drum with a diameter of 0.49 m will mixing of powders take place in a ball mill?
5). What indicator of tablet quality is affected by the homogeneity of the pressed mass and how is it ensured? Justify the answer.
6). The tablet workshop of the enterprise produces tablets covered with a shell that dissolves in the intestines. The technologist-operator uses ethyl cellulose and acetylphthalyl cellulose as auxiliary substances for this coating. Evaluate the actions of the technologist-operator. Justify the answer.

III. Formation of professional skills and abilities:

3.1. Content of the task of practical work:

1. Device and principle of operation of grinding machines.
2. Devices for classification of crushed material.
3. Devices for mixing solid materials.
4. Principle of operation of devices for granulation.
5. Device and principle of operation of tablet machines.
6. Equipment for coating tablets.

Educational tasks for practical work:

Task No. 1 Grind 250 g of sugar in a ball mill and make a material balance for this stage, determine the percentage of output, the percentage of technological costs and the expenditure ratio. Conduct a sieve analysis of crushed sugar and determine the fractional composition (2, 1, 0.5, 0.25 mm) in grams and percentages.

Amount of crushed material, g	Particle sizes, %				
	+2мм	-2мм +1мм	-1мм +0,5мм	-0,5мм +0,25мм	-0,25мм

Sift the powdered sugar. Make a material balance taking into account the waste at this stage. Calculate the yield percentage, costs and the cost factor.

Task No. 2 Determine the productivity of a ball mill that grinds 15 kg of raw materials in 20 minutes.

Task No. 3 Prepare sodium chloride tablets of 0.9 20 pieces. List the indicators that evaluate the quality of finished products. Draw up a material balance for finished products in the form of an equation and a table, calculate output, loss, expenditure ratio.

Substances are spent	Quantity, g	The final product is received	Quantity, g
sodium chloride		Tablets of sodium chloride 0.9	
		Costs	

In total		In total	

Theoretical questions

1. Why is it necessary to grind plant material without residue?
2. What factors affect the performance of sieves?
3. What are tablets as a dosage form?
4. How can the technological properties of powders be improved and direct pressing be carried out?
5. What groups are excipients in the production of tablets divided into?
6. Explain the purpose of binders. In what cases are dry binders used?
7. Give examples of auxiliary substances that cause the destruction of tablets due to their swelling.
8. How is wet granulation performed? Disadvantages of this method.
9. Methods of structural granulation. In what cases is structural granulation performed?

3.2. requirements for work results, including to registration; According to the progress of the practical lesson, complete the individual task in your workbook.

3.3. requirements for work results, including registration; According to the recommendations (instructions) for the tasks.

2.4. control materials for the final stage of the lesson: problems, assignments, tests, etc.:

№	Question	Answer options	Explanation of the correct wever
1	A tablet shop produces trituration tablets. What quality indicators **ARE NOT** relevant for these tablets?	* Abrasion, resistance to crushing Abrasion, resistance to crushing B. Disintegration and dissolution C. Homogeneity of dosage D. Homogeneity of content E. Microbiological purity	Unlike pressed tablets, trituration tablets are not subject to pressure; the adhesion of the particles of these tablets is carried out as a result of autogeny when dried, so the tablets have low strength.
2	A pharmaceutical factory produces tablets of sodium chloride. What is the method of their poduction?	A. * Direct compression without additional substances B. Moulding C. Direct compression with the addition of excipients D. Wet granulation	Substances belonging to the cubic system are compressed into tablets directly, that is, by direct compression, without granulation and excipients (sodium chloride,

		prior to compression E. Dry granulation prior to compression	potassium bromide, ammonium bromide) .
3	A tablet shop produces trituration tablets. What quality indicators **ARE NOT** relevant for these tablets?	A. Abrasion, resistance to crushing B. Disintegration and dissolution C. Homogeneity of dosage D. Homogeneity of content E. Microbiological purity	Unlike pressed tablets, trituration tablets are not subject to pressure; the adhesion of the particles of these tablets is carried out as a result of autogeny when dried, so the tablets have low strength.
4	A tablet production unit produces presscoated tablets. What equipment is used for this purpose?	A. * Double pressing tabletting machine B. Dragee pan C. Marmerizer D. Eccentric tabletting machine E. Triturating machine	To obtain extruded coatings, a Drikot (or RTM-24D) dual-press tablet machine is used, which is a dual unit consisting of two rotors. On the 1st rotor receive tablets kernels, which with the help of a special conveyor device are transferred to the 2nd rotor, where they are directly applied to the pressed dry coating.
5	A pharmaceutical enterprise produces nitroglycerine tablets. What is the method of their production?	A. * Extrusion B. Direct pressing, without adjuvants C. Direct pressing with addition of adjuvants D. Pressing with preliminary wet granulation E. Pressing with preliminary dry granulation	Extrusion method (physical method of microencapsulation). When microencapsulation by extrusion, a thin viscous film of film-forming material is formed on the surface with small diameter holes through which the encapsulating substance is forced through. The thus formed shell is further stabilized by cooling or polymerization of its monomers.

6	While filling hard gelatin capsules such glidants as 0,1% - 0,3% aerosil or magnesium stearate along with 0,5% - 1% talc are often added to the filling agent in order to improve the following properties:	A. * Flowability B. Homogeneity C. Regulation of moisture content D. Homogeneity of mixing E. Ability to contact molding	If you improve the bulk properties of the filler is added sliding auxiliaries. For example, the introduction of 0.1 - 0.3% aerosil or magnesium stearate from 0.5 - 1.0% talc may be sufficient.
7	What tablet coating protects stomach from harmful influence of active ingredients?	A. * Intestinally absorbed B. Water-soluble C. Gastrically absorbed D. Fat-soluble Non-soluble	Coating is a process by which an essentially dry, outer layer of coating material is applied to the surface of a dosage form in order to confer specific benefits over uncoated variety. It involves application of a sugar or polymeric coat on the tablet. The advantages of tablet coating are taste masking, odor masking, physical and chemical protection, protects the drug in the stomach, and to control its release profile.
8	A pharmaceutical company produces tablets. Tabletting by means of direct compression requires:	A. * No prior granulation B. Prior granulation C. Formation of masses D. Prior homogenization E. Application of hydraulic press	Today, the term direct compression (or direct compaction) is used to define the process by which tablets are compressed directly from powdered active drug substance and suitable excipients into a firm compact without employing the process of granulation.
9	What factors affect tablet disintegration?	A. * Amount and nature of disintegrating agents B. Poor flowability	Bioavailability of a drug depends in absorption of the drug, which is affected by solubility of the drug in the gastrointestinal fluid.

		C. High specific gravity of powders D. Tablet powder contains lamellar crystals E. Heterogeneity of granulated material	The rate of drug dissolution is greatly influenced by disintegration.
10	Among various types of tablet external layers there are enterosoluble coatings. Where in the body are they dissolved?	A. * Intestine B. Stomach C. Oral cavity D. Rectum E. Esophagus	An enteric coating is a polymer barrier applied on oral medication that prevents its dissolution or disintegration in the gastric environment. they will not dissolve in the gastric acids of the stomach (pH ~3), but they will in the alkaline (pH 7–9) environment present in the small intestine.

IV. Summing up

List of recommended literature:

Main:

- Промислова технологія лікарських засобів: базовий підручник для студ. вищ. навч.закладу (фармац. ф-тів) / Є. В. Гладух, О. А. Рубан, І. В. Сайко [та ін.] – Х. : НФаУ : Оригінал, 2016. – 632 с. : іл.
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- Навчальний посібник для самостійної підготовки студентів фармацевтичного факультету до ліцензійного інтегрованого іспиту «Крок 2. Фармація» / О.А. Рубан, В.Д. Рибачук, Л.М. Хохлова, Д.С. Пуляєв – Х.: НФаУ, 2016. – 63 с.
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- Державна Фармакопея України / Державне підприємство «Український науковий фармакопейний центр якості лікарських засобів» – 2-е вид. – Харків: Державне підприємство «Український науковий фармакопейний центр якості лікарських засобів», 2015. – Т. 1. – 1128 с.
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Electronic information resources

1. Department of pharmaceutical chemistry and drug technology of ONMedU – website of the Department of pharmaceutical chemistry and drug technology of ONMedU
2. Scientific library of ONMedU (odmu.edu.ua) - Scientific library of ONMedU
3. www.moz.gov.ua – official website of the Ministry of Health of Ukraine
4. Odessa National Medical University (onmedu.edu.ua) – ONMedU official website
5. State Register of Medicinal Products of Ukraine. - [Electronic resource]. - Access mode: http://www.drlz.com.ua/ − as of 10.01.2017.

Practical lesson № 3

Topic: Production of solid dosage forms according to GMP requirements (capsules in gelatin shell).

Purpose: learn how to use the state pharmacopoeia, normative technical documentation and reference literature to find the necessary information for preparing capsules in a gelatin shell; to study the assortment and properties of auxiliary substances for the production of capsules in a gelatin shell; to study methods of capsule production; to be able to choose the optimal technology for their production; know the methods of obtaining hard and soft gelatin capsules, types of machines, their structure and principle of operation; carry out the compilation of a block diagram of the production of capsules, the main technological operations during their receipt, the selection of equipment at each stage and the determination of quality indicators.

Basic concepts: capsules in a gelatin shell, hard gelatin capsules, soft gelatin capsules.

Equipment: capsules in a gelatin shell, schemes.

Study time: 8 hours.

I. Organizational moment.

II. Control of reference knowledge

2.1. Requirements for students' theoretical readiness to perform practical classes (knowledge requirements, list of didactic units)

Requirements for theoretical knowledge:

Capsules are solid medicinal products with a hard or soft shell of various shapes and capacities, containing one or more active substances. The shell is prepared from gelatin and auxiliary substances. The consistency of the shell can be ensured by introducing into the gelatin solution substances such as glycerin or sorbitol, surfactants, antimicrobial preservatives, sweeteners, dyes, flavorings approved for medical use. Capsules are intended for oral, less often rectal and vaginal administration. Depending on the localization of action, oral capsules are divided into: - sublingual (validol, nitroglycerin); - stomach soluble (vitamins E, A); - enteric-soluble, etc. According to the technological principle, capsules are classified into: - hard capsules; - soft capsules; - enteric capsules; - capsules with modified release of medicinal substances. A separate group consists of capsules with adjustable release - retard capsules. In recent years, work has been carried out to create soft, elastic capsules for chewing. Soft capsules can have a spherical, ovoid, oblong or cylindrical shape with hemispherical ends, with or without a seam. Capsules can have a capacity of 0.1 to 1.5 ml. They encapsulate viscous liquids, oil solutions, pasty medicinal substances that do not interact with the mold-forming substance - gelatin. Production of soft capsules in factory conditions is carried out by two methods: drip and pressing (rotary-matrix). Hard capsules are intended for dosing loose powdery, granular and microencapsulated substances. They have a cylindrical shape with hemispherical ends and consist of two parts - the body and the lid, which should fit freely into each other without creating gaps. To provide a "lock", they can have special grooves or protrusions. Depending on the capacity, hard capsules are made in eight sizes - from 000 (the largest size) to 5 (the smallest size).

The production of capsules is a complex technological process and consists of the following main stages: - preparation of gelatin mass; - production (forming) of capsule shells; - filling and sealing of capsules; - their processing; - quality control of finished products; - packaging, packaging and labeling In the process of producing capsules using different methods, some stages can be combined (see Appendix 7-8). Today, a number of foreign companies produce automatic lines for the production of hard gelatin capsules: "Hofliger und Karg" (Germany); 'Elanco', 'Parke Davis', 'Colton' (USA); "Zanazi" (Italy) and others. These machines differ little from each other (the number of pins, the shape of the frame holders, the productivity, which varies from 36 to 72 thousand capsules per hour). Such equipment necessarily consists of: an immersion bath in a thermostatic casing, an immersion mechanism with pins; drying chamber, automatic trimming unit, removing and filling capsules. Empty hard capsules are filled with medicinal substances on special automatic filling machines. We will consider the principle of operation of machines for

filling capsules using the example of the machine of the "Zanazi" company. This machine allows you to dose powders of any type; up to three dosing devices can be installed here. Instead of dosing devices for powder or granules, a dosing device for liquid composition can be installed. The maximum productivity of the machine is 70,000 capsules per hour. The main parts of the machine for filling solid capsules: the frame, which houses the electric wire, the compressor, the vacuum pump, the control panel. On the bed there is an assembly for storing capsules and a sorting device, a rotating table with lid holders; a filler hopper with a feeding and dosing device; a device for removing capsules with defects; device for closing capsules; a device for pushing out filled capsules and a cleaning device.

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2.2. Questions (test tasks, tasks, clinical situations) to check basic knowledge on the subject of the lesson:

1. Methods of obtaining and properties of gelatin as a form-forming substance.
2. What types of medical capsules are used in medical practice?
3. What is the difference between the mode of production of hard and soft gelatin capsules?
4. What preservatives are most often included in the gelatin mass for the production of capsules?
5. The essence of obtaining capsules by the pressing method, by the drop method, the principles of their implementation?
6. General characteristics of microcapsules, the main purpose of the microencapsulation process, the main methods of obtaining microcapsules.
7. Groups of auxiliary substances in the preparation of microcapsules.

III. Formation of professional skills and abilities:

3.1. Content of the task of practical work:

1. Equipment for obtaining gelatin shells - forming capsules.

2. Devices for microencapsulation. Educational tasks for practical work:

Task No. 1 Prepare the gelatin mass to obtain soft capsules (without the gelatin swelling process). Cooking technology. The calculated volume of purified water is added to the closed container of the laboratory unit, equipped with a water jacket, automatic temperature controller and paddle stirrer, and heated to 70-75°C, preservatives and plasticizers are successively dissolved in the heated water, after which gelatin is loaded with the stirrer turned on. Stir until it is completely dissolved within 20-30 minutes. After turning off the stirrer and heating, the gelatin mass is left in the reactor for 1 hour with a vacuum connected to remove air bubbles from the mass. The prepared mass is transferred for stabilization to a thermostatic container with a controlled temperature and kept at a temperature of 45-50°C for 1.5-2 hours. Before the start of encapsulation, the value of viscosity is controlled, which should be within (650-700) 103 Pa·s.

Task No. 2 Form soft gelatin capsules by immersion method (under laboratory conditions). Formation of capsules. Metal forms are wiped with a gauze pad soaked in peach oil, and cooled at a temperature of 3-5º C for 30 minutes. The cooled forms are slowly immersed in the gelatin mass for 1-2 seconds. To evenly distribute the mass, the forms are slowly raised, simultaneously turning them in a horizontal position around their axis. When the film thickens, the form is placed in the refrigerator for gelatinization at a temperature of 5ºC for 6-7 minutes. The cooled frame is taken out of the refrigerator, the gelatin shells are removed and they are placed on a plastic plate with nests. Properly prepared capsules should be transparent and free of air bubbles and mechanical impurities.

Task No. 3 Fill soft gelatin capsules with castor oil and seal. Filling capsules. Filling with castor oil is carried out using a syringe, which is inserted into the opening of the capsule without wetting the edges with oil. Sealing capsules. Capsules are sealed by sealing with an electric soldering iron heated to a temperature of 55-56ºC. The molten mass hermetically closes the neck of the capsule. Sealing can be carried out with a drop of molten gelatin mass, which is applied to the neck of the capsule with the help of a metal loop. Capsules are dried at a temperature of 23-26ºC and washed with isopropyl alcohol, then dried again.

Task No. 4 Carry out quality control of capsules according to the following indicators: description (appearance), uniformity of mass; uniformity of capsule contents, determination of disintegration.

3.2. requirements for work results, including to registration; According to the progress of the practical lesson, complete the individual task in your workbook.

3.3. requirements for work results, including registration; According to the recommendations (instructions) for the tasks.

2.4. control materials for the final stage of the lesson: problems, assignments, tests, etc.:

1. In what ways are capsules obtained and can all of them be used to obtain soft gelatin capsules, hard capsules with lids?
2. What properties of the capsules are affected by a violation of the temperature regime of mass dissolution?
3. What is the scheme of obtaining capsules by the immersion method and for what purpose does the gelatin mass stand for a long time?
4. For what purpose and which auxiliary substances are used in the preparation of enteric capsules?
5. Is it possible to release poisonous and potent substances in capsules?
6. How is the thickness of the shells of hard and soft gelatin capsules and the accuracy of the dosage of the medicinal substance checked?
7. Physical methods of microencapsulation.
8. Physico-chemical methods of microencapsulation.
9. Obtaining microcapsules by chemical methods. 10. Characteristics of microcapsule shells and their varieties.
11. Shape, size and structure of microcapsules.

№	Question	Answer options	Explanation of the correct wever
1	To improve the structural and mechanical properties of capsule shells, to ensure their proper elasticity and reduce their brittleness, the following substances are introduced into the gelatin mass:	**A.** * Plasticizers **B.** Thickeners **C.** Stabilizers **D.** Pigments **E.** Preservatives	In order to improve the structural and mechanical properties and provide adequate elasticity, increase the strength and reduce the fragility of the shells in the composition of the gelatin mass is introduced plasticizers. Many substances are used for this purpose, among them the most popular are glycerin, sorbitol, PEO-400, polyethylene glycol,

			polypropylene, hexanthropol, and others.
2	Microcapsules are made by coating solid particles of the substance being encapsulated with a shell consisting of metallic silver, zinc, etc. Name this method of making microcapsules:	**A.** * Galvanization **B.** Pelleting **C.** Slurrying of the nuclei **D.** Coacervation **E.** Polymerization	Vacuum deposition or galvanization is the application of a shell of metallic aluminum, silver, gold, zinc, cadmium, chromium, nickel and the like to the solid particles of the encapsulated substance.

IV. Summing up

List of recommended literature:

Main:

- Промислова технологія лікарських засобів: базовий підручник для студ. вищ. навч.закладу (фармац. ф-тів) / Є. В. Гладух, О. А. Рубан, І. В. Сайко [та ін.] – Х. : НФаУ : Оригінал, 2016. – 632 с. : іл.
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Practical lesson № 4

Topic: Production of sterile drugs according to GMP requirements (dosage forms for injection in ampoules, vials, infusion solutions in containers, etc.).

Purpose: learn to use the state pharmacopoeia, regulatory and technical documentation and reference literature to find the necessary information for the preparation of sterile medicinal products; to study the assortment and properties of auxiliary substances for the production of injections, infusions or implantations in the human body, as well as ophthalmic dosage forms; to study methods of production of primary packaging for sterile products; learn the methods of obtaining water for injections in industrial conditions; to be able to choose the optimal technology for the production of parenteral solutions; to know the methods of obtaining ophthalmic dosage forms; types of machines, their structure and principle of operation; to draw up a block diagram of the production of sterile medicinal products, the main technological operations during their receipt, the selection of equipment at each stage and the determination of quality indicators.

Basic concepts: sterile drugs, infusions, parenteral solutions.

Equipment: sterile drugs, infusions, parenteral solutions.

Study time: 8 hours.

I. Organizational moment.

II. Control of reference knowledge

2.1. Requirements for students' theoretical readiness to perform practical classes (knowledge requirements, list of didactic units)

Requirements for theoretical knowledge:

Medicinal products for parenteral use are sterile preparations intended for administration by injection, infusion or implantation into the human or animal body. These include aqueous and non-aqueous solutions, emulsions, suspensions, powders and tablets for obtaining solutions and implantation, lyophilized drugs that are administered parenterally (subcutaneously, intramuscularly, intravenously, retrobulbarly or subconjunctivally, in various cavities, etc.). Today, parenteral drugs account for almost 30% of all ready-made medicinal products produced by the domestic pharmaceutical industry. Injectable dosage forms occupy a prominent place in the nomenclature of medicinal products. Injectable drugs account for 10% to 15% of articles in various pharmacopoeias of the world. Parenteral medicinal products are a relatively young medicinal form. The parenteral route of drug administration has a number of advantages over other methods:

— quick action and complete bioavailability of the medicinal substance;

— accuracy and convenience of dosing;

— the possibility of administering a medicinal substance to a patient who is in an unconscious state, or when the medicine cannot be administered orally;

— lack of influence of gastrointestinal tract secretions and liver enzymes, which occurs when drugs are taken internally;

— the possibility of creating large stocks of sterile drugs, which facilitates and accelerates their release from pharmacies.

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

— when liquids are injected through the damaged skin, pathogenic microorganisms can easily enter the blood;

— together with the drug for injections, air may be introduced into the body, which will cause vascular embolism or heart failure;

— even a small amount of extraneous impurities can have a negative effect on the patient's body;

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

— administration of sterile drugs should be carried out only by qualified specialists.

Introduction of Parenteral medicinal products is carried out by means of injections (injection of a small volume), infusions (infusion of more than 100 ml at the same time by drop or jet) or implantations with the help of special devices with a violation of the integrity of the skin or mucous membranes. This application is quite painful, so recently, less painful methods of needle-free introduction of injection solutions have been used in the form of the thinnest (about 0.1-0.12 mm in diameter) jet under high pressure, which is ejected from the hole of a special injector at a speed of 300 m /s and penetrates through the skin to a depth of 3 cm. For this, manual injectors such as "Bee", "Hynospray", "Jetinjection" are used. According to the SFU, medicinal products for parenteral use are classified according to the following groups:

1) injectable drugs;

2) intravenous infusion drugs;

3) concentrates for injection or intravenous infusion medicinal products;

4) powders for injection or intravenous infusion drugs;

5) implants.

The requirements of this article do not apply to preparations made from human blood, immunological and radiopharmaceutical preparations, implantable prostheses. Injectable drugs are sterile solutions, emulsions or suspensions. Solutions for injections should be clear and free of particles. Emulsions for injections should not show signs of delamination. In suspensions for injections, a sediment may be observed, but it should disperse instantly when shaken, forming a suspension. The resulting suspension should be stable enough to provide the required dose when administered. Intravenous infusion drugs are sterile aqueous solutions or emulsions (water as a dispersion medium) that must be free of pyrogens and usually isotonic with blood. They are intended for use in large doses, so they should not contain any antimicrobial preservatives. Concentrates for injection or intravenous infusion medicinal products are sterile solutions intended for injections or infusions after dilution. Before use, the concentrates are diluted to the indicated volume with the appropriate liquid. After dilution, the resulting solution must meet the requirements for injection or infusion drugs. Powders for injection or intravenous infusion of drugs are solid sterile substances placed in a sterile container. When shaken with the indicated volume of the appropriate sterile liquid, they should quickly form either a transparent, particle-free solution or a homogeneous suspension. After dissolution or suspension, they must meet the requirements set forth for injection or infusion medicinal products. Implants are sterile solid medicinal products of a size and shape suitable for parenteral implantation and active substances that are released over a long period. They should be packed in individual sterile containers Parenteral use of drugs involves a violation of the skin, which is associated with possible infection by pathogenic microorganisms and the introduction of mechanical inclusions. Therefore, sterile production, in comparison with other branches of industry, has specific features dictated by the requirements for injectable dosage forms. The main ones are the absence of mechanical impurities, sterility, stability, pyrogenicity, etc., and for some drugs, isotonicity, osmolality or osmolarity, isoionicity, isohydricity, viscosity, which is indicated in the relevant regulatory and technical documentation.

Solutions for injections are made in special facilities in A or C cleanliness class premises in compliance with all rules asepsis Preparation of aqueous or non-viscous solutions for injections is carried out by the mass-volume method, using hermetically sealed reactors equipped with a shell and a stirring device. In cases where the density of the solvent is significantly different from the density of water, mass is used a method in which both the medicinal substance and the solvent are taken for by mass Dissolution of slowly or poorly soluble medicinal substances is carried out by heating and stirring. The stage of preparation

of the solution includes the following operations: dissolution, isotonization, stabilization, introduction of preservatives, filtering. Depending on the properties of medicinal substances, some of the operations may be excluded, for example, isotonization, stabilization, administration of preservatives. Among injection solutions, a special group is isotonic, which means solutions with an osmotic pressure equal to the osmotic pressure of body fluids (blood plasma, lymph, cerebrospinal fluid, etc.).

Isotonic concentrations of medicinal substances in solutions can be calculated by the following methods: — a method based on Van't Hoff's law; — cryoscopic method based on Raoult's law; — the method of equivalents of medicinal substances according to sodium chloride. Abroad, they also use a graphical method of calculating isotonic concentrations, which allow to quickly, but with some approximation, determine the amount of sodium chloride necessary for isotonizing a solution of a medicinal substance based on the developed nomograms.

During the manufacture and storage of some medicinal products, a change in their properties is often observed, which occurs with different speed and degree of manifestation. This is due to a decrease in the content of medicinal substances or a decrease in their pharmacological activity, a change in the properties of medicinal forms, etc. Such changes affect the shelf life (storage) of drugs, which can range from a few hours (antibiotic solutions) or days (enzyme solutions) to several years. Today, special attention is paid to the task of improving the stability of medicinal products. Processes occurring in drugs can be conditionally classified into physical, chemical and biological. The convention lies in their relationship: chemical transformations can cause changes in physical properties, while physical changes cause unwanted chemical processes. Biological processes are accompanied by both chemical and physical transformations. The physical processes that occur mainly during storage include agglomeration of particles of the dispersed phase, delamination, change in consistency, evaporation, sublimation, etc. Chemical processes often take place during the preparation of the drug, especially during thermal sterilization, and are accompanied by various chemical reactions - hydrolysis, saponification, oxidation-reduction processes, photochemical and enzymatic transformations, polymerization and isomerization, etc. are less often observed. 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.

2.2. Questions (test tasks, tasks, clinical situations) to check basic knowledge on the subject of the lesson:

1. What are the conditions for the manufacture of sterile dosage forms? List the cleanliness classes of industrial premises.
2. What are the requirements for starting medicinal substances for injections?

3. List the proposed requirements for water for injection. List the ways to get it. What are the ways to improve its quality?
4. List the requirements proposed for ampoule glass. Name its composition and properties.
5. Concept of osmolality and osmolarity.
6. Characteristics of injection solutions, their use.
7. Modern classification and requirements for infusion solutions.
8. Features of factory production of ophthalmic dosage forms.

III. Formation of professional skills and abilities:

3.1. Content of the task of practical work:

1. Equipment for the manufacture, calibration, washing and drying of glass wire.

2. Equipment for manufacturing ampoules and preparing them for filling.

3. Equipment for water treatment.

4. Equipment for filtering injection solutions, filling ampoules, sealing and sterilization.
Educational tasks for practical work:
Task No. 1 Prepare a 10% glucose solution with the appropriate composition: Anhydrous glucose 100.0 g 0.1 M hydrochloric acid solution to pH 3.0-4.0 Sodium chloride 0.26 g Water for injections up to 1 l The technological process begins with washing and drying bottles of neutral glass. Internal washing is carried out with the help of laboratory vacuum or syringe washers. Bottles are dried and sterilized in a drying cabinet at a temperature of 180-200°C. According to the working instructions, the necessary amount of glucose (taking into account its moisture content) grade "for injections" is weighed and dissolved in a sterile measuring flask with a capacity of 50 ml in half the amount of water for injections. The calculated amount of sterile Weibel stabilizer solution is added to the solution. After dissolving glucose, the solution is brought up to the mark with water for injections and mixed. The resulting solution is adjusted for glucose content and pH, filtered using a sterile glass filter with a maximum pore size of 0.3 μm, and vials are filled using the syringe method, taking into account the filling norms. Vials are closed with rubber stoppers and rolled with aluminum caps, after which they are subjected to sterilization with flowing steam at a temperature of 100°C for 30 minutes or steam under pressure at a temperature of 120°C for 8 minutes. The quality control of the solution in bottles is carried out according to the following technological parameters: determination of tightness, volume, control for the presence of mechanical inclusions, determination of pH and transparency of the solution.
Task No. 2 Specify the composition of Weibel's reagent.
Task No. 3 To describe methods of detecting pyrogenic substances and methods of releasing solutions from them.

Tasks for self-control 1. Using literary sources, fill in the table: indicate groups of infusion solutions depending on the functions performed when administered to the body, purpose and examples of medicinal substances.

Group of infusion solutions	**Group of infusion solutions**	**Examples of medicinal substances**

2. Draw up a working prescription for the preparation of 120 vials of 200 ml of solution for infusions "Reopoliglyukin" according to the appropriate composition: dextrin 10 g / l, sodium chloride 9 g / l; water for injections up to 1000 ml, if the expenditure ratio is equal to 1.046. 3. Prepared 38 liters of 18% magnesium sulfate solution. How much magnesium sulfate should be added to obtain a 20% solution? 4. Prepared 150 ml of caffeine sodium benzoate solution. The analysis showed that the solution contains 15% of the drug. How much water should be added to obtain a 10% solution? Situational tasks. 1. Control of mechanical inclusions is carried out by inspecting the vials against a black and white

background under 60 W lighting. For a more objective assessment of the quality of the solution with this parameter, the technologist used other methods. Evaluate his actions.

3.2. requirements for work results, including to registration; According to the progress of the practical lesson, complete the individual task in your workbook.
3.3. requirements for work results, including registration; According to the recommendations (instructions) for the tasks.
2.4. control materials for the final stage of the lesson: problems, assignments, tests, etc.:
1. What chemical transformations occur on the surface of ampoule glass during long-term contact with neutral, alkaline, and cystic solutions of the reaction medium? 2. What indicators are provided for assessing the quality of ampoule glass? 3. How is pyrogenicity of water and solutions for injection checked? 4. Pyrogenic substances. Properties and methods of their detection. 5. Methods of releasing solutions from pyrogenic substances. 6. What measures are taken to stabilize solutions of easily hydrolyzable medicinal substances? 7. What are the features of filtering injection solutions? List the proposed requirements for filter materials. 8. What methods of sterilization are used in the technology of injection solutions? 9. What is the essence of preparing vials and capping material for filling? 10. What packaging is used for ophthalmic dosage forms? Advantages and disadvantages. 11. Assortment of domestic and foreign infusion drugs. 12. Lyophilized dosage forms.

1. The ampulsion workshop of the enterprise produces solutions for injections. Indicate which stabilizer is added to 1% solution of injectable hydrochloride morphine.
A * 0.1 n solution of acidic hydrochloric acid
B 0.1 N solution of sodium chloride
C aminopropylene glycol
D Ronalat
E Sodium metabisulphite

2. Ampulsion workshop of the enterprise produces 5% oil solution of tocopherol acetate for injections. Specify which method of filling ampoules to use rationally when filling ampoules with this solution.
A * syringe
B Vacuum
C steam-condensation
D syringe and vacuum
E syringe and steam condensation

3. Ampoule shop produces solutions for injection. Specify methods for determining the tightness of ampoules filled with oil injectable solutions.
A * with a soap solution
B with methylene blue
C by ultrasound

D using methyl orange
E using a flow method

4. One of the indicators for testing the quality of finished ampoules is the absence of residual stresses in the glass. Specify which operation from the stage "Preparation of ampoules for filling" eliminates this drawback:
A * annealing ampoules
B discovery of capillaries
C washing ampoules
D drying ampoules
E sterilization of ampoules

IV. Summing up

List of recommended literature:

Main:

- Промислова технологія лікарських засобів: базовий підручник для студ. вищ. навч.закладу (фармац. ф-тів) / Є. В. Гладух, О. А. Рубан, І. В. Сайко [та ін.] – Х. : НФаУ : Оригінал, 2016. – 632 с. : іл.
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- Навчальний посібник для самостійної підготовки студентів фармацевтичного факультету до ліцензійного інтегрованого іспиту «Крок 2. Фармація» / О.А. Рубан, В.Д. Рибачук, Л.М. Хохлова, Д.С. Пуляєв – Х.: НФаУ, 2016. – 63 с.
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- Сучасні фармацевтичні технології: навч. посіб. до лабораторних занять магістрантів денної, вечірньої та заочної форми навчання спеціальності 8.110201 «Фармація» / під ред. О.А. Рубан. – Х.: Вид-во НФаУ, 2016. – 256 с.
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Practical lesson № 5

Topic: Production of soft dosage forms according to GMP requirements (ointments, gels, suspensions, emulsions, suppositories, patches, etc.)

Purpose: learn to use the state pharmacopoeia, regulatory and technical documentation and reference literature to find the necessary information for the preparation of soft dosage forms; to study the assortment and properties of auxiliary substances for the production of ointments, gels, suspensions, emulsions, liniments, as well as dosage forms for rectal and vaginal use; to study methods of production of soft dosage forms in industrial conditions; be able to calculate the amount of medicinal substances included in the composition, select the bases for the preparation of MLF, choose the optimal technology for their production; rationally choose equipment, know the types of machines, their structure and principle of operation; to draw up a block diagram of the production of soft dosage forms, the main technological operations during their production, the selection of equipment at each stage and the determination of quality indicators.

Basic concepts: soft dosage forms, ointments, gels, suppositories, plasters.

Equipment: soft dosage forms, ointments, gels, suppositories, plasters.

Study time: 8 hours.

I. Organizational moment.

II. Control of reference knowledge

2.1. Requirements for students' theoretical readiness to perform practical classes (knowledge requirements, list of didactic units)

Requirements for theoretical knowledge:

Production of ointments, liniments, pastes Soft medicinal products are mainly intended for application to the skin, wounds, and mucous membranes. They are characterized by specific rheological properties at the set storage temperature: non-Newtonian type of flow, appropriate structural viscosity, pseudoplastic or plastic properties. They should be uniform in appearance. Soft medicines contain active and auxiliary substances. Auxiliary substances according to their functional purpose can be classified as: - soft bases-carriers (vaseline, lanolin, polyethylene oxides, etc.); - substances that increase the melting point and viscosity (paraffin, spermaceti, hydrogenated vegetable oils, waxes, etc.); - hydrophobic solvents (mineral oils and vegetable oils, isopropyl palmitate, isopropyl myristate, benzyl benzoate); - water and hydrophilic solvents (ethanol, isopropanol, propylene glycol, propylene carbonate, dimethyl sulfoxide); - emulsifiers of the o/w type (sodium lauryl sulfate, emulsifying wax (emulsifier No. 1), salts of higher fatty acids, etc.); - emulsifiers of the v/o type (higher fatty alcohols, cholesterol, wool wax alcohols, etc.); - gelatinizers (alginic acid and its salts, low molecular weight polyethylene, bentonites, kaolin, colloidal silicon dioxide, gelatin, etc.); - antimicrobial preservatives (benzalkonium chloride, benzoic and sorbic acids and their salts, benzyl alcohol, cresol, chlorocresol, ethanol, etc.); - antioxidants (y-tocopherol, ascorbic acid, butylhydroxytoluene, sodium metabisulfite, etc.); - solubilizers (beta-cyclodextrin, hydrophilic surfactants); - substances for creating or stabilizing a certain pH value (citric acid, sodium phosphate salts, etc.); - dyes. Soft drugs can be classified as: - ointments; - creams; - dragles; - pasta; - liniments. Ointments are soft medicinal products for local use, the dispersion medium of which at the set storage temperature has a non-Newtonian type of flow and high values of rheological parameters. Hydrophobic ointments Hydrophobic ointments are prepared on hydrocarbon bases (vaseline, petroleum jelly, paraffin) and may contain other lipophilic auxiliary substances (vegetable oils, animal fats, wax, synthetic glycerides, etc.).

Hydrophobic absorbent ointments Hydrophobic absorbent ointments are ointments that, when rubbed into the skin, can absorb exudate. The bases for them can be divided into two groups: - hydrophobic bases, which consist of hydrocarbons and emulsifiers of the w/o type (vaseline, lanolin, alcohols of wool wax, a significant amount of water or aqueous solutions can be added to their composition to form an emulsion of the w/o type); - hydrophobic bases that are w/o or o/w/o emulsions (water vaseline and lanolin). Hydrophilic ointments Hydrophilic ointments, as a rule, are hyperosmolar and when applied can absorb a significant amount of exudate. The bases for them can be divided into two groups: - water-soluble bases that contain hydrophilic non-aqueous solvents (polyethylene oxide-400, propylene glycol, etc.); - water-washing bases, which, in addition to water-soluble polymers and hydrophilic non-aqueous solvents, contain lipophilic substances (higher fatty alcohols, petroleum jelly, petroleum jelly, lanolin, wax). Creams Creams are soft drugs for local use, which are two- or multi-phase dispersion systems, the dispersion medium of which at the set storage temperature has a non-Newtonian type of flow and low values of rheological

parameters. Creams can be hydrophilic and hydrophobic. Paste Pastes are soft drugs for local use, which are suspensions containing more than 20% of a solid dispersed phase evenly distributed in the base. Bases for ointments, creams, jelly can be used as bases for pastes. Liniments Liniments are soft drugs for local use that melt at body temperature; are used, as a rule, by rubbing (linera) into the skin. The technological process of production of ointments includes the following stages: - production preparation; - preparation of medicinal and auxiliary substances, bases; - introduction of medicinal substances into the base; - homogenization: - packaging and labeling of finished products. When preparing medicinal and auxiliary substances and introducing active components into the base, it is necessary to take into account the type of dispersion system, the type of ointment base, and the physicochemical properties of medicinal and auxiliary substances. Preparation of medicinal and auxiliary substances, as a rule, is reduced to grinding, sieving, weighing and (or) dissolving medicinal substances. The components of the ointment base are subjected to melting, mixing or emulsification followed by filtration to remove mechanical impurities. When mixing large quantities of heterogeneous ointments in reactors, it is not possible to achieve uniform dispersion of the medicinal substance in the ointment base. For this purpose, the ointment is subjected to homogenization, which is carried out in most cases at an elevated temperature, in the range of 40-70 °C, depending on the type of ointment base. For this purpose, various types of maseters, colloid mills, rotary-pulsation apparatus and other equipment are used.

Soft medicinal products are controlled according to the following quality indicators: description, identification, homogeneity, weight of package contents, microbiological purity, accompanying impurities, quantitative determination. If necessary, particle size, pH, acid and peroxide values, colloidal thermal stability are additionally controlled for soft drugs. The packaging for soft drugs should be indifferent to the drug; be tightly closed to prevent contact of the contents with the environment; if necessary, airtight and light-proof. Preference should be given to metal tubes that are irreversibly compressed, with an internal varnish coating, a protective membrane and a latex ring. Other types of primary packaging that meet the specified requirements may be used. Packages of sterile soft drugs must be hermetic and have a device to control the first opening, for example, a protective membrane. Packages for nasal, ear, eye, rectal and vaginal soft drugs must be provided with appropriate applicators.

2.2. Questions (test tasks, tasks, clinical situations) to check basic knowledge on the subject of the lesson:

Answer the question: 1. Requirements for ointments and ointment bases. 2. Ointment bases. Classification. Characteristic. 3. Assortment of auxiliary substances in the production of soft medicines 4. Introduction of medicinal substances to ointment bases. 5. General characteristics of suppositories. 6. Classification of suppository bases. 7. Features of the

introduction of active substances into suppository bases depending on the physical and chemical properties. 8. Prospects for the development of rectal and vaginal dosage forms.

III. Formation of professional skills and abilities:

3.1. Content of the task of practical work:

1. Equipment for mechanical dispersion.

2. Equipment for ultrasonic dispersion.

3. Equipment for the production of ointments.

4. Equipment for the production of suppositories.

Educational tasks for practical work: Task No. 1 Carry out calculations for drawing up a working prescription and a material balance in the form of an equation and a table for preparing 150 kg of calendula ointment on a consistent basis. At the same time, take into account that the consumption factor at the stage of preparing the consistent base is equal to 1.005; cost factor at the stage of introduction of the medicinal substance into the base 1.003; at the stage of homogenization - 1.007. Composition: tincture of calendula 10 parts. a consistent base of 90 parts Composition of the base: Vaseline 60 parts water purified 30 parts emulsifier T-2 10 parts

Ointment composition		**Stages of the process**		
Medicinal substance	**Number**	**1**	**2**	**3**

Task No. 2 Draw up a technological scheme for the production of calendula ointment on a consistent basis by stages with an indication of the equipment used at each stage

Task No. 3 Prepare 150 g of emulsion-based sulfuric ointment. Simple sulfur ointment/ Unguentum sulfuratum simples Storage: Purified sulfur powder 50 g emulsion consistency Water / petroleum jelly 100 g The composition of the emulsion is water / petroleum jelly

Vaseline 60 g Emulsifier T-2 10 g Water 30 g Preparation technology: T-2 emulsifier, petroleum jelly are placed in a 0.5 liter porcelain glass and melted at 85 ° C in a water bath. Distilled water heated to 90 ° C is added and emulsified using a propeller stirrer for 15 minutes before cooling. Sulfur is mixed with emulsion in a mortar and homogenized. Packed in glass jars of 25, 30, 50 m.

3.2. requirements for work results, including to registration; According to the progress of the practical lesson, complete the individual task in your workbook.
3.3. requirements for work results, including registration; According to the recommendations (instructions) for the tasks.
2.4. control materials for the final stage of the lesson: problems, assignments, tests, etc.:
1. Parameters characterizing the structural and mechanical properties of soft drugs. 2. What factors determine the stability of suspensions and emulsions? 3. What role do auxiliary substances play in the production of suspensions and emulsions? 4. What stages does the process of obtaining dispersion preparations consist of? 5. Factors affecting the stability of ointments. 6. What is the homogenization of ointments and in what cases is it mandatory? 7. What are the advantages of RPA over other machines in the production of suspension ointments? 8. Give examples of industrially produced ointments. What are the features of their technology? 9. What are the basic rules for introducing medicinal substances into the suppository base? 10. How is the process of forming suppositories carried out? What machines are used for this purpose? What is the principle of their work? 11. Standardization of soft dosage forms. 12. Determination of homogeneity of suspension ointments according to DFU.

Situational tasks. 1. At a pharmaceutical enterprise, when obtaining an ointment with a high degree of viscosity, an employee used a portable propeller stirrer for homogenization. Will it achieve sufficient homogenization? Why? 2. At the pharmaceutical enterprise, a new drug was introduced - suppositories, which include biogenic stimulants that are destroyed at high temperatures. Suppositories were prepared by the pouring method, drying was carried out at a temperature of 15°C for 2 hours. Evaluate the technologist's actions. 3. Suppositories with 0.00015 g of digitoxin were manufactured at the pharmaceutical enterprise. The technologist-operator was faced with the question of how to produce them. Evaluate his actions.

IV. Summing up

List of recommended literature:

Main:

- Промислова технологія лікарських засобів: базовий підручник для студ. вищ. навч.закладу (фармац. ф-тів) / Є. В. Гладух, О. А. Рубан, І. В. Сайко [та ін.] – Х. : НФаУ : Оригінал, 2016. – 632 с. : іл.

- Практикум з промислової технології лікарських засобів: навч. посіб. для студ. вищ. навч. закладів зі спеціальності «Фармація» / О.А. Рубан, Д.І. Дмитрієвський, Л.М. Хохлова [та ін.]; за ред. О.А. Рубан. – Х.: НФаУ; Оригінал, 2015. – 320 с.
- Промислова технологія лікарських засобів: навч. посіб. для самостійної роботи студентів / О.А. Рубан, В.Д. Рибачук, Л.М. Хохлова та ін. – Х.: НФаУ, 2015. – 120 с.
- Промислова технологія лікарських засобів. Навчальний посібник для самостійної роботи студентів: опрацьоване та доповнене. / Сост. О.А. Рубан, В.Д. Рибачук, Л. М. Хохлова, Ю. С. Маслій та ін. – Х.: НФаУ, 2015. - 120 с.
- Навчальний посібник з підготовки до підсумкового модульного контролю та Державної атестації з Промислової технології лікарських засобів для студентів денного та заочного відділення спеціальності «Фармація» / Під ред. О.А. Рубан. – Х.: НФаУ, 2016. – 80 с.
- Навчальний посібник для самостійної підготовки студентів фармацевтичного факультету до ліцензійного інтегрованого іспиту «Крок 2. Фармація» / О.А. Рубан, В.Д. Рибачук, Л.М. Хохлова, Д.С. Пуляєв – Х.: НФаУ, 2016. – 63 с.
- Допоміжні речовини у виробництві ліків: навч. посіб. для студ. вищ. фармац. навч. закл. / О.А. Рубан, І.М. Перцев, С.А. Куценко, Ю.С. Маслій; за ред. І.М. Перцева. – Х.: Золоті сторінки, 2016. – 720 с.
- Сучасні фармацевтичні технології: навч. посіб. до лабораторних занять магістрантів денної, вечірньої та заочної форми навчання спеціальності 8.110201 «Фармація» / під ред. О.А. Рубан. – Х.: Вид-во НФаУ, 2016. – 256 с.
- Державна Фармакопея України / Державне підприємство «Український науковий фармакопейний центр якості лікарських засобів» – 2-е вид. – Харків: Державне підприємство «Український науковий фармакопейний центр якості лікарських засобів», 2015. – Т. 1. – 1128 с.
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- Стандарт МОЗ України «Вимоги до виготовлення нестерильных лікарських засобів в умовах аптек» СТ-Н МОЗУ 42 – 4.5 : 2015 // За ред. проф. О. І. Тихонова і проф. Т.Г. Ярних. – Київ, 2015. – 109 с. (Затверджено наказом МОЗ Украіри № 398 от 01.07.2015 р.).
- Стандарт МОЗ України «Вимоги до виготовлення стерильных і асептичних лікарських засобів в умовах аптек» СТ-Н МОЗУ 42 – 4.6 : 2015 // За ред. проф. О.І. Тихонова і проф. Т.Г. Ярних. – Київ, 2015. – 76 с. (Затверджено наказом МОЗ України № 398 от 01.07.2015 р.).

Additional literature

- Фармацевтична енциклопедія / Голова ред. ради та автор передмови В.П. Черних. – 3-тє вид., переробл. і доповн. – К.: «МОРІОН», 2016. – 1952 с.
- Екстемпоральні прописи для терапії дерматологічних захворювань: навч. посіб. для студентів медичних та фармацевтичних вузів / Н.П. Половко, Л.І. Вишневська, Т.М. Ковальова та ін. – Х.: Вид-во НФаУ, 2017. – 91 с.
- Технологія виготовлення екстемпоральних лікарських апіпрепаратів і їх застосування в фармації, медицині та косметології: методичні рекомендації / О.І. Тихонов, Т.Г. Ярних, С.О. Тихонова, О.Г. Башура, О.С. Шпичак, Л.О. Бондаренко, П.С. Сирота, Б.Т. Кудрик, Р.І. Скрипник-Тихонов, Н.С. Богдан, С.Г. Бобро, Л.В. Каношевич, О.Є. Богуцька; за ред. О.І. Тихонова. – Х. : НФаУ, 2016. – 75 с.
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Electronic information resources

1. Department of pharmaceutical chemistry and drug technology of ONMedU – website of the Department of pharmaceutical chemistry and drug technology of ONMedU
2. Scientific library of ONMedU (odmu.edu.ua) - Scientific library of ONMedU
3. www.moz.gov.ua – official website of the Ministry of Health of Ukraine
4. Odessa National Medical University (onmedu.edu.ua) – ONMedU official website
5. State Register of Medicinal Products of Ukraine. - [Electronic resource]. - Access mode: http://www.drlz.com.ua/ − as of 10.01.2017.

Practical lesson №6

Topic: Production of phytochemicals according to GMP requirements.

Purpose: study the modern range of extractants and their requirements; factors affecting the extraction process; to study the methods of obtaining extraction preparations; stages of the technological process of preparation of total preparations, novogalen preparations,

preparations of individual substances; choose the optimal technology for their production; rationally choose equipment, know the types of machines, their structure and principle of operation; to draw up a block diagram of the production of extraction preparations from plant and animal raw materials, the main technological operations during their production, the selection of equipment at each stage and the determination of quality indicators.

Basic concepts: phytochemical preparations, extractant, extractor, strot.

Equipment: production schemes, extractor.

Study time: 8 hours.

I. Organizational moment.

II. Control of reference knowledge

2.1. Requirements for students' theoretical readiness to perform practical classes (knowledge requirements, list of didactic units)

Requirements for theoretical knowledge:

To date, in most countries of the world, there is a trend of expanding the production of preparations from fresh plant materials, the feature of which is the content of the BAR complex in an unchanged state. Juices occupy a significant part of the assortment of this group of drugs and, depending on the production technology, are divided into non-condensed or natural juices, condensed and dry juices; depending on the raw materials used - vegetable, fruit and medicinal plant juices. Juices are the most physiologically complete form of plant food intake, which preserves the maximum amount of unstable, but physiologically active substances necessary for the body in their natural or slightly modified form. Juices can be used as independent drinks, and can also be part of therapeutic and preventive drugs. The industry produces juices from the following types of plants: belladonna (Sucradbel), digitalis (Succudifer), feijoa (Sucfeisel), lilies of the valley, plantain, aloe, kalanchoe, valerian, 25 dope, horsetail, celandine, water pepper, thyme, mother-and- stepmothers, nettles, etc. The technology for the production of non-condensed juices includes the following operations: grinding and squeezing of fresh vegetable raw materials, as well as canning. Spindle machines, rollers or a roller electroplasmolizer are used for grinding. In addition to the press, you can use a centrifuge or a centrifugal juicer to squeeze the juice. Moreover, juices obtained using a centrifuge or juicer are better than juices obtained using a press. Centrifuge juice is prepared 3-4 times faster, oxidizes less. In addition, such juice contains up to 10% pulp and is nectar. Much more active substances pass into it, and therefore it is biologically more valuable for the body. The methods of pasteurization and boiling are used to preserve juices, followed by bottling the juice while hot. In some cases, preservatives and antioxidants are added. They also use a type of special

packaging such as "Tetrapak". The scheme for the production of dry juices includes the following stages: preparation of plant extracts, concentration of juices, agglomeration, blending, packaging and labeling. Juices are filtered, pasteurized and concentrated in vacuum evaporators to a concentration of 67-70% by mass. Agglomeration is carried out by mixing granulated sugar with a mixture of liquid components, and then drying is carried out on a SPT-100 type installation in a fluidized bed at a temperature of 50°C to a humidity of 2%. The resulting granules are crushed many times on a disintegrator to a powder with a homogeneous structure, after which they are mixed in a mixer with dry components and flavorings. Coupage (French coupage) is the mixing of different food products or their components in certain proportions to improve the quality of the finished product, as well as to obtain products of a certain type and composition.

Phytopreparations in the form of balms and elixirs also occupy a special place among total herbal preparations. Elixirs (Latin ―elixirum‖, ―elixir‖ from the Arabic ―elixir‖ - stone, ―philosopher's stone‖) - a liquid medicinal form for oral use, which is a transparent, often colored, mixture of alcohol-water extracts from plant materials with the addition of medicinal substances, sugars and flavorings. Balms are natural substances that contain mainly essential oils and resins, have the appearance of thick, resinous liquids with a strong specific aroma. They flow out when the bark of trees or shrubs is damaged, quickly thicken and dry in the air. Balsams, as a ready-made medicinal form, can be used both externally and orally. Balsams for external use (Latin ―balsama‖; Greek ―balsamon‖ — aromatic resin) are ointments containing aromatic compounds (oil 26 ether, resins, benzoin and cinnamic acids, aldehydes, etc.) and have a characteristic "balsamic" smell. Balsams for internal use are extractive compositions obtained from spicy ethereal and resinous plant raw materials. These drugs are thick liquids with a fairly high alcohol content (40-50%), aromatic smell and burning spicy taste. The question of distinguishing oral balms and elixirs, which are also used orally, may seem debatable, but there is a difference between them. Elixirs (as their definition implies) are always transparent, oral balms are not. Balms and elixirs, thanks to their multicomponent composition, have a wide range of pharmacological effects: anti-inflammatory, general tonic, general tonic, sedative, analgesic, etc. Until the beginning of the 20th century, Kopai, Peruvian, Tolutan, Canadian, frankincense, cedar and other balms were considered miraculous remedies for various skin lesions, diseases of the lungs and upper respiratory tract, and the gastrointestinal tract. Currently, Peruvian and Tolutan balsams are included in the European Pharmacopoeia. Peruvian balsam is a dark brown viscous liquid extracted from the burned, cut trunks of the plant Myroxylon balsamum (L). Insoluble in water and fatty oils, easily soluble in ethanol, contains from 45 to 70% complex esters, mainly benzyl benzoate and cinnamic benzyl ether.

Tolutan balsam - a resin obtained from intact trunks of the Myroxylon balsamum plant - a hard, brittle mass of red-brown color with a vanilla smell, insoluble in water and petroleum ether, easily soluble in alcohol. Contains from 25 to 50% of free or bound

aromatic acids (mainly cinnamic). One of the natural balms is honey, which contains more than 300 chemicals. A natural balm such as mummy is also widely known. It is a substance containing more than 25 micro- and macroelements (salts of calcium, magnesium, phosphorus, manganese, copper, lead, tin, iron, sulfur, cobalt). In addition, the mummy contains resins, gums, protein substances, benzoic acid and a number of fatty acids. Nowadays, the range of medicinal balms and elixirs is constantly expanding due to the introduction into medical practice of previously known compositions (balms of Bittner, Maurer, Karavaev, Vishnevsky, etc.) and in connection with the development of new ones (Gastrovitol, Flora, Fitulvent, "Grail", balsamic extraction oils, etc.), elixirs Demidovskaya, Altaisky, Kedrovit, Kliophyt.

2.2. Questions (test tasks, tasks, clinical situations) to check basic knowledge on the subject of the lesson:

1. Definition and classification of preparations from fresh plant material. 2. Advantages and disadvantages of preparations in the form of juices, balms and elixirs. 3. Nomenclature of pharmacopoeial balms and elixirs. 4. Commodity analysis of plant raw materials, which are used to obtain juices and medical and preventive drinks. 5. Food (vitamin) juices. Production technology and used equipment. 6. Juices obtained from medicinal plant raw materials. 7. Concentrated juices. Production technology and used equipment. 8. Preparation of powdered mixtures for therapeutic and preventive drinks. 9. Preservation of juices. 10. Features of the composition of balms and elixirs, their differences from other phytochemical preparations. 11. Technological process of balsam production. 12. Features of elixir technology. 13. Quality control of balms and elixirs.

III. Formation of professional skills and abilities:

3.1. Content of the task of practical work:

1. The device of extractors of various designs.

2. Equipment for circulation extraction.

3. Rectification installations Educational tasks for practical work:

Task No. 1 Preparation and research of St. John's wort tincture Storage: coarsely ground St. John's wort grass 20 g of 40% alcohol to obtain 100 ml Application: in functional disorders of cardiac activity, in angina pectoris, in atrial fibrillation and paroxysmal tachycardia. Description: transparent liquid of dark brown color. Preparation is carried out by the method of percolation and the method of vortex extraction with full theoretical and practical justification in comparison with the percolation method, taking into account the output of extractives and active substances, consumption of raw materials and extractant, extraction time and standard costs for the performance of these works. Grinding is obtained in the RT-2 micro-shredder of fabric (rotation speed of the stirrer 3000-5000 rpm). To obtain 100 ml

of the finished product, 20 g of coarsely ground St. John's wort grass (1-8 mm) is placed in the beaker of the apparatus and poured with 140 ml of 40% alcohol (taking into account the absorption coefficient. Turn on the apparatus at a speed of 5000 rpm and extract for 5 minutes, then turn it off for 10 minutes. After that, the extraction is repeated 2 more times. Thus, 15 minutes are spent on extraction (not including breaks). The extract is poured into a cylinder through a funnel with cotton wool, squeezed out using a double-layer gauze napkin, and the squeezed liquid is added to the extraction. In case to obtain a tincture of less than 100 ml, the raw materials are washed with 40% alcohol, squeezed and added to the tincture. The resulting extract is poured into a glass with a polished stopper and left for cleaning from ballast substances for 3-4 days in a cool place (8-10°C). Conduct research: establish authenticity, purity, determine dry residue, alcohol content, active substances. Task No. 2 Carry out the appropriate calculations for the preparation of the extractant to obtain 100 kg of liquid nettle extract Task No. 3 Draw up a technological scheme for obtaining a dry extract from senna leaves by stages with an indication of the equipment used at each stage

3.2. requirements for work results, including to registration; According to the progress of the practical lesson, complete the individual task in your workbook.
3.3. requirements for work results, including registration; According to the recommendations (instructions) for the tasks.
2.4. control materials for the final stage of the lesson: problems, assignments, tests, etc.:
1. What is the place and role of mass transfer processes in pharmaceutical technology? 2. Give the classification and characteristics of extraction preparations. 3. Features of extraction of fresh and dehydrated raw materials. 4. Preparation of raw materials for extraction, the importance of particle size and the nature of grinding. 5. The effect of extracting capacity, selectivity, desorption, polarity, viscosity, surface tension and the reaction of the extractant medium on increasing the speed and completeness of extraction. 6. The main technological factors affecting the completeness and speed of extraction. 7. Ways of intensification of mass exchange. 8. Physical foundations of rectification processes.

1) Calculate the percolation rate, if the height of the raw material and the mirror in the percolator is 16 cm, the diameter is 2 cm.

2) Determine the ethanol content in motherwort tincture, if the boiling temperature of the tincture is 81.10, and the atmospheric pressure is 750 mmHg.

Situational tasks. 1. Explain the essence of evaporation under vacuum and indicate the effect of temperature on the quality of extraction preparations 2. What types of drying units should be rationally used when obtaining phytopreparations?

IV. Summing up

List of recommended literature:

Main:

- Промислова технологія лікарських засобів: базовий підручник для студ. вищ. навч.закладу (фармац. ф-тів) / Є. В. Гладух, О. А. Рубан, І. В. Сайко [та ін.] – Х. : НФаУ : Оригінал, 2016. – 632 с. : іл.
- Практикум з промислової технології лікарських засобів: навч. посіб. для студ. вищ. навч. закладів зі спеціальності «Фармація» / О.А. Рубан, Д.І. Дмитрієвський, Л.М. Хохлова [та ін.]; за ред. О.А. Рубан. – Х.: НФаУ; Оригінал, 2015. – 320 с.
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- Навчальний посібник для самостійної підготовки студентів фармацевтичного факультету до ліцензійного інтегрованого іспиту «Крок 2. Фармація» / О.А. Рубан, В.Д. Рибачук, Л.М. Хохлова, Д.С. Пуляєв – Х.: НФаУ, 2016. – 63 с.
- Допоміжні речовини у виробництві ліків: навч. посіб. для студ. вищ. фармац. навч. закл. / О.А. Рубан, І.М. Перцев, С.А. Куценко, Ю.С. Маслій; за ред. І.М. Перцева. – Х.: Золоті сторінки, 2016. – 720 с.
- Сучасні фармацевтичні технології: навч. посіб. до лабораторних занять магістрантів денної, вечірньої та заочної форми навчання спеціальності 8.110201 «Фармація» / під ред. О.А. Рубан. – Х.: Вид-во НФаУ, 2016. – 256 с.
- Державна Фармакопея України / Державне підприємство «Український науковий фармакопейний центр якості лікарських засобів» – 2-е вид. – Харків: Державне підприємство «Український науковий фармакопейний центр якості лікарських засобів», 2015. – Т. 1. – 1128 с.
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- Екстемпоральні прописи для терапії дерматологічних захворювань: навч. посіб. для студентів медичних та фармацевтичних вузів / Н.П. Половко, Л.І. Вишневська, Т.М. Ковальова та ін. – Х.: Вид-во НФаУ, 2017. – 91 с.
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Electronic information resources

1. Department of pharmaceutical chemistry and drug technology of ONMedU – website of the Department of pharmaceutical chemistry and drug technology of ONMedU
2. Scientific library of ONMedU (odmu.edu.ua) - Scientific library of ONMedU
3. www.moz.gov.ua – official website of the Ministry of Health of Ukraine
4. Odessa National Medical University (onmedu.edu.ua) – ONMedU official website
5. State Register of Medicinal Products of Ukraine. - [Electronic resource]. - Access mode: http://www.drlz.com.ua/ − as of 10.01.2017.

Practical lesson № 7

Topic: Packing and packaging of finished products.

Purpose: study State standards for containers and packaging materials; learn how to use DFU, NTD and reference literature to find the necessary information for packaging ready-made medicinal forms; to study the modern range of containers and packaging material in the pharmaceutical industry; packaging in the conditions of large enterprises; to study the effect of sorption of drug components by the packaging material of finished drugs on their preservation; to study methods of production of polymer containers, medical glass, cardboard and paper, metal, rubber and combined containers; choose equipment, know the types of machines, their structure and principle of operation for packaging solid, soft, liquid medicines.

Basic concepts: container, packing, primary packaging, sealing means.

Equipment: production schemes, device samples.

Study time: 8 hours.

I. Organizational moment.

II. Control of reference knowledge

2.1. Requirements for students' theoretical readiness to perform practical classes (knowledge requirements, list of didactic units)

Requirements for theoretical knowledge:

The problem of packaging of ready-made medicines requires constant attention, because large material costs for packaging, irrational choice of it leads to a decrease in quality and significant losses of raw materials, materials, and medicines. Therefore, containers and packaging in pharmacy play a special role, ensuring not only the possibility of convenient use of drugs, but also the preservation of their properties during storage. Until now, many workers in the field of production and consumption do not clearly understand the difference between containers and packaging. Packaging is a set of methods and measures designed to protect the drug from environmental influences, damage, losses, and facilitate the circulation process. The container is an element of packaging, it is a product intended for placing products. Packaging combines containers, medicines, sealing and auxiliary elements that determine the consumer properties of the product. An empty bottle is a container, and a bottle with a drug, stopper, label and other auxiliary means is a package. In the production of finished medicines, packaging is classified by type. Primary packaging is individual or consumer packaging in which there is direct contact of the medicinal product with the packaging material. It is designed to create the necessary conditions that ensure the long-term integrity of the dosage form placed in it. Secondary packaging is packaging that is designed to protect the primary packaging (their integrity) and for more complete

informative information. For example, recently, the text about the use of medicines is printed on the secondary packaging. Secondary packaging provides the simplest and most convenient product accounting and control. Cardboard bundles and boxes are used as secondary packaging, where tablets, dragees, capsules, vials and ampoules with liquid and powdered medicinal products, metal and glass tubes with tablets, tubes with ointments, sachets with powdered medicinal products are contained in the primary cellular contour packaging. In some cases, secondary packaging creates additional sealing and protection of primary packaging from the influence of external factors. Secondary packaging also belongs to consumer. Group packaging (or block packaging) is a group of primary or secondary packaging and is formed in machines or automatic machines during packaging of products in shrink film, paper, cardboard boxes. Transport packaging — packaging in a transport container in which products are delivered to places of distribution and sale. It must be unique for each series of drugs. Ensuring the necessary consumer properties of the package is recognized as equally important: it should be convenient for movement, contain information on storage and reception of the product, control of the first opening of the package, sterility and an attractive appearance. Depending on the functional purpose, the container is divided into consumer and transport.

Types of consumer containers for different dosage forms Solid medicines Tablets, dragees, granules, capsules are packed in contour containers, cans made of fiberglass with a screw neck, cans made of fiberglass or wire with a triangular crown, convalutes, tubes made of glass wire. Screw-on plastic caps, a gripping cap with a rolled thread, plastic pull-on caps with a sealing element, aluminum caps with a rubber plug, plastic plugs with a sealing element, metal screw-on caps are used as sealing means for the mentioned container. The Mariupol plant of technological equipment manufactures a machine model 557 for packing tablets in one-sided cell-contour packaging made of polymer film and foil. Machines for receiving such packages are divided into: 1) according to the method of feeding the film: — on continuous; — cyclical; 2) by the method of formation: — on vacuum; — pneumo-vacuum; — with previous mechanical extraction.

Powders, granules, collections. These dosage forms are available in fiberglass cans, plastic cans (baby powder), as well as in bags made of polymer materials.

Capsules. Capsules are mostly packed in cellular-contour packaging with the help of a 573 model machine. This is a mixed-type machine and performs continuous film formation, loading it with capsules, sealing, marking and cutting of finished packages.

Currently, a number of machines for packaging capsules, dragees, tablets in polymer film and foil are operating at pharmaceutical enterprises. Capsules are also packed in glass, plastic cans.

These include tinctures, extracts, pharmaceutical solutions. Liquid medicines are produced in glass bottles with a screw neck, glass jars and bottles for food liquids, in dropper bottles. Different methods are used for pouring and dosing liquids into glass bottles, the

choice of which depends on the specified conditions for the dosing and filling process and on the properties of the liquid. There are machines for pouring liquids with dispensers. Liquid galenic preparations with a small viscosity coefficient can be dosed both by volume and by level. Filling and dosing machines are classified into rotary and linear. Most of the modern machines for pouring liquids, regardless of the principle of operation, belong to the rotary type machines and consist of the following components: a bed with devices located on it; a rotating tank for receiving liquid with filling devices or dosing devices and a float system that maintains a constant level of liquid in the tank during pouring; distribution and feeding mechanisms that ensure uniform and synchronous feeding of containers for filling and removal and after filling; rotary table with lifting tables. The lifting tables are located on the same axis as the dispensers and serve to lower and raise the containers during filling. Medicinal products for parenteral use and ophthalmic dosage forms. Various primary containers (glass and polymer) and sealing means (rubber stoppers made of natural and synthetic rubber, aluminum caps) are used for their packaging. Assortment of glass and polymer containers for injectable medicinal products: — vials made of wire for insulin and general purpose with a capacity of 5, 10, 15, 20, 30 ml; — glass bottles for blood, transfusion and infusion preparations with a screw neck with a capacity of 50, 100, 250, 450, 500, 1000, 2000 ml and a smooth neck — 50, 100, 250, 500 ml; — glass ampoules of six types with a capacity of 1, 2, 3, 5, 10, 20, 30, 50 ml: — cans polymer BPm; — polymer cans with wide necks BPm; — tube ampoules with a capacity of 0.5, 1, 2 ml; — flexible (soft) containers with a capacity of 250, 500, 1000 ml. Ophthalmic drugs are manufactured by: — in glass bottles; — dropper bottles; — dropper tubes. Sealing with the help of gas burners (for glass ampoules), heat welding (for polymer ampoules, syringe ampoules, flexible containers) and sealing materials (rubber stoppers and aluminum caps) for vials are used to seal vessels.

Assortment of sealing means: — shaped rubber stoppers for insulin and general-purpose vials; — shaped rubber stoppers for blocking blood preparations, transfusion and infusion preparations; — aluminum lids that can be rolled up or screwed on.

The last decades are characterized by the creation of plastic packaging for storing sterile dosage forms. Plastics are materials based on natural or synthetic polymers that also contain fillers, catalysts, plasticizers, stabilizers, and other components that are able to acquire a given shape when heated under pressure and retain it after cooling. The interest in polymer materials is explained by the fact that they have such a combination of valuable properties that none of the other materials have. Thus, in comparison with glass, polymeric materials show less fragility or are completely devoid of it with satisfactory mechanical strength, rigidity and surface hardness. Many plastics are inert, neutral and, at the same time, resistant to alkalis, acids, many oxidants and reducing agents. They are quite easily processed into products of complex configuration, and the elasticity of some polymers allows to create fundamentally new designs of containers and packaging from them. A distinctive feature of these types of packaging is that the sterile dosage form is placed in

them automatically at the filling stage and immediately sealed by thermal welding. This makes it possible to create conditions of such technological purity that ensures reliable protection of both the packaging itself and the sterile medicinal product from microbial contamination and meets modern requirements of good manufacturing practice.

The first materials approved for medical use were high and low pressure polyethylene. Now the assortment has expanded significantly due to the successful use of polyvinyl chloride, polytetrafluoroethylene, polycarbonates, polyesters, etc. A copolymer of ethylene and vinyl acetate is also a promising material for disposable products. Polystyrene and its copolymers are used in pharmacy in the manufacture of a number of products and packaging materials for some medicinal products. The use of this class of materials was restrained for a long time due to the high content of styrene monomer in the polymer. However, in recent years, several new brands of polystyrene and styrene copolymers, suitable for the production of droppers, transfusion needles in blood transfusion systems, disposable syringes, have been developed and studied. Among the listed products for medical purposes for pharmaceutical production and ophthalmology, various containers made of plastic materials are of great interest. They can be made from one or more polymers that do not contain substances harmful to the body, which can be extracted into the liquid placed in them or have a toxic effect. So, a syringe ampoule is a polyethylene container with a capacity of 1.0 (0.15) ml for packaging, sterile storage, transportation and use of aqueous solutions of drugs for injections. It consists of a body that is sealed in aseptic conditions after filling with a sterile solution, an injection needle and a protective cap. The body of the polymer ampoule is made of high-pressure polyethylene, which does not contain stabilizers and dyes. The protective cap is made of non-stabilized low-pressure polyethylene.

Processing of polymer material is one of the main stages of the technological process of manufacturing a sterile medicinal product in polymer packaging. The technological process includes the following stages: — preparation of material for processing; — formation of parts and their processing (sterilization); — assembly of parts into assemblies or products; — filling and capping of containers; sterilization of ready-made packages with solutions. Among the methods of processing polymer materials and making packages from them, extrusion processes should be highlighted, which are carried out by extrusion and blow molding of hollow products with the help of blow molding units, in which multi-nest formation of containers from one extruded blank with the design of screw necks and filling containers for filling syringes takes place. ampoules or dropper tubes with medicinal substances. One of the methods of obtaining multilayer polymer materials with high quality characteristics (low vapor permeability, etc.) is coextrusion of polymers. The most promising equipment for the production of single-use packaging by injection molding is considered to be multi-position rotary and turret type casting machines, which, like ordinary casting machines, have an electronic control device for maintaining and self-adjusting the given mode of operation. The modern technology of blowing - filling - sealing is of great

interest. This is a rational way of packaging liquid medicines, in which containers (containers) of all types made of polyethylene, polypropylene, polystyrene, polyvinyl chloride and other similar materials can be obtained by blowing, filled and sealed within one continuous technological cycle and one automatic complex. The cycle begins with the processing of granules of polymer materials. As a rule, thermoplastic is extruded by a screw press and formed by the extruder head into a tube of a certain diameter. When the tube reaches the desired length, the lower die is closed, the clamps hold the tube in position, and the cutter separates it from the extruder head. At the end of this operation, the closed mold moves in the direction for blowing, filling and closing the container. For this, a special core is immersed to the level of the lower mold, and after blowing with a sterile jet of air, the walls of the hot tube stick to the walls of the mold. At the same time, a liquid medicine is fed into the resulting container through the feeder and the dispenser. When the container is filled, the air contained in it is discharged through the outlet channel. Upon contact with the liquid, the wall of the container instantly solidifies, the core returns to its original position, and the mold closes, simultaneously forming the neck of the container, and the hermetically sealed container leaves the installation.

This method guarantees the complete sterility of the containers, because before the formation of the tube, the granules of the polymer material, which are in the extruder for several minutes under a pressure of 20.6-24.5 MPa and at a temperature of 160-230 °C, are completely sterilized. But the production of polymer containers on other types of equipment requires their sterilization. In addition, polymer droppers, cannulae with a syringe needle and protective caps must be subject to mandatory sterilization. When sterilizing products made of polymer materials, possible changes in the properties of these materials under the influence of sterilization factors should be taken into account. An incorrectly chosen sterilization method leads to significant changes in the operational properties of polymers as a result of complex processes after sterilization aging. To protect the polymer product from adverse (most often destructive) conditions of sterilization and other types of processing, various low-molecular compounds, including stabilizers, are introduced into the composition of the polymer, which give the finished product a set of necessary consumer properties. Recently, structural stabilization of polymers, which does not require the introduction of chemical additives, is most often used. For medical polymers, this method, based on the action of ionizing radiation on the polymer in a vacuum, is the most promising, as it allows to reduce the intensity of oxidation processes occurring in the polymer matrix, without introducing chemical antioxidants into it. Structural stabilization methods are widely used for radiation modification of polyethylene and allow changing its physicochemical, thermal and electrophysical properties, relaxation and chemical stability, durability, etc. in the desired direction. After radiation treatment, polyethylene acquires a "memory effect", first described by Charlesby (1962). This effect consists in the property of the polymer to "remember" a certain state in which it was irradiated. In the future, this

sample can be deformed or stretched to another state, but when heated, it again restores its original shape and dimensions. Increased radiation and temperature strengthen and accelerate the ability of polyethylene to recover from deformation, while increasing its strength.

Products made of polymer materials, as a rule, require the use of cold sterilization methods. This is explained by the fact that most medical polymers are sensitive to high temperatures, which can cause various changes in their mechanical and physicochemical properties. The most promising methods of sterilizing such materials are the use of a number of chemical compounds that have a sterilizing effect in the gaseous state, as well as various types of ionizing radiation. The use of gases for sterilization of medicinal products is called gas sterilization, which has certain advantages: — allows sterilization of medical products in the final packaging obtained from almost any polymer materials; — capable of disinfecting solutions with thermolabile substances; — capable of sterilizing products in additional packaging made of polymer films, which guarantees long-term preservation of sterility. However, this method is not without flaws. Due to the fact that all the gases used are toxic to humans, it is necessary to carefully follow the safety rules. In addition, the slow removal of sterilization gases dictates the need for long-term ventilation of sterilized objects (from several hours to 6-7 days). Some researchers proposed multiple vacuuming of sterilized objects to speed up the gas desorption process. The gases used include ethylene oxide, bromomethyl, propylene oxide, glutaraldehyde, ozone, P-propiolactone, etc. In recent years, ethylene oxide is often used as a sterilization gas. One of the reasons for the widespread use of ethylene oxide in the sterilization of polymer products is its exceptionally high ability to diffuse into polymer materials, which allows the sterilization of finished products in hermetic packaging. According to its technological and economic indicators, sterilization with ethylene oxide successfully competes with ionizing radiation, and unlike the latter, ethylene oxide practically does not affect the physical and chemical properties of containers. Gas sterilizers, such as "ETO" (Italy), "Etoxenom" (Czech Republic), etc., work on this principle. However, ethylene oxide is explosive and, due to its exceptionally high reactivity, can react with stabilizers in various polymer compositions, changing their properties. Therefore, during gas sterilization, it is necessary to include such a stabilizer in the polymer matrix, which would not only have the properties of an antioxidant, but also protect the polymer from the chemical influence of the sterilizing agent. To reduce the explosiveness of ethylene oxide, carbon dioxide is introduced in a ratio of 9:1.

Ointments, pastes, liniments, creams, gels. they are packed in aluminum or plastic tubes, cans made of fiberglass with a screw neck or glass wire with a triangular crown. Aluminum tubes for medical ointments are made of two types: ordinary and with an elongated spout. Both types of tubes are produced in different capacities from 16 to 136 cm3, and for tubes with a spout smaller ones are provided: 4.8-13.5 cm3. The inner surface of the tubes is covered with a protective varnish, and the outer surface is covered with a

decorative water-resistant enamel, on which a label is applied. The series number is stamped on the shank of the tube when it is sealed. Two types of plugs are available for plugging tubes: polygonal and conical elongated fluted plugs for ordinary tubes and an extended plug for plugging tubes with a spout. If the composition of the ointment includes antibiotics, poisonous or easily oxidizing substances, then they are often dosed in a small package or in a package for one-time use. The tube scheme is shown in fig. 13. Recently, various devices have been created for dosed delivery of tube contents. An example of such a device can be a package consisting of a main and a dosing chamber with a valve between them. When the outlet opening is opened, the valve blocks the supply of product from the main chamber to the dosing chamber. The machine of the UFM-2 model, which consists of the following main units, packages soft medicinal forms: a valve-piston dispenser and a hopper. All nodes and the drive are mounted in the case. Productivity is regulated by changing the gear ratio of the V-belt transmission. The dose is adjusted by changing the stroke distance of the piston. The piston of the dispenser acquires reciprocating motion from the drive through an eccentric. Open the faucet of the dispenser and fill the container (tube or can, etc.).

2.2. Questions (test tasks, tasks, clinical situations) to check basic knowledge on the subject of the lesson:

Answer the theoretical questions. 1. Basic terms and definitions related to the packaging of medicinal products. 2 GMP requirements for the packaging of medicinal products. 3. Requirements for primary packaging materials. 4. The impact of packaging on the stability of finished products. 5. Capping agents. Classification, assortment. 6. Containers for medicines. Assortment. 7. Requirements for materials for the manufacture of consumer containers and sealing means.

III. Formation of professional skills and abilities:

3.1. Content of the task of practical work:

1. Machines for packing tablets in polymer film and foil. Marking Packages with a medicinal product (or substance) must be clearly labeled with the following information: Producing country. Manufacturing company, its trademark, legal address. The manufacturer of the medical device (if it does not coincide with the manufacturer). The name of the drug in Latin and Ukrainian or Russian (for Ukraine) languages. The Latin name should be written in a smaller font than the name in Ukrainian or Russian languages. The composition of the drug (the concentration of active components is indicated), activity, amount of the drug. Purpose of the drug (for injections, external, etc.). The number of the registration certificate, which is usually denoted by the letter "P", followed by numbers indicating the year of its registration by order of the Ministry of Health of Ukraine, followed by four dots - the number of this order and the item to which this medicinal product belongs. Warning labels ("Sterile", "Use as prescribed by a doctor", etc.). Storage conditions. Expiration date. In data on expiration dates, Roman numerals indicate the month, Arabic numerals indicate the year.

Bar code. Serial number consisting of digits, where the last four are mean the month and year of production of this product, and the previous ones are the production number. Price. For injectable drugs, where it is impossible to place all the information on the ampoules, it should be minimal in the scope of points 4, 5, 12. In addition to labeling, instructions for use are placed on the secondary packaging. In order to prevent falsification of labeling, manufacturing companies began to introduce quality control of the material (usually polymer) packaging into NTD. At the same time, as a rule, thermal methods of determination are used (softening temperature, etc.) or the manufacturer's trademark, the name of the drug, etc., are applied to the polymer packaging by the method of hot embossing.
2. Analyze the labeling proposed by the teacher.

3.2. requirements for work results, including to registration; According to the progress of the practical lesson, complete the individual task in your workbook.
3.3. requirements for work results, including registration; According to the recommendations (instructions) for the tasks.
2.4. control materials for the final stage of the lesson: problems, assignments, tests, etc.:
1. How to store herbal medicinal raw materials; 2. How to avoid oxidation processes when storing medicines; 3. Determine the characteristics, requirements for medicinal products; 4. Conditions of industrial production, storage, packaging and labeling of drugs according to the rules of GMR.

IV. Summing up

List of recommended literature:

Main:

- Промислова технологія лікарських засобів: базовий підручник для студ. вищ. навч.закладу (фармац. ф-тів) / Є. В. Гладух, О. А. Рубан, І. В. Сайко [та ін.] – Х. : НФаУ : Оригінал, 2016. – 632 с. : іл.
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- Сучасні фармацевтичні технології: навч. посіб. до лабораторних занять магістрантів денної, вечірньої та заочної форми навчання спеціальності 8.110201 «Фармація» / під ред. О.А. Рубан. – Х.: Вид-во НФаУ, 2016. – 256 с.
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Electronic information resources

1. Department of pharmaceutical chemistry and drug technology of ONMedU – website of the Department of pharmaceutical chemistry and drug technology of ONMedU
2. Scientific library of ONMedU (odmu.edu.ua) - Scientific library of ONMedU
3. www.moz.gov.ua – official website of the Ministry of Health of Ukraine
4. Odessa National Medical University (onmedu.edu.ua) – ONMedU official website
5. State Register of Medicinal Products of Ukraine. - [Electronic resource]. - Access mode: http://www.drlz.com.ua/ − as of 10.01.2017.

Practical lesson №8

Topic: Familiarity with the work of the department of quality control of medicines and the central factory laboratory.

Purpose: familiarize yourself with the categories, structure of regulatory documentation and industrial production of drugs according to the rules of GMR; know the definition of characteristics, requirements for medicinal products; to analyze the expansion of the assortment of industrially produced medicinal products, the organization of the production of pharmaceutical enterprises.

Basic concepts: technological regulation, GMP, regulatory and technical documentation, excipient, production stage.

Equipment: production schemes, device samples.

Study time: 6 hours.

I. Organizational moment.

II. Control of reference knowledge

2.1. Requirements for students' theoretical readiness to perform practical classes (knowledge requirements, list of didactic units)

Requirements for theoretical knowledge:

Basic principles of GMP. The main principle of GMP is that the drug manufacturer must establish and implement an effective quality assurance system, including the active participation of management and all personnel. A quality system is a set of organizational structure, methods, processes and resources necessary for the implementation of the quality management process. The GMP standard is intended for the construction of quality systems at enterprises that produce medicinal products. Chapter 1 "Quality Management" outlines the fundamental concept of the quality assurance system during the production of medicinal products. In the following sections, its principles and rules are considered in more detail so that they can be adequately interpreted, as well as successfully applied in the development and implementation of quality systems at manufacturing enterprises. The main principle regarding personnel is as follows: since the quality system and production depend on people, the staff must be staffed with a sufficient number of qualified personnel who are able to solve all the tasks in the field of responsibility of the enterprise at an appropriate level. Each employee must clearly know his powers and responsibilities, as well as be aware of individual responsibility (they should be reflected in the job instructions), know and strictly follow the GMP rules when performing his job duties. All employees are required to undergo detailed training on the principles and rules of GMP, including the rules of personal hygiene; then in the process of activity, they should regularly upgrade their qualifications. The following principle applies to premises and equipment that must be designed, located, constructed, fitted out, fitted out, maintained and maintained in such a way that they are fit for purpose and suitable for the intended work. their size, design and location should minimize the risk of production errors and ensure effective cleaning and operation in order to avoid cross-contamination, accumulation of dust and other contaminants that can negatively affect product quality. If the location of the premises and the technical level of the equipment do not ensure the quality of the products, then their modification is required. Documentation is an important part of the quality assurance system. It should regulate all aspects of production and quality control of medicinal products. The production of medicinal products must be carried out according to technological regulations, taking into account the principles and rules of good manufacturing practice (GMP). This is necessary to obtain finished products of the required quality that would meet the requirements of registration and license documentation. Compliance of registration and license documentation and authorization of significant changes by authorized state bodies is the most important provision of all GMP standards and EU directives. Production control and validation are necessary production links. Validation is an expert assessment and provision of documented objective evidence in accordance with GMP principles, which confirms that

any objects really meet their purpose and established requirements, and their use leads to the expected results. The next principle of GMP belongs to quality control. Quality control includes works related to sampling, regulatory documentation (specifications) and tests, as well as methods of organizing these works, their documentation and issuance of permits in the prescribed manner, which ensure that all necessary tests are actually carried out. Raw materials, materials, intermediate products and intermediate products are not allowed for use, and finished products are not allowed for sale until their quality is recognized as satisfactory. The main requirement for quality control is its independence from production.

A separate section of GMP is devoted to works performed under a contract. It states that when analyzing the contract, all conditions of production and/or testing must be clearly and comprehensively defined, agreed and controlled in order to avoid misunderstandings and inconsistencies that may cause unsatisfactory quality of products, work performed or tests. It is also important to have a written contract (agreement) drawn up according to the established procedure between two legal entities, called respectively the Customer and the Executor. The contract must have legal force, and it must clearly define the rights and obligations of each party, in particular compliance with GMP rules. In the contract, it is necessary to determine the procedure for issuing a permit for the sale of each series of products or a quality certificate by an authorized person. The GMP rules delineate the responsibility between the Contractor and the Customer before the authorized state bodies that carry out registration and licensing, but they do not concern the mutual responsibility of the Customer and the Contractor for the quality of products (services) to the consumer, which they bear in accordance with the legislation of Ukraine. The following principle states that all complaints and other information about non-conformance of potentially defective products should be thoroughly investigated according to standard operating procedures. A system must be organized at the manufacturing enterprise, which allows, if necessary, to quickly and effectively recall the sold products, if there are established or possible quality defects in them. And, finally, the last inviolable principle: self-inspection and quality audit should operate at the enterprise, the purpose of which is to comprehensively supervise the implementation of GMP rules and, if necessary, make recommendations for preventive and corrective actions. If we summarize the rules of GMP as a single document regulating the quality system of the enterprise, then their essence is as follows. Each individual rule of GMP is quite clear, but they must all be implemented in a complex, creating a quality system. It was because of the violation of this principle that it was not possible to introduce RD 64-125-91, which was deprived of a number of GMP rules, and therefore assumed the existence of individual elements of GMP at enterprises, rather than modern quality systems. The second feature is that GMP regulations set requirements, but do not provide specific technical solutions. A clear example is the requirements for premises and equipment. For example: "The premises must be located in such a way as to minimize the risk of contamination" or: "The equipment must correspond to its purpose and the intended

technological process." The technical decision remains with the enterprise, i.e. the management and the entire team should not simply fulfill the "will" of the standard, but show a creative approach, since the GMP standards regulate what exactly needs to be done, but do not specify how. Often, the means of implementing technical solutions are very complex and expensive. The complexity also increases because these means must not contradict the legislation of Ukraine, as well as legal regulations. In connection with this, there was a need to bring SNS of the 80s into line with the modern level of technology. Therefore, from January 1, 1997, the design and construction of new, expansion of existing enterprises and production facilities began to be carried out only in accordance with GMP rules. Reconstruction and technical re-equipment of enterprises taking into account GMP rules has been introduced since June 1, 1998.

3 01.01.2002 GMP rules become mandatory in Ukraine. The transition to the production of medicines according to the new principles and rules will be carried out in stages, according to schedules that will be developed for each enterprise.

2.2. Questions (test tasks, tasks, clinical situations) to check basic knowledge on the subject of the lesson:

Answer the question: 1. Name the main regulatory and technical documents that regulate the activity of a technologist and are used for the preparation of medicinal products; 2. What do you know about the general principles of production of ready-made medicinal forms; 3. What categories and structure of regulatory documentation exist; 4. Name the main terms used in the production of medicinal products; 5. How the technological process, production regulations, technical and economic balance is planned; 6. Determine the characteristics, requirements for medicinal products; 7. Conditions of industrial production of drugs according to the rules of GMR.

III. Formation of professional skills and abilities:

3.1. Content of the task of practical work:

1. Basic terms of the industrial technology of drugs. 2. Organizational structure of the pharmaceutical enterprise, characteristics of its shops and branches 3. GMP requirements for the organization of production and quality control of medicinal products 4. Normative documentation in the production of GLZ 5. Basic provisions of the technological regulations for the production of medicinal products Educational tasks for practical work:

Task No. 1 Determine the category of NTD: A) technological document of current serial production of goods. B) a technological document that completes scientific research in laboratory conditions during the development of a technology for the production of a new type of product or a new technological method of production for mass-produced products.

Task No. 2 Determine the NTD, approved for a limited period, which establishes quality requirements for medicinal products or medicinal plant raw materials.

Task No. 3 Determine the functions of the technological control department at pharmaceutical enterprises.

Task No. 4 Determine the NTD, approved for a limited period, which establishes quality requirements for medicinal products or medicinal plant raw materials.

Task No. 5 Compile the organizational structure of regulatory documentation at the pharmaceutical enterprise.

3.2. requirements for work results, including to registration; According to the progress of the practical lesson, complete the individual task in your workbook.
3.3. requirements for work results, including registration; According to the recommendations (instructions) for the tasks.
2.4. control materials for the final stage of the lesson: problems, assignments, tests, etc.:
1. Organizational structure of the enterprise and connection schemes of its divisions. 2. The structure of regulatory and technical documentation at pharmaceutical enterprises. 3. Basic principles of the drug registration system. 4. The main parts of the registration dossier. 5. Specifications for raw materials, intermediate products, and finished products. 6. Quality control of medicines at a pharmaceutical enterprise. 7. The essence of the material balance. 8. How does the material balance of the series differ from the material balance of the stage? 9. What documents reflect the content of the technological regulations? 10. What are the main indicators of raw materials reflected in the certificate?
Repetition of test questions.

IV. Summing up

List of recommended literature:

Main:

- Промислова технологія лікарських засобів: базовий підручник для студ. вищ. навч.закладу (фармац. ф-тів) / Є. В. Гладух, О. А. Рубан, І. В. Сайко [та ін.] – Х. : НФаУ : Оригінал, 2016. – 632 с. : іл.
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