MINISTRY OF HEALTH OF UKRAINE
ZAPORIZHZHIA STATE MEDICAL AND PHARMACEUTICAL UNIVERSITY
DEPARTMENT OF MEDICINES TECHNOLOGY

THE TECHNOLOGY OF MEDICATIONS

ISSUES OF PHARMACEUTICAL MANUFACTURING

Manual to practical classes in
for pharmaceutical students 4-d year study
specialty 226 “Pharmacy”
Second edition, revised and enlarged

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P56

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P56 The issues of pharmaceutical manufacturing for pharmaceutical students 4-d year of study speciality 226 “Pharmacy” Second edition, revised and enlarged / Burlaka B.S., Gladyshev V.V., Nagorniy V.V., Puchkan L.O.,Gladysheva S.A. – Zaporizhzhia, 2024. – 109 p.

Based on the requirements of the Technology of Medications Work Program, this book presents the main theoretical issues and provides practical tasks for compounding of medicines – Maximum purified preparations, tablets, injectable solutions capsules etc. The book contributes to the students comprehension and visualization of Pharmaceutical Compounding and designed in a clear scheme.

Заснований на вимогах робочої програми з технології ліків, цей посібник представляє основні теоретичні питання та практичні завдання стосовно промислового виготовлення максимально-очищених препаратів, таблеток, ін’єкційних засобів, капсул. Складений за прозорою схемою, посібник сприяє розумінню та уявленню студентами промислового виготовлення ліків.

SAFETY RULES

• Laboratory coats and caps provide an important barrier for your clothes and, more important, your skin from chemicals. The laboratory coat should fit comfortably, have long sleeves, and should be clean.

• The coats, backpacks, etc., should not be left on the lab benches and table.

• Eating, drinking, and smoking are strictly prohibited in the laboratory.

• Long hair must be tied back when using open flames.

• Learn where the safety and first-aid equipment is located. This includes fire extinguishers, fire blankets, and eye-wash stations.

• Always wash your hands before leaving the lab.

• Inform the teacher immediately in case of an accident.

ORGANIZATION AND METHODOLOGY OF PRACTICAL TRAINING

The pharmaceutical technology course includes practical sessions that take place in well-equipped educational laboratories. These labs contain apparatus that replicates real-world industrial conditions for manufacturing medicines. During lab sessions, students are required to wear white lab coats, hats or headscarves, and appropriate footwear. Each student is assigned their own workstation. Adherence to strict personal hygiene and safety rules is crucial while working in the laboratory. Additionally, student protocols are in place to maintain orderliness and ensure compliance with safety measures. Methods for conducting practical exercises involve assessing students' initial knowledge levels through technical instructional objectives and testing. The teacher engages the entire academic group in discussing key lesson topics both from their seats and at the blackboard, incorporating visual aids like graphs, tables, diagrams, and slides. The lessons delves into common equipment and potential challenges that may arise during the technological process of producing dosage forms. Practical tasks are executed based on the teacher's instructions.

Progress reports on the work conducted are presented to the teacher in the form of structured protocols (lab reports) and manufactured medications. The testing methodology encompasses several steps. Following the provided prescription, the student drafts a technological plan for drug production and rationalizes the appropriate equipment for the process. Utilizing the technological parameters furnished by the teacher, the student calculates the working formulation of the drug. If needed, the formulation is standardized, accounting for the quality parameters specified by the teacher.

Lesson No1

Topic: Maximum purified preparations. Biostimulators. Preparations of fresh plants

Didactic goals and motivation of the lesson: to become familiar with the methodology of conducting laboratory sessions in the pharmaceutical manufacturing course, to comprehend safety instructions, to grasp the layout of technological production protocols, to acquire proficiency in creating material balances, and to tackle contextual challenges. Gain an understanding of the composition of machinery and equipment used for grinding and sieving.

THEORETICAL QUESTIONS

1. Definition of the concept of neogalenic preparations, characteristics, and differences from galenic preparations.
2. Specific methods of primary purification – fractional precipitation, solvent change, solvent extraction, chromatography, dialysis. Apparatus.
3. Extraction process in liquid-to-liquid systems. Main Types of Extractors Used in Liquid-to-Liquid Systems
4. Classification of neogalenic preparations. Private technology of lantoside, adoniside, corglycone, ergotal, raunatin, silibor, flamin, plantaglucid, caleflon, avisan.
5. Standardization of new galenic preparations. Packaging. Storage. Nomenclature of injectable neogalenic preparations.
6. Preparations of biogenic stimulants, their properties, and nomenclature.

METHODOLOGY OF PRACTICAL WORK

After the safety briefing, the students proceed to the self-production of adoniside, starting with the circulating extraction of the Montenegrin grass. To do

this, 25.0 g of crushed medicinal plant raw materials are placed in paper, a Soxhlet-type device is mounted, a water bath is turned on and extraction is carried out until exhaustion. The number of circulating drains is fixed in the regulations. The resulting extraction is distilled to 25 ml of residue. After that, 25 ml of purified water is added to the distillation flask and the distillation is continued until the alcohol and chloroform are completely removed. The resulting preparation is cooled and filtered through a pleated filter with a layer of 0.1 – 0.2 g of aluminium oxide applied to it. The filtrate is standardized using sodium nitroprusside. The finished drug - adonizide is packed in dark glass flasks and labeled.

During the extraction period, other educational issues of this lesson are considered, with special attention paid to the ability to read the instrumental schemes for the production of adoniside, lantoside, corglycone, ergotal, raunatin, plantaglucide. During independent work, students' knowledge is tested on the independently studied topic "Preparations of fresh plants", the ability to solve situational problems.

PRACTICAL TASKS

1. Calculate the volume of the finished adonizide (25 LED) if the production result is 37.5 liters of semi-finished product with an activity of 32 LED.

Answer: 48 L

2. How much diluent should be added to 75 litres of adonizide concentrate with 86 LED activity to bring it up to the standard (25 LED)?

Answer: 183 l.

3. Calculate the volume of 95% ethanol required to stabilize 100 liters of adoniside.

Answer: 21,053 liters

4. How much chlorobutanol hydrate should be added to 120 L of adoniside?

Answer: 0.6 kg.

5. Calculate the amount of the finished product, the volume of diluent, the amount of alcohol 96% and chlorobutanol hydrate to be injected when bringing 50 liters of adonizide concentrate with an activity of 95 LED to the standard.

Answer: 190 l; 140 l; 39.583 kg; 0.95 l;

6. In the production of digalene-neo for internal use, 36 liters of the drug with an activity of 8.2 LEDs were obtained. Bring to the standard (6 LED) by calculating the quantities of diluent, glycerol of pharmacopoeial qualification (90%) and chlorobutanol hydrate required for this, and the amount of finished product.

Answer: 49.2 L; 32.8 l; 1.48 l

7. Bring 100 liters of lantoside with 8 LED activity to the standard (10 LED), using a preparation with 14 LED activity for strengthening. How much of the product should be added?

Answer: 50.0 L

8. Determine the amount of alcohol (anhydrous) contained in 190 l of 97% of the introductory alcohol solution with a temperature of +25°C.

Answer: 183,293 L

9. How many liters of 96.5% alcohol should be measured at -3°C to get 100 decaliters of alcohol (water)?

Answer: 101,179 dcl

10. In the production of lantoside at the stage of solvent extraction of glycosides, 100 liters of 96% ethanol measured at a temperature of +21°C were consumed.

Answer: 95.89 L

11. As a result of alcohol recovery, 300 liters of distillate containing 86.2% ethanol and having a temperature of +23.5°C were obtained from lily of the valley leaves.

Answer: 257,652 L

12. When preparing the extractant for the production of lantoside (24%), 125 liters of 96.6% alcohol were measured at a temperature of +15.8°C. Calculate the amount of alcohol (anhydrous) used at this technological stage of production.

An example of solving problem No. 5:

95 LED 25 L

25 LED

0 LED 70 L

95 L

25 L (95 LED) require diluent 70 L

50 L (95 ICE) require X1 diluent

X1 = (50 ● 70) : 25 = 140 L

From 25 liters (95 LED) you get 95 liters of finished product (25 LED)

From 50 liters (95 ICE) you get. X2 of finished product

X2 = =(50 ● 95) : 25 = 190 L

2. How much 96% ethanol is required to preserve 190L of adoniside?

X = (P ● b) : a = (120 ● 20) : 96 = 39.583 L

3. How much chlorobutanol hydrate should be added to the product?

X = (190 ● 0.5) : 100 = 0.95 kg

SOME THEORETICAL ISSUES

New galenic or maximally purified preparations are a group of phytopreparations containing a complex of active substances in their native (natural) state, maximally freed from concomitant substances.

New-galenic preparations differ significantly from galenic preparations in the almost complete absence of ballast and concomitant substances, therefore, in their pharmacological action, they are close to chemically pure substances. Deep purification of extracts and isolation of individual biologically active substances makes it possible to increase their stability, significantly reduce side effects and use them for injection. Unlike galenic preparations, which are often standardized for extractive substances, new-galenic preparations are produced by standardized biological or chemical methods for active substances.

All neogalenic preparations can be divided into 2 groups: total preparations and preparations of individual substances. The technology of their production is characterized by an individual approach due to the nature of the initial medicinal plant raw materials, the properties of the active and accompanying substances, as well as the nature of the resulting drug. The process of obtaining individual substances is more complex and multi-stage, mainly at the stages of their isolation and purification.

General technological scheme for the production of neogalenic preparations:

– Preparation of medicinal plant raw materials and preparation of the selected extractant.

– Extraction of raw materials.

– Purification of the resulting extraction (pre-cleaning and deep cleaning).

– Concentration of extraction.

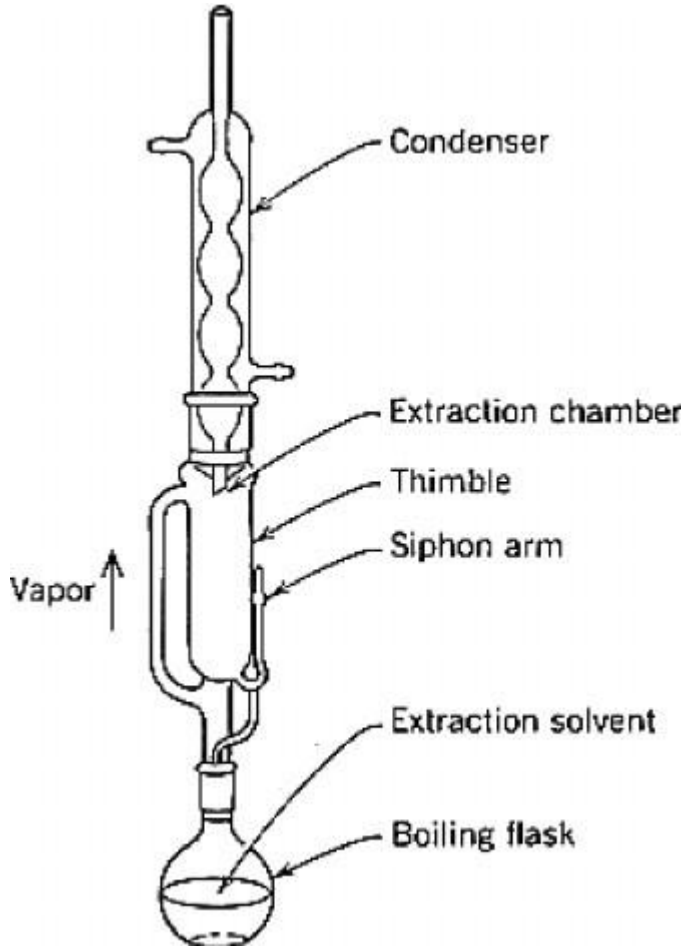
– Obtaining a complex (summative) drug.

– Isolation of highly purified individual substances.

– Standardization of the finished product.

– Product packaging and labeling.

At the stage of extraction of plant raw materials, special attention is paid to the choice of extractant and the method of extraction. The extractant is selected experimentally, taking into account selectivity, i.e. that it extracts the complex of active substances as much as possible and ballast substances as little as possible. This explains the use of a mixture of solvents. In the production of novogalenic preparations, along with widely used extractants (ethanol, water), aqueous solutions of acids, salts, mixtures of ethanol with chloroform or methylene chloride are used.



Img 1. Schematic of a Soxhlet extractor
(site:images.google.com)

Countercurrent extraction, maceration with extractant circulation or mechanical mixing, and circulation extraction (if volatile extractants are used) are most widely used in the production of maximally purified preparations. Sometimes the raw material is specially processed before extraction (fermentation, in the production of digitoxin).

At the stage of purification, the extractions are subjected to sequential processing, the purpose of which is to purify and isolate a complex of active substances or individual biologically active substances free from concomitant substances.

The sequence of purification and isolation stages is as follows:

Separation of insoluble substances. Filtration, centrifugation, sedimentation, decantation, protein denaturation and salting are commonly used for this purpose. Protein denaturation is often used to purify extracts, which is carried out by means of temperature exposure

Maximum purification of biologically active substances**.** At the stage of purification of biologically active substances, there is usually a separation of impurities, as well as further concentration of the product. In this case, solvent replacement, fractional precipitation of active or ballast substances, extraction in liquid-liquid systems, separation using membranes, and various sorption-chromatographic methods are most often used.

Final purification and separation of highly purified biologically active substances**.** Fractional precipitation, crystallization, spray drying, freeze drying (freezing) are commonly used.

Precipitation is a process in which the addition of certain reactants or a change in physicochemical conditions causes a solute (most often protein) to precipitate.

Salting. It is known that the solubility of proteins in salt solutions is lower than in pure water. The addition of salt to a protein solution causes the solubility of the

protein to become lower than its concentration in solution at a certain salt concentration, and the protein begins to precipitate.

Precipitation with organic solvents. Precipitation of biopolymers with organic solvents, carried out during cooling, is one of the most common methods of concentrating solutions containing proteins, mucilage, pectins. When an organic solvent (ethanol, methanol, isopropanol, acetone, etc.) is added to the extraction, the dielectric constant of the medium is reduced.

Fractional precipitation can be achieved by solvent change, when extracted with a non-polar or low-polar (organic) solvent, the extraction is purified from hydrophobic substances (chlorophyll, resins, etc.) by removing (distilling) the extractant and adding a polar solvent (water) to the residue.

Dialysis is the process of purification of solutions of high-molecular substances from low-molecular-weight substances dissolved in them using a semi-permeable membrane. The method is based on the properties of biopolymer molecules, which have large sizes, not to pass through semi-permeable membranes, while substances with smaller molecule sizes pass through them quite freely. For dialysis, films of gelatin, cellophane, collodion, nitrocellulose, parchment, reinforced cellophane and other materials.

Sorption is the process of absorption of gases, vapors, dissolved substances by solid and liquid sorbents. There are several types of sorption – adsorption, absorption and chemisorption.

Adsorption is the absorption of a substance on the surface of the sorbent. The adsorption process is selective and allows certain substances to be adsorbed from the solution. Adsorption occurs due to the interaction of intermolecular attraction forces in nonpolar adsorbents (activated carbon) and electrical interaction forces in polar adsorbents (silica gel).

Affine chromatography. Sorbents for affine chromatography are mainly polymers used for gelling chromatography after targeted modification (agarose, polyacrylamides, celluloses, porous glasses).

Raunatin. A preparation containing a sum of alkaloids (reserpine, serpentine, aimaline) is obtained from the roots of Rauwolfia serpentina. The extraction of the sum of alkaloids from finely ground raw materials is carried out with a 10% acetic acid solution, since the raw material contains a group of bases, using countercurrent extraction in a battery of extractors. First, 1 part of the raw material is used to obtain parts of the extract containing 0.5 - 0.8 % alkaloids. The hood is then transferred to a reactor to isolate the alkaloids – bases, for which it is alkalized with a 25% ammonia solution to pH 9-10. This is followed by solvent extraction with chloroform or methylene chloride for 30 minutes. After the separation of the phases (settling method), a layer of organic solvent is lowered into a separation column. And 1-2 more times it is blurted out with chloroform or methylene chloride until a negative reaction to alkaloids. The hood collected in the separation column and containing 0.7% alkaloids is thickened under vacuum to 0.25% of the feed feedstock.

TEST QUESTIONS

Questions contain five answers and only one correct answer (example with an asterisk).

1. What are new-galenic preparations characterized by?

A) Containing synthetic active substances.

B) Having a high content of ballast substances.

C) * Being maximally purified from concomitant substances.

D) Being standardized for extractive substances only.

E) Being less stable compared to galenic preparations.

2. What is the primary purpose of using a mixture of solvents in the extraction process of plant materials?

A) To increase the concentration of the product.

B) To dissolve insoluble substances.

C) * To maximize the extraction of active substances and minimize ballast substances.

D) To standardize the final product.

E) To precipitate proteins during extraction.

3. Which extraction methods are most commonly used in the production of maximally purified preparations?

A) Reflux extraction and filtration.

B) * Countercurrent extraction and maceration with circulation of extractant.

C) Simple maceration and drying.

D) Distillation and crystallization.

E) Simple boiling and evaporation.

4. What is the role of fractional precipitation in the purification process?

A) To remove chlorophyll from the extract.

B) To increase the concentration of ballast substances.

C) To isolate highly purified biologically active substances.

D) To standardize the final product based on extractive substances.

E) To neutralize the pH of the solution.

5. What is dialysis used for in the context of new-galenic preparation?

A) To concentrate solutions of proteins and mucilage.

B) To purify high-molecular substances from low-molecular substances using a semi-permeable membrane.

C) To dissolve hydrophobic substances in the extract.

D) To crystallize individual biologically active substances.

E) To freeze-dry the final product.

6. What is a key difference between galenic and new-galenic preparations?

A) New-galenic preparations contain more ballast substances.

B) Galenic preparations are free from concomitant substances.

C) New-galenic preparations are closer to chemically pure substances in their pharmacological action.

D) Galenic preparations are only used for injection.

E) New-galenic preparations are standardized for extractive substances only.

7. Which stage in the production of new-galenic preparations involves removing insoluble substances?

A) Standardization of the finished product.

B) Extraction of raw materials.

C) Initial purification of extracts using filtration, centrifugation, sedimentation, and decantation.

D) Product packaging and labeling.

E) Final purification using dialysis.

8. What is the purpose of using protein denaturation in the purification process?

A) To increase the solubility of proteins in organic solvents.

B) To selectively extract active substances from plant materials.

C) To purify extracts by separating proteins from other components.

D) To reduce the concentration of the active substance.

E) To neutralize the pH of the extract.

9. What does the process of sorption involve?

A) Dissolving gases and vapors in liquid solvents.

B) The absorption of gases, vapors, or dissolved substances by solid or liquid sorbents.

C) The evaporation of solvents to concentrate extracts.

D) The crystallization of active substances from solutions.

E) The chemical reaction between sorbents and solvents.

10. What is the significance of using ethanol mixed with chloroform or methylene chloride in the extraction process?

A) To increase the solubility of proteins.

B) To enhance the selectivity of the extraction process for active substances.

C) To reduce the concentration of ballast substances.

D) To facilitate the standardization of the final product.

E) To purify hydrophilic substances from the extract.

Lesson No2

Topic: Technology of individual substances medications. Rutin

Didactic goals and motivation of the lesson: The student must acquire and consolidate theoretical knowledge on the topics, learn the principles of obtaining . to master the basic methods of purification of natural substances, to be able to read the instrumental diagrams of such natural substances as digitoxin, digoxin, celanide, ergotamine hydrotartrate, ergometrine maleate.

THEORETICAL QUESTIONS

1. Definition of the concept of individual preparations of natural substances, their difference from new galenic and galenic preparations. Dosage forms.
2. Methods of isolation, purification and standardization of preparations of individual substances.
3. Technological scheme of obtaining rutin.
4. Preparations of individual substances from digitalis, and knotweed. Technological scheme of production, dosage forms.
5. Enzyme preparations. Classification. Pepsin, pancreatin, deoxyriboculease, ronidase, lidase. Splenin.
6. Immobilized enzymes. Methods of immobilization. Examples of immobilized enzymes and their applications.
7. Enzymes of microbiological synthesis. Drugs and dosage forms.
8. General methods of organ preparations. Their classification. Insulin and insulin preparations.
9. Pituitary preparations.

10. Adrenal gland preparations.

METHODOLOGY OF PRACTICAL WORK

20.0 raw materials (buckwheat herbs) are placed in a porcelain beaker, poured with 120 ml of boiling water and extracted by boiling for 10-15 minutes (do not overheat!). The extraction is drained, the raw material is pressed on a press filter and re-extracted with 30 ml of boiling water for 10-15 minutes, pressed. The extracts are combined, filtered, evaporated in an evaporation cup to 8-15 ml of cubic residue, placed in a wide-mouthed flask, corked and left in the freezer of the refrigerator to crystallize the raw rutin for 0.5 – 1 hour. Heated until completely dissolved and quickly filtered through a filter previously treated with boiling water. A glass beaker (flask) with filtrate is left in the cold for 1 hour, the released rutin crystals are filtered on a nutch filter, washed with 1-2 ml of cold water, the liquid is sucked out again, removed from the filter paper, dried in the air.

During the period of recrystallization, routine examines educational issues on the topic of classes.

PRACTICAL TASKS

1. How much diluent should be added to 100 L of 0.08% celanide solution to bring it up to the standard (0.05%)? What is the volume of the finished product?

Answer: 60 l, .160 L

2. There are ergotamine hydrogen tartrate residues in the workshop: 40L with a concentration of 0.15% and with a concentration of 0.08%. What is the volume of the finished product (0.1%); will be obtained after blending these solutions? 35 L

Answer: 88 l.

3. In the production of ergometrine maleate, 45 liters of 0.018% solution were obtained. Bring the solution to the standard if the density of 0.02% of the solution is 1.025.

Answer: 0.878 g.

4. 10 litres of pituitrin solution were obtained, 1 ml of which contains 8 IU. Bring to normal (5 IU).

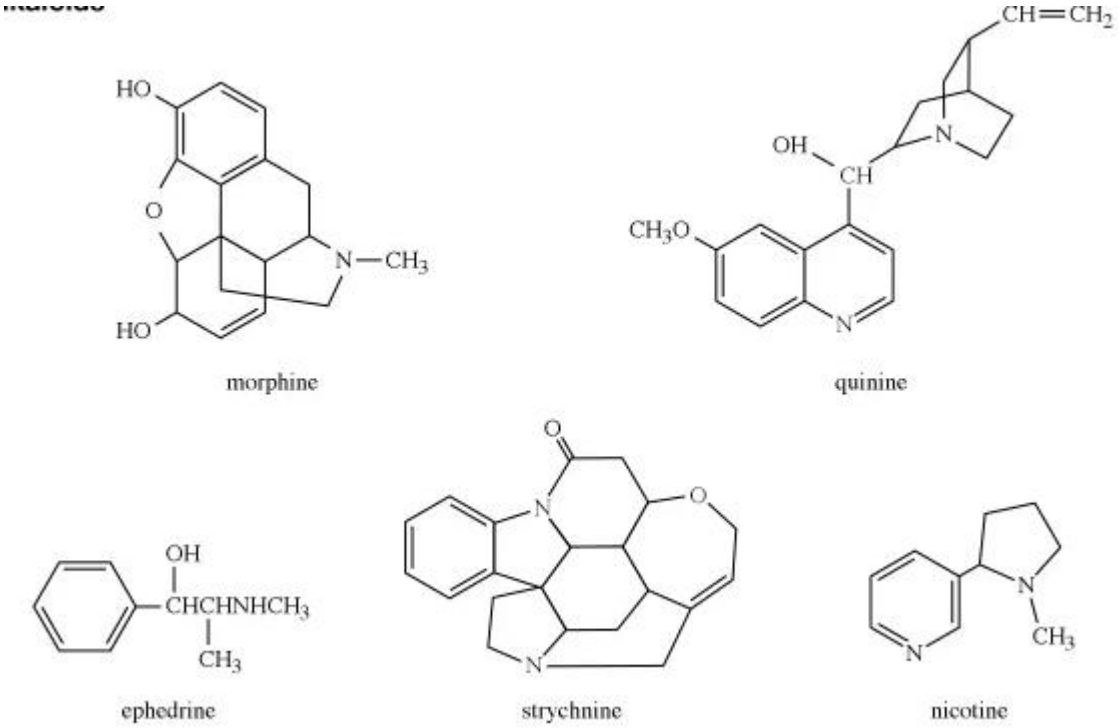
Answer: 6 L, . 16 L

5. How much phenol should be added as a preservative to 20 L of pituitrin solution for injection?

Answer: 55 g.

SOME THEORETICAL ISSUES

Alkaloids are structurally complex organic nitrogen-containing compounds of a basic nature, formed mainly in plant organisms. Of the entire plant world, alkaloids are synthesized by 10% of plants. The plant contains a mixture of several alkaloids, sometimes as many as 20, most of which are similar in structure, but some plants contain only one alkaloid. The content of alkaloids in raw materials can vary from tenths and hundredths of a percent (henbane leaves 0.01 – 0.07%) to 10-15% (cinchona bark, barberry roots). In plants, alkaloids are contained in the form of salts of organic acids: citric, succinic, malic, acetic, oxalic; Sometimes in the form of salts of mineral acids: sulfuric, phosphoric. Inorganic bases, as well as carbonates and hydrogen carbonates of sodium and potassium, convert alkaloids from salts into bases, which is widely used in the technology of extracting alkaloids from aqueous extractions. In the production of herbal medicines, the sum of alkaloids in the form of salts or bases is most often extracted.



Img. 2. Some alkaloids structure
(site:images.google.com)

Isolation and purification of alkaloids. To extract alkaloids in the form of salts, the raw material is treated with water or dilute acid (tartaric, citric, acetic) to convert the alkaloids into salts. Extraction is carried out by the countercurrent method. In this way, more concentrated extractions of alkaloids and with lower extractant costs are obtained.

Proteins, resins, tannins, etc., are extracted together with the active substances. To purify the concomitant substances, the acidic aqueous extraction is alkalized with an ammonia solution or, if permissible, with a solution of sodium hydroxide or carbonate. The base alkaloids that are formed in this process are extracted with an organic solvent that does not mix with water. This makes it possible to separate alkaloids from a large number of related substances: sugars, salts, proteins, and colouring substances. To separate pigments from alkaloids, a 1-5% solution of

hydrochloric or sulfuric acid is added. The base alkaloids become salts again, which pass into the water-acid layer, and all lipophilic compounds remain in the organic solvent.

To remove the residues of pigments, iron salts, etc., the aqueous solution of alkaloids is treated with activated carbon, after which the solution is filtered and again alkalized with a 25% ammonia solution to pH 11-12. The resulting solution of the alkaloid base is purer, and after the solvent has been distilled, it gives the so-called "sum of alkaloids", which is further processed. At the same time, 45-60% of alkaloids are extracted from plant raw materials.

The technological scheme for the production of alkaloids by ion exchange consists of the following stages:

1. Extraction of alkaloids from plant raw materials. Extraction is carried out with water or a dilute solution of hydrochloric or sulfuric acids, which depends on the basicity of the alkaloids and the nature of organic acids, in the form of salts of which alkaloids are contained in the raw materials.

2. Sorption of the sum of alkaloids on cationite, which is carried out under dynamic conditions in a battery of 4-5 column-type devices. The ionite layer is immovable, the extraction from the LRS moves according to the principle of direct flow, which makes it possible to saturate the ion exchange with alkaloids to the maximum.

3. Desorption of alkaloids in the form of a purified sum from cationite with a solution of ammonia in ethyl, methyl or isopropyl alcohol. The desorption process is carried out according to the principle of counterflow, whereby alkaloids are desorbed in the form of bases.

4. Isolation of alkaloids from alcohol-ammonia eluate using conventional chemical methods. As a rule, this is the distillation of alcohol in a vacuum with the precipitation of alkaloids

Features of the technology of preparations containing alkaloids

Ergotal *is a* preparation containing the sum of phosphoric acid salts of ergot alkaloids. The raw material for the production of ergotal is ergot, which contains seven pairs of stereoisomeric alkaloids. Each levorotatory and biologically active alkaloid corresponds to its dextrorotatory, practically inactive stereoisomer. Of these, 6 pairs of alkaloids: ergotamine-ergotaminin, ergostine-ergostinin, ergocristine-ergocritinine, ergocriptine-ergocriptynin, are a group of water-insoluble, and ergomitrin-ergomitrinin – water-soluble. Ergot alkaloids are very unstable compounds, sensitive to light, oxygen in the air, and high temperature. They easily change from one isomeric form to another, decompose and form strong complexes with their dextrorotatory isomers and solvents. Therefore, all operations for the isolation of ergot alkaloids are carried out at a low temperature in the carbon dioxide current.

Ergot is soaked in water at a temperature not exceeding 10°C for 1-2 hours. Swollen and washed ergot is passed through roller mills and turned into thin flattened plates with a large total surface. The crushed raw material is treated with an aqueous solution of hydrochloric acid in an extractor with a steam jacket, through which cold water is supplied. Under these conditions, mainly coloring and other concomitant substances pass into the solution, alkaloids are practically not extracted. The resulting extract is drained, and the ergot is extracted with an aqueous solution of hydrochloric acid (pH value 1.9-2.1) at a temperature not exceeding 10ºC.

Ergotal is a white or gray powder. It is available in tablets of 0.0005 and 0.001 g and in the form of a 0.05 % solution for injection in ampoules of 1 ml. The solution is prepared under aseptic conditions with the addition of a preservative - chlorobutanol hydrate 0.05 % and stabilizers - sodium metabisulfite, and tartaric acid. They are mainly used in gynaecological practice.

Ergotamine hydrotartrate is obtained by extraction from ergot horns. The extract is purified, the sum of alkaloids is obtained, ergotamine sulfate, ergotamine-benzene-crystals, ergotamine-acetone-crystals, ergotamine hydrotartrate are

isolated. All operations are carried out in a darkened room, under red light and low temperature.

ORGAN PREPARATIONS. FEATURES OF THE TECHNOLOGY

In modern conditions, most organ preparations are obtained by chemical synthesis and genetic engineering. But organs and tissues of animal origin are still an important source of raw materials for the production of prostaglandins, hormones, enzymes and other drugs of animal origin.

Raw materials for the production of organ preparations (tissues and glands) are obtained from healthy animals. Fresh organs contain a significant amount of water, ballast proteins, lipids, minerals, and metabolic products. Animal raw materials are extremely labile and deteriorate quickly due to their high instability to the action of microorganisms and enzymes that stimulate hydrolytic processes. Therefore, the raw materials obtained after the slaughter of animals are quickly processed or immediately preserved, mainly by freezing at a temperature of 30-40 degrees below zero in quick-freezing ovens.

According to the technological feature, organ preparations are divided into:

- preparations that are dried, defatted and crushed glands;
- Extraction organ preparations;
- organ preparations for parenteral administration.

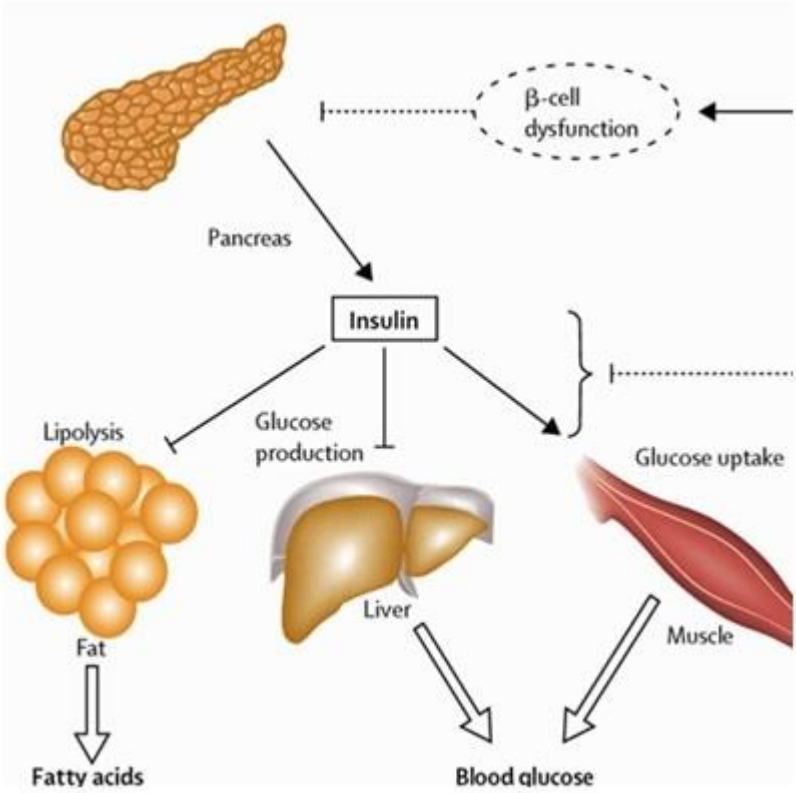
The technology of preparations that are dried, degreased and crushed glands. When obtaining drugs of this group (thyroidine, audiuretin, etc.), the raw materials are immediately dried in a vacuum dryer at a temperature not exceeding 50 ºC in a thin layer, spreading the minced meat on glass or enamel baking sheets. After gentle drying, the material is degreased by extracting in Soxhlet-type devices with organic solvents with a low boiling point, which extract fats well and do not destroy biologically active substances. Solvent residues are removed from the raw material

by drying in a vacuum dryer or air in a fume hood. The dry degreased material is made into powder in porcelain ball mills.

Insulin (Insulinum, *from Latin:* Insulinum) *Insula is* a pancreatic hormone produced by the beta cells of the islets of Langerhans.

Insulin production consists of the following stages:

1. Crushing frozen pancreas and extraction with acidic alcohol solution.
2. Precipitation of ballast proteins (pH 7.5) and release of lipids.
3. Isoelectric precipitation of the insulin fraction (at pH 5.5) and precipitation with alcohol, acetone, ether.
4. Insulin purification: salt precipitation, fractionation by chromatography, gel filtration, etc.
5. Insulin crystallization.
6. Transposition of zinc-insulin.



Img. 3. What is Insulin?

(site:images.google.com)

Fresh or frozen pancreas are crushed in a grinder and extracted by remaceration for the first time with 80-85% ethanol in an agitated reactor. The second time is extracted with 57% ethanol, which is acidified with orthophosphoric acid (hydrochloric or sulfuric) to a pH value of 2.8-3. Extraction is carried out for 1.5 - 4 hours with constant mixing. Acidified alcohol helps to inactivate the enzyme trypsin, which is located in the pancreas, thanks to which it is possible to keep insulin unchanged.

Insulin for injection (Insulinum pro injectionibus) is produced by dissolving crystalline insulin in water acidified with hydrochloric acid to a pH value of 3.0-3.5. A solubilizer (1.61.8% glycerol) and phenol (0.25-0.3%) are added to the solution as a preservative. The solution is sterilized by filtration through sterilizing filters. 1 ml contains 40 or 80 IU.

Img. 4. Insulin for injection
(site:images.google.com)

Suisulinum is a solution of crystalline insulin obtained from the pancreas of pigs in acetate buffer. The solution has a pH value of 7.0-7.5; Nipagin is used as a preservative. 1 ml contains 40 or 80 IU. Dosage form is 5 or 10 ml in vials sealed with rubber stoppers and aluminum caps.

Suspension of insulin-protamine for injection (Suspensio insulin-protamini pro injectionibus). It is prepared from crystalline insulin with the addition of protamine sulfate and sodium phosphate disubstituted; It is preserved by meta-cresol, phenol or nipagin with the addition of glycerin. The glucose-lowering effect occurs 2-4 hours after the injection and lasts 16-18 hours.

TEST QUESTIONS

Questions contain five answers and only one correct answer (example with an asterisk).

1. What percentage of plants are known to synthesize alkaloids?

A) 2%

B) 5%

C) 10% *

D) 20%

E) 30%

2. In which form are alkaloids most commonly found in plants?

A) As free bases

B) As salts of organic acids *

C) As salts of mineral acids

D) As proteins

E) As lipids

3. What is the primary purpose of using inorganic bases in the extraction of alkaloids?

A) To increase the concentration of sugars in the solution

B) To convert alkaloids from salts to bases *

C) To separate lipids from alkaloids

D) To stabilize alkaloids during extraction

E) To enhance the color of the extraction

4. During the production of insulin, which substance is used to inactivate trypsin?

A) Hydrochloric acid

B) Sulfuric acid

C) Acidified alcohol

D) Acetic acid

E) Ammonia solution

5. What is the function of using activated carbon during the alkaloid purification process?

A) To remove lipophilic compounds

B) To remove residues of pigments, iron salts, and other impurities

C) To crystallize alkaloids

D) To neutralize the extraction

E) To enhance the solubility of alkaloids

These questions cover various aspects of alkaloids, their extraction and purification processes, and the production of specific organ preparations, as outlined in the provided text.

6. What is a common feature of the extraction process for alkaloids using dilute acids?

A) It results in the formation of alkaloid bases.

B) It converts alkaloids into salts.

C) It uses high temperatures to enhance extraction.

D) It involves the use of organic solvents only.

E) It is primarily used to extract lipids.

7. Which acid is commonly used to extract alkaloids in the form of salts?

A) Succinic acid

B) Acetic acid

C) Hydrochloric acid

D) Oxalic acid

E) Phosphoric acid

8. What is the purpose of alkalizing the acidic aqueous extraction with an ammonia solution during alkaloid purification?

A) To enhance the color of the solution

B) To precipitate proteins

C) To convert alkaloids from salts into their base form

D) To stabilize the extraction process

E) To dissolve sugars and other organic compounds

9. In the production of insulin, which stage involves the use of isoelectric precipitation?

A) Crushing the pancreas

B) Extraction with acidic alcohol

C) Precipitation of ballast proteins

D) Isoelectric precipitation of the insulin fraction

E) Insulin crystallization

10. Why are operations for the isolation of ergot alkaloids carried out at low temperatures?

A) To prevent the decomposition of lipids

B) To reduce the activity of enzymes

C) To maintain the stability of alkaloids

D) To enhance the extraction of pigments

E) To increase the solubility of ergot alkaloids

Lesson No3

Topic: Subtest. Seminar

Didactic goals and motivation of the lesson:

Consolidate theoretical knowledge on the topic. Know the basic patterns and methods of extraction of plant raw materials, the influence of various factors on increasing the speed and completeness of extraction; To know the applicability of the basic principles of the theory of extraction to the practical implementation of extraction by different methods and with the use of various apparatuses and machines. Expand knowledge of the nomenclature of extraction preparations. Be able to perform situational tasks for the standardization of extraction preparations.

THEORETICAL QUESTIONS

1. Extraction preparations from fresh plants. Methods of receipt, nomenclature.

2. Plant juices. The method of obtaining them. Technology for making psyllium, aloe, and kalanchoe juices. Application.

3. The concept of biogenic stimulants. Biogenic stimulant preparations - liquid aloe extract, bioseed, peloidin.

4. The concept of "neogalenic preparations". Technology of Production of neogalenic preparations. Methods of cleaning extracts, equipment used for these purposes. Private technology for the production of adoniside, lantoside, corglycone, ergotal, raunatin, flamin, plantaglucid, ramnil, avisan.

5. Preparations of individual substances, medicinal plant raw materials. Classification. Technology for Obtaining Preparations of Individual Substances. Private technology for the production of digitoxin, celanide, ergotamine hydrotartrate, ergometrine maleate, rutin.

6. General methods of preparation of organ preparations. Hormone preparations - thyroidine, pituitrin for injection.

7. Anterior and posterior pituitary hormone preparations.

8. Insulin and its preparations.

9. Classification of enzymes. Enzyme preparations. Pepsin. Pancreatin. DNase, RNase, trypsin, ronidase, lidase, pantocrine, spleen.

10. Enzymes of microbiological synthesis. Examples of drug technology are oraza, solizim, asparaginase.

11. Immobilized enzymes. Methods of immobilization and peculiarities of obtaining. Examples of the use of immobilized enzymes.

12. Yeast and yeast preparations

PRACTICAL TASKS

1. Calculate the amount of Montenegrin herb, the biological activity of which is 66 LED in 1 g for the preparation of 100 ml of adoniside.

Answer: 37.88 g (25 LED).

2. Calculate the number of foxglove leaves, the biological activity of which is 60 LEDs in 1 g for the preparation of 100 ml of lantoside.

Answer: 20 g (12 LED).

3. Calculate the amount of extractant (24% ethanol) to prepare 100 ml of lantoside from 25 g of foxglove leaves by countercurrent extraction.

Answer: 500 ml.

Lesson No4

Topic: INJECTABLE SOLUTIONS IN AMPOULES-1.

Didactic goals and motivation of the lesson: to acquire and consolidate theoretical knowledge on the topic, to know the composition of ampoule glass, the relationship between the quality of glass and its composition, to be able to determine the chemical and thermal resistance of ampoules by various methods, to know the process of production of glass darts and empty ampoules, to be able to open, wash, fill and seal ampoules, to determine the depth of vacuum for filling ampoules with a given volume of solution. Learn how to prepare injection solutions that require special purification, know the technological scheme for the production of injection solutions, methods of obtaining water for injections, make calculations for strengthening and diluting solutions for injections. Know filtration methods and equipment.

THEORETICAL QUESTIONS

1. Characteristics of injectable agents, requirements of the State Pharmacopoeia of Ukraine, I ed. to them.

2. Glass for injection solutions, its grades. Technical requirements. Effect of additives on glass quality. Polymeric materials in ampoule production.

3. Study of chemical and thermal stability of ampoules and vials. Test methods.

4. Glass dart production and preparation: quality inspection, calibration, washing, drying and pre-packing.

5. Manufacture of ampoules. Annealing of ampoules. Purpose, essence, annealing mode and methods for determining the temperature and testing the annealing quality.

6. Opening and methods of washing ampoules: turbo-vacuum, syringe, vapor-condensation, vibration, etc. Apparatus.

7. Solvents used in the production of ampoule solutions. Requirements for water for injection. Aqua distillers for industrial production of pyrogen-free water. Storage of water for injection.

8. Non-aqueous solvents, their characteristics.

9. Excipients used in the production of injectable drugs in ampoules - solubilizers, stabilizers, preservatives.

10. Requirements for the conditions of production of injectable drugs in ampoules. Production facilities, raw materials, working personnel, equipment.

11. Characteristics of types of filtration of injection solutions. "Depth" and "membrane" filters. Examples and characteristics.

12. Filtration units. Filter design: druk- and nutch-.

13. Production of ampoules requiring additional purification. Technological schemes for the production of solutions for injections of magnesium sulfate and calcium chloride.

METHODOLOGY OF PRACTICAL WORK

Each student determines the chemical stability of the ampoule glass using an acidic solution of methyl red or phenolphthalein method. To do this, the student uses 3 ampoules of a given volume, opens, washes with a syringe, fills with the appropriate solution, and seals. Two of them are sterilized in an autoclave, one is left as a control. After sterilization, all ampoules are tested for thermal stability.

Next, students determine the depth of dilution for filling ampoules with solutions using ampoules with a capacity of 1 ml or 2 ml, according to the methodological guidelines.

Then, students determine the chemical stability of the ampoule glass by pH shear and determine the effect of the specific surface area of the ampoules on the leaching of the glass. To perform the work, 2 ampoules with a capacity of 10 ml,

3 ampoules with a capacity of 5 ml and 10 ampoules with a capacity of 2 ml are used.

PRACTICAL TASKS

1. Determine the class of the ampoule glass if, when determining the chemical resistance by changing the pH, the pH shift was: 0.8; 1.2; 1,8.

Answer: NS-1,NS-3, NS-2

2. When determining the thermal stability, 3 ampoules out of a batch of 200 ampoules failed the test. Will the batch be rejected?

Answer: No, 98.5%

3. What vacuum should be created to fill an ampoule with a capacity of 1 ml with a solution, if at a vacuum of 0.4 atmospheres the ampoule weighs 1.92 g, and at a vacuum of 0.6 atmospheres - , and an empty ampoule weighs ?2,52 g1,22 g

Answer: 0.53 atm.

4. Determine the brand of glass if after autoclaving ampoules filled with phenolphthalein solution, red staining appears, but it was not present after sterilization at a temperature of 100°C for 30 minutes.

Answer: NS-2

5. 3.6 liters of 10.8% calcium chloride solution for injection were obtained. Bring the solution to normal by calculating the volume of the product.

Answer:3,888 L;

6. 43.4 liters of 24.2% magnesium sulfate solution for injection were obtained. Bring the solution to normal (25%, $\rho = 1.118$).

Answer: 0.4 kg;

7 20 liters of 9.6% calcium chloride solution for injection were obtained. Bring the solution to normal (10%, $\rho = 1.0411$).

Answer: 0.2L 50% or ;0,101 кг

8 50 liters of 26% magnesium sulphate solution for injection were obtained. Bring the solution to normal (25%).

Answer: 2 liters of water;

9 20 L of 24% and 27% magnesium sulphate solution was obtained. How much can you get from these two solutions?20 л

Answer: 40.8 L;

An example of solving a problem 2.

1.How many ampoules have passed the thermal resistance test?

200 – 3 = 197 amp.

2.What percentage is this of the test batch?

200 - 100

197 - Y, Y=(197 ● 100) 200=98,5 (%)

An example of solving problem No. 5.

1. How much water for injection do I need to add?

10,8 10

10

0 0,8

10 - 0,8

3,6- **x,** x =0,288L

2. What is the volume of the finished product?

3,6+0,288=3,888 L

or using the formula:

$$y = \frac{V \bullet (a - b)}{b}$$, Where is

y is the amount of water required for dissolution, ml (l);

b is the amount of solution prepared, ml (L);

b is the required concentration of the solution, %;

a is the actual concentration of the solution, %.

$$y = \frac{3{,}6 \bullet (10{,}8 - 10)}{10} = 0{,}288 \text{ L}$$

SOME THEORETICAL ISSUES

Parenteral drugs are sterile drugs intended to be administered by injection, infusion or implantation into the human or animal body. These include aqueous and non-aqueous solutions, emulsions, suspensions, powders and tablets for the preparation of solutions and implantation, lyophilized drugs injected into the body parenterally (subcutaneously, intramuscularly, intravenously, intra-arterially, retrobulbarically or subconjunctivally, into various cavities.

Img.5. Parenteral drugs examples

(site:images.google.com)

Parenteral drug administration has several *advantages* over other methods:

- rapid action and complete bioavailability of the medicinal substance;

- accuracy and convenience of dosing;

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

- absence of the influence of gastrointestinal secretions and liver enzymes, which occurs with the internal use of medicines;

- the ability to create large stocks of sterile solutions, which facilitates and speeds up their release from pharmacies.

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

- when drugs are injected through the damaged skin, pathogenic microorganisms can easily get into the blood;

- air may be injected into the body along with the parenteral agent, causing vascular embolism or cardiac disorders;

- even small amounts of foreign impurities can have a harmful effect on the patient's body;

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

- administration of sterile drugs should be carried out by qualified professionals.

According to the Pharmacopoeia of Ukraine (1st ed.), medicinal products for parenteral use are classified as follows:

- Injectable medicines
- Intravenous infusion medications
- Concentrates for injectable or intravenous infusion drugs
- Powders for injectable or intravenous infusion drugs
- Implants

Injectable medicinal products are sterile solutions, emulsions or suspensions. Solutions for injection must be transparent and practically free of particles. Emulsions for injection must show no signs of delamination.

Intravenous infusion medicinal products are sterile aqueous solutions or emulsions with water as a dispersion medium; must be free of pyrogens and are usually isotonic to the blood. They are intended for use in large doses, so they should not contain any antimicrobial preservatives.

Concentrates for injectable or intravenous infusion drugs are sterile solutions intended for injection or infusion after dilution. Concentrates are diluted to the specified volume with the appropriate liquid before use.

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

Implants are sterile solid drugs that have a size and shape suitable for parenteral implantation, and release active substances over a long period of time. They must be packed in individual sterile containers.

A "cleanroom" or "cleanroom" is a room in which the countable concentration of aerosol particles and the number of microorganisms in the air are maintained within strictly defined limits. A particle is a solid, liquid, or multiphase object or microorganism with dimensions ranging from 0.005 to 100 μm. In the classification of cleanrooms, particles between 0.1 and 5 μm are considered.

Factory-made parenteral medicines are produced in glass vessels (ampoules, carpule cartridges, vials, bottles, syringes), in transparent plastic packages made of polymeric materials (vials, syringe ampoules, syringes, soft containers).

Containers for parenteral medicinal products are divided into two groups:

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

- multidose, providing the possibility of multiple withdrawals of a certain amount of the drug contained in it from the vessel without violating sterility.

Multi-dose aqueous parenteral medicinal products must contain the appropriate antimicrobial preservative in the required concentration, except for those with appropriate antimicrobial properties. When the product is released for parenteral administration in a multi-dose container, the precautions for its administration and especially the storage conditions between doses should be indicated.

Single-dose vessels include a syringe-ampoule - these are tubes made of polymeric materials with an injection needle protected by a cap.

Img. 6. Single-dose syringes
(site:images.google.com)

Ampoules are glass vessels of various capacities (1; 2; 3; 5; 10; 20 and 50 ml) and molds consisting of an expanded part - a body, where medicinal substances are placed (in a solution or other state) and 1-2 capillaries ("stems"), which serve to fill

and empty ampoules. Capillaries can be flat, belled or pinched. The clamping on the capillary prevents the solution from entering the upper part of the capillary during sealing and improves the conditions for opening the ampoules before injection.

Pharmaceutical companies have the option of using pre-made glass ampoules from manufacturers or producing them in-house at glassblowing facilities. The primary material used in making ampoules is glass, a solid solution formed by cooling a molten blend of silicates, metal oxides, and certain salts. It comprises a variety of oxides including Si02, Na20, CaO, MgO, and B2O. Silicate glass alloyed on the basis of silica is an important type of inorganic glass, alongside borosilicate and borate glasses. By introducing specific oxides into its composition, glass with predetermined physical and chemical properties can be achieved. The simplest composition is glass obtained by melting quartz sand (95-98% silicon dioxide) to form a glassy mass, from which the highly durable quartz tableware is made. However, due to its high melting point (over 1500 ºC), it's nearly impossible to make and seal an ampoule from quartz glass. To lower the melting point, metal oxides are added to the glass composition, which may reduce its chemical resistance. The introduction of boron and aluminum oxides into the glass composition enhances its chemical resistance, while the addition of magnesium oxide greatly increases its thermal stability. Adjusting the content of boron, aluminum, and magnesium oxides can increase impact strength and reduce glass brittleness. By altering the composition of the components and their concentration, glass with specific desired properties can be obtained.

The specifications for ampoule glass include colorlessness and transparency to ensure the absence of mechanical inclusions and the ability to detect any damage to the solution. Additionally, the glass should have high fusibility for effective sealing, water resistance, and mechanical strength to withstand the pressures during production, transportation, and storage, while also being fragile enough for easy opening. Thermal resistance is crucial to prevent breakage during temperature

fluctuations, especially during sterilization, and chemical (hydrolytic) stability is necessary to maintain the integrity of the drug's components.

Glass, as a complex material, releases its constituent parts when it comes into prolonged contact with water or aqueous solutions, especially when heated. This process is known as leaching, which involves the dissolution of the top layer of glass as it transitions from a predominantly alkali and alkaline earth metal oxide structure to an aqueous solution due to the high mobility of these constituents compared to the tetravalent silicon with high charge.

Img. 7. Ampoules
(site:images.google.com)

Syringe and vacuum filling ampoules are available with different markings:
Vacuum Filling Ampoules:
VPO - vacuum filling with clamping open;
VO - vacuum filling without clamping open;

Syringe filling ampoules:

IP-V - syringe filling open;

IP-S - syringe filling with an open bell;

Chemical resistance of glass. Chemical resistance characterizes the resistance of glass to the destructive effect of aggressive media.

Leaching is the transition from the glass structure of predominantly alkaline and alkaline earth metal oxides to an aqueous solution, due to its high mobility compared to the high charge of tetravalent silicon.

In this case, the following phenomena are possible:

• precipitation of free bases of alkaloids from their salts;

• precipitation of substances from colloidal solutions as a result of pH changes;

• Precipitation of metal hydroxides or oxides from their salts;

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

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

• Oxidation of oxygen-sensitive substances in a neutral or slightly alkaline environment, e.g. morphine, adrenaline, etc.

Leaching of calcium ions from glass can lead to the formation of precipitates of poorly soluble calcium salts. This phenomenon is observed in solutions containing phosphates (in the case of buffers) or acid sulfite, sodium pyrosulfite (added oxidation inhibitors).

Classes and grades of glass. Depending on the qualitative and quantitative composition, as well as the properties obtained, there are currently several classes and grades of glass used in the production of PLC. One of the important indicators of the quality of glass containers is their chemical stability.

The quality of ampoule glass is assessed according to the following parameters: hydrolytic resistance, residual stresses, thermal resistance, and light-protective properties. To assess the quality of some neutral glasses, the temperature coefficient

of linear expansion, water resistance and alkali resistance can be additionally determined.

The solvents used in the production of parenteral solutions must meet strict requirements, including high solubility, chemical purity, pharmacological neutrality, compatibility with active pharmaceutical ingredients, storage stability, availability, and cost-effectiveness.

Water for injection is the most widely used solvent for parenteral drugs due to its physiological compatibility as the primary component of body fluids and its role in transporting nutrients and metabolic products in the body.

In the preparation of parenteral dosage forms, non-aqueous solvents are utilized alongside water for injection. These solvents facilitate the creation of solutions from substances that are insoluble or poorly soluble in water, prevent the hydrolysis of biologically active substances, and extend the therapeutic effectiveness of medications.

In accordance with regulatory requirements, water for injection (Aqua pro ingectionibus) must comply with all the standards for purified water, and it must also be sterile and non-pyrogenic. It should be free of any visible particles, as determined by relevant guidance documents. The recommended period of use for water for injection is 24 hours from the date of receipt, provided that it is stored under aseptic conditions. Prolonged storage can lead to the absorption of carbon dioxide and oxygen from the air, as well as potential interaction with medicinal substances and packaging materials, resulting in the migration of metal ions or creating an environment conducive to microbial growth. Freshly prepared water is the preferred option to mitigate these risks.

In an industrial setting, the production of water intended for injections and purified water, which is used for the preparation of production and primary packaging, is achieved through the utilization of high-performance body devices, thermocompression distillers of various designs, and multi-stage reverse osmosis units.

Non-aqueous solvents can be categorized into various groups based on their chemical properties, including fatty vegetable oils, mono- and polyhydric alcohols, ethers and esters, amides, sulfones, and sulfoxides. These solvents, both individually and in combination, are utilized in the preparation of parenteral solutions, such as water-glycerin, water-propylene, and alcohol-water-glycerin. Additionally, widely used are mixtures of fatty oils with benzyl benzoate and ethyl oleate. Mixed solvents demonstrate increased solubility compared to individual solvents, a phenomenon known as co-dissolution, and these solvents are referred to as cosolvents.

Vegetable oils are non-aqueous solvents commonly used in the preparation of injectable drugs. They are among the most widely used solvents after water. Injectable preparations based on fatty oils are primarily used for intramuscular injections, and less frequently for subcutaneous injections.

Drawbacks of oil solutions include their relatively high viscosity, which can lead to painful injections, poor absorption, and the potential for granuloma formation at the injection site. To lessen viscosity, ethyl or ethyl glycol ether is occasionally added in some cases.

TEST QUESTIONS

Questions contain five answers and only one correct answer (example with an asterisk).

1. What is a key advantage of parenteral drug administration over other methods?

A) Delayed drug action

B) * Avoidance of gastrointestinal secretions and liver enzymes

C) Reduced bioavailability

D) Necessity for oral administration

E) Inaccuracy of dosing

2. Which of the following is a disadvantage of the parenteral route of drug administration?

A) The drug can only be administered orally

B) High bioavailability of the drug

C) * Risk of introducing air into the body

D) Convenient dosing

E) Resistance to pathogenic microorganisms

3. According to the Pharmacopoeia of Ukraine, which of the following is not a type of parenteral medicinal product?

A) Injectable medicines

B) Intravenous infusion medications

C) Powders for injectable drugs

D) * Topical ointments

E) Implants

4. What type of containers are commonly used for factory-made parenteral medicines?

A) Metal containers

B) Glass vessels like ampoules and vials

C) Wooden boxes

D) Paper bags

E) Ceramic pots

5. What is the purpose of adding antimicrobial preservatives to multi-dose parenteral medicinal products?

A) To enhance the drug's effectiveness

B) To prevent contamination during multiple withdrawals

C) To increase the drug's potency

D) To improve the taste of the drug

E) To enhance the drug's color

6. What is a cleanroom, as described in the context of parenteral drug production?

A) A room where drug impurities are removed

B) A room with strict limits on the concentration of aerosol particles and microorganisms in the air

C) A room used for storing finished drug products

D) A room for sterilizing equipment

E) A room used for quality control testing

7. Which type of parenteral medicinal product releases active substances over a long period of time?

A) Injectable medicines

B) Intravenous infusion medications

C) Concentrates for injection

D) Powders for injection

E) Implants

8. What is one of the main purposes of using ampoules for parenteral drugs?

A) To allow for easy oral administration

B) To protect drugs from light and oxygen exposure

C) To increase the drug's shelf life

D) To enhance the drug's taste

E) To ensure the drug is delivered slowly over time

9. What is a common issue that can occur due to the leaching of glass used in parenteral drug containers?

A) Formation of highly soluble calcium salts

B) Precipitation of poorly soluble calcium salts

C) Complete evaporation of the drug

D) Improvement of drug potency

E) Increase in drug color intensity

10. Which of the following substances is added to the glass composition to enhance its chemical resistance?

A) Iron oxides

B) Sodium oxides

C) Aluminum oxides

D) Potassium oxides

E) Zinc oxides

Lesson No5

Topic: INJECTABLE SOLUTIONS IN AMPOULES - 2

Didactic goals and motivation of the lesson: Students should consolidate the theoretical material on the topic, learn the methods of preparing some injectable solutions in ampoules using acid and alkaline stabilizers, determine the quality of solutions, know the modern nomenclature of injection solutions in ampoules, their composition, method of storage and application, be able to solve situational problems for compiling working prescriptions for ampoule solutions, taking into account the flow coefficient and the degree of humidity of the initial Materials. Know the structure and principle of operation of machines and devices used in the production of ampoule solutions. Be able to assess the quality of solutions in ampoules.

THEORETICAL QUESTIONS

1. Filling ampoules with solutions. Advantages and disadvantages of individual filling methods.
2. Sealing of ampoules. Sealing machines. Sealing of ampoules in an inert environment. Quality control of sealing of ampoules and vials.
3. Sterilization of ampoule solutions. Sterilization methods (thermal, chemical, mechanical, radiation and others), their characteristics, advantages and disadvantages.
4. Control of ampoules for mechanical inclusions. Characteristics of membrane-microscopic methods, flow-through and visual-optical methods. Membrane filtration method.
5. Labeling and packaging of ampoules. Device for marking ampoules.
6. Stabilization. Physical and chemical methods for preserving the properties of solutions for injection. Acid stabilizers. Stabilization mechanism.

7. Technological schemes and features of production of injectable solutions of glucose, atropine sulfate, scopolamine hydrobromide, gelatin.

8. Technological schemes for the production of solutions of euphylline, hexamethylenetetramine, cyanocobalamin.

9. Syringe tubes. Production features.

10. Nomenclature and features of production of suspensions and emulsions for injections. Requirements of the State Pharmacopoeia for these products.

11. Technological schemes for the production of ampoule solutions of sodium thiosulfate, caffeine-sodium benzoate, nicotinic acid.

12. Features of Stabilization of Solutions of Easily Oxidizing Substances in Industrial Production of Injection Solutions in Ampoules. An assortment of antioxidant stabilizers. Negative stabilizers.

13. Technological schemes for the production of solutions of ascorbic acid, aminazine, vicasol, ethazole-sodium, novocainamide.

14. Features and characteristics of the device for ampoule in the flow of inert gas. Give an example of a technological scheme for the production of an ampoule solution using gas shielding.

15. Preservatives in the production of injectable drugs in ampoules. Examples of technological schemes for the production of injectable solutions with preservatives.

16. Ampoule of powders for injections. Nomenclature and brief characteristics of such preparations. Quality tests in accordance with the requirements of the State. Pharmacopoeia of Ukraine I edition.

METHODOLOGY OF PRACTICAL WORK

Each student prepares 50 mL of 10%, 25%, or 40% glucose solution. For this purpose, 3 ampoules with a capacity of 10 ml are prepared, manually opened, washed by syringe; Drying is not necessary in this case.

The calculated amount of glucose is added to the volumetric flask, 5% of the volume of the finished solution of the Weibel reagent (5.2 g of sodium chloride, 4.4 ml of diluted hydrochloric acid, water to), brought to the mark (pH 3.0-4.0), poured into a heat-resistant flask, closed with a cotton swab, boiled for 15 minutes, treated with activated carbon (2-5% of the amount of glucose taken) by shaking for 30 minutes, then the carbon is filtered through a pleated filter, Then, through a fungus filter, check the presence of mechanical impurities, the percentage of glucose, check the pH of the solution, pour into ampoules using a syringe of 10.5 ml; The capillaries are washed with hot steam. They are sealed by capillary pulling and sterilized in an autoclave at a temperature of 110-121°C, a pressure equal to 1 atmosphere, for 5-7 minutes. Sterilized ampoules are checked for leaks by immersion in an aqueous solution of methylene blue and rejected. High-quality ampoules are labeled and handed over to the teacher. Finished products are repeatedly subjected to selective control, the work is formalized in the form of laboratory and industrial regulations.

PRACTICAL TASKS

1. Draw up a working prescription for obtaining 1000 ampoules with a capacity of 50 ml of a 40% glucose solution (according to the prescription of NF X ed.), if K_{cons}.. is equal to 1.030, glucose moisture is 10%.

Answer: See an example of the solution

2. Draw up a working prescription for obtaining 10000 ampoules of 0.1% atropine sulfate solution of 1.0 ml each, if K_{cons}.. is equal to 1.01.

Answer: Atropine sulfate 11.11 g; hydrochloric acid solution 0.1 n. 11 ml, water for injection up to .111,1 L

3. Draw up a working prescription for the preparation of a 20% solution of ethazole-sodium required for the production of 5000 ampoules with a capacity of 10 ml, if K_{cons}.. is 1,015.

Answer: Ethazole-sodium 10.656 kg, rongalite, water for injection up to .266,44 g 53,288 L

4. Prepared 100 liters of 21.2% sodium caffeine-benzoate solution. Calculate the amount of water and caustic soda solution of 0.1 N required to bring the solution to the norm (20%).

Answer: 24 ml, 5,976 L

5. At what vacuum should standard ampoules of 2.15 ml be filled, if at a pressure of 486 mm Hg an ampoule filled with water has a mass , at Hg - , and an empty one - ?
4,25 g 460 mm 4,0 g 2,0 g

Answer: 475 mmHg

6. Calculate the vacuum that ensures the filling of ampoules with 5.3 ml of aqueous solution if, at a residual pressure of 620 mm Hg, an ampoule filled with water weighs , at Hg - , empty - .9,0 g 540 mm 8,6 г3,5 g

Answer: 580 mm Hg Art.

7 In the production of ampoule 20% sodium caffeine benzoate solution, the contents of one of the production batches have acquired a yellow-brown color after sterilization, and dark flakes are observed in some ampoules. What is the reason for this defect and what are the ways to prevent it?

Example of solving problem No. 1.

1. How much of a 40% glucose solution will be required for ampoule?

According to HFCs, 50 mL ampoules should contain a 51 mL glucose solution.

51 ● 1000 ● 1.03=52.53 л

2.How many kg of anhydrous glucose will it take?

1 - 0,4 kg

52,53 - x, x=21,01 kg

3.How much water glucose will be consumed?

$$X = \frac{a \bullet 100}{100 - b} = \frac{21{,}01 \bullet 100}{100 - 10} = 23{,}34 \text{ kg}$$

4.How many g of sodium chloride will be needed to stabilize the solution?

0,26 г - 1 L

x - 52,53 L , x=13,66 g

1. How many empty ampoules are put into production?

1000 * 1.03=1030 pcs

6. The working list on the main points includes:

Aqueous glucose 23.34 kg;

Sodium chloride 13.66 g;

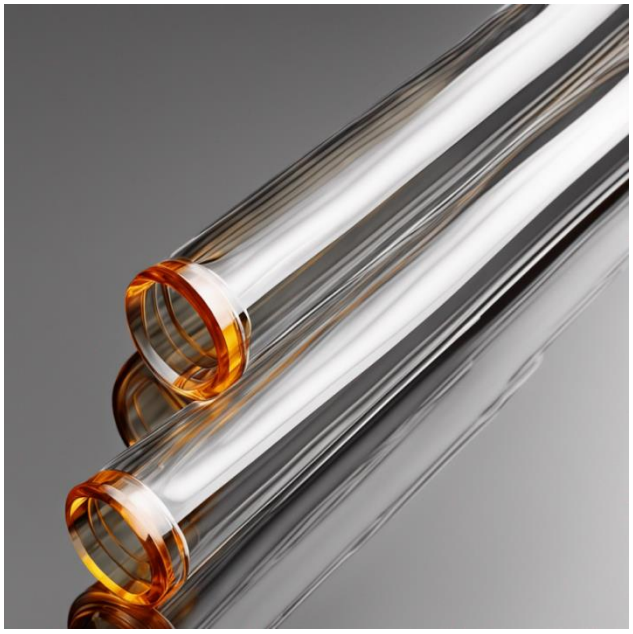
Hydrochloric acid solution 0.1 n to pH 3-4;

Water for injection up to 52.53 l of solution;

Ampoules (50 ml) 1030 pcs.

SOME THEORETICAL ISSUES

The production of glass ampoules involves several main stages: creating glass darts, washing and drying the darts, and dressing the ampoules. Glass darts are made from medical glass at glass factories, and their quality is regulated by indicators such as equiwall, straightness, standardized size, and washability of contaminants. It's essential for the darts to be homogeneous, free of air bubbles and mechanical inclusions, and have a regular shape in section.



Img.8. Pharmaceutical Glass Tubing
(site:images.google.com)

Calibration of the dart. To obtain ampoules of the same batch (series), it is necessary to use tubes of the same diameter and with the same wall thickness, so that the ampoules of the same series have a given capacity. The accuracy of the calibration determines the standardization of the ampoule and is of great importance.

The preparation of glass ampoules for filling involves a series of operations: washing, drying, and/or sterilization. In cases where paired ampoules are utilized in the manufacturing process, these operations are preceded by the opening of capillaries, a task that necessitates the use of specialized devices or separate machines.

Washing and drying of the dart. There are several ways to wash a dart. The most common is the chamber method. The rinsing unit consists of two hermetically sealed chambers loaded with vertically standing dart bundles. The chambers are filled with hot water or detergent solution and steam or compressed air is supplied through the bubbler. The liquid from the chamber is then drained and the drum is

washed by showering with desalinated water under pressure. For drying, hot filtered air is fed into the chamber.

The use of ultrasound for washing is highly effective. The tube washing process involves feeding the tubes horizontally onto the transport discs, bringing them close to the gas burners for reflow on one side, and immersing them in a bath filled with hot purified water. The bottom of the bath contains a series of magnetostrictive ultrasound generators.

Ampoules are produced on rotary-type glass-forming machines with tubes in a vertical position and continuous rotation of the rotor. The preparation of ampoules for filling involves several steps, including opening the capillaries of paired ampoules, washing and drying them, and sterilization.

Methods of washing ampoules. Ampoules can be washed internally or externally.

Img. 9. Rotary Ampoule Washing Machine
(site:images.google.com)

Internal washing of ampoules can be carried out in the following ways: *vacuum, ultrasonic and vibration ultrasound, thermal and syringe.*

The turbo-vacuum method is known for its highly efficient cleaning, achieved through instantaneous vacuum suppression and step-by-step vacuuming. This process takes place in a turbovacuum apparatus with automatic control based on specified parameters.

Syringe washing involves inserting a hollow syringe needle into a downward-oriented ampoule, through which water is pressure-fed. The turbulent water stream from the needle washes the inner surface of the ampoule and is then removed through the gap between the needle and the capillary opening.

After washing, the ampoules are promptly subjected to drying or sterilization, depending on their condition (unless the washing method already includes these processes). Drying can be performed in specialized (dry-heat) drying ovens at a temperature of 120-130°C for 15-20 minutes. When sterilization is necessary, drying and sterilization are combined, and the ampoules are placed in a dry-air sterilizer at 180°C for 60 minutes.

The primary packaging of parenteral drugs often uses polyethylene, polypropylene, and polyvinyl chloride as the preferred polymeric materials.

When it comes to polymer packaging requirements, it's crucial that containers are able to withstand sterilization conditions. The design and sterilization method must ensure that all parts of the container that come into contact with the drug can be sterilized. Closures are an integral part of the container, and after sealing, polymer containers must maintain sterility and integrity during storage and transportation. To enhance storage reliability, the container is typically packed in a protective shell. The packaging should also be transparent enough to allow for visual inspection of the contents at all times. Polymer containers may also feature a device for attaching an infusion kit, designed to ensure a secure connection.

Img. 10. Polymer packaging for parenteral dosage forms (site:images.google.com)

Solvents used for parenteral drugs include water for injection, isotonic solutions of certain medicinal substances, and non-aqueous solvents of natural, synthetic, and semi-synthetic origin that must meet the requirements of regulatory documentation. These solvents must adhere to strict standards, including high solvent capacity, chemical purity, pharmacological neutrality, chemical compatibility with medicinal substances (no chemical interaction), stability during storage, accessibility, and cost-effectiveness.

Water is the most widely used solvent for parenteral preparations due to its physiological compatibility. It is the primary component of all bodily secretions and serves as the main transporter of nutrients and metabolic products in the body.

In some countries' pharmacopoeias, water for injection is categorized as follows:

- Water for injection "in bulk": used as a solvent in the production of sterile forms.

- Sterile water for injection: packaged in suitable airtight containers and sterilized by heat treatment, it is used to dissolve or dilute substances, concentrates, or parenteral drugs before administration.

Pyrogenicity: The parenteral administration of drugs, particularly through intravascular injection, can result in a rapid increase in body temperature to 40°C.

This reaction is accompanied by an elevated pulse, chills, profuse sweating, nausea, and headache. In severe cases, these symptoms can be fatal. They are attributed to the presence of pyrogens in the solution.

Pyrogenicity is associated with living microorganisms, their byproducts (endotoxins), and the remnants of dead bacteria, which may be present in solutions after sterilization. Pyrogenic substances are typically classified as exogenous (primarily bacterial) and endogenous (cell-tissue).

Methods for removing pyrogenic substances: Depyrogenation involves the elimination, destruction, or inactivation of pyrogens. A wide range of items (solvents, substances, excipients, primary containers, equipment, etc.) can undergo depyrogenation. Due to the diverse nature of these items, there are numerous depyrogenation treatment options available. Generally, methods for removing pyrogens are categorized into two main groups. The first group consists of techniques that remove endotoxins from the surfaces of products, equipment, or solutions. The second group comprises methods that result in the destruction or inactivation of endotoxins.

Depyrogenation methods are also divided according to the nature of the processes occurring into: - *chemical;* - *enzymatic; and physical.*

The process of preparing parenteral solutions involves several key operations, such as dissolving substances, adjusting tonicity, ensuring stability, adding preservatives, and filtration. Depending on the nature of the active pharmaceutical ingredient (API), certain operations such as tonicity adjustment, stabilization, and preservative addition may not be necessary.

Parenteral solutions are produced in specialized production facilities that adhere to strict aseptic principles and are classified as purity classes C or A/B. The preparation of aqueous or non-viscous injection solutions is typically carried out using the mass-volume method in hermetically sealed reactors made of inert materials, equipped with a shell and mixing device. In cases where the solvent density significantly differs from that of water, the mass method is employed,

wherein both the drug substance and the solvent are measured by weight. Dissolving slowly or poorly soluble medicinal substances involves the use of heat and stirring.

The surfaces of reactors and collectors in contact with the product are constructed of materials that are non-reactive, non-absorbent, and do not release substances in quantities that would impact product quality. Presently, the dissolution of substances is primarily conducted in stainless steel reactors equipped with a lower turbine stirrer to prevent the introduction of lubricants into the solution.

Stabilization of solutions is an important consideration in the manufacturing and storage of certain drugs. It is common to observe changes in the properties of these drugs, which may occur at varying rates and degrees. These changes can result in a decrease in the content of active pharmaceutical ingredients (APIs) or a reduction in their pharmacological activity, as well as alterations in the properties of dosage forms. As a result, the shelf life of these drugs can vary significantly, ranging from a few hours (in the case of antibiotic solutions) or days (for enzyme solutions) to several years.

The various processes associated with drugs may be categorized into physical, chemical, and biological classifications. These classifications are distinguished by their interconnected nature, whereby chemical transformations can instigate alterations in physical properties, and physical changes can lead to inadvertent chemical processes.

The stabilization of homogeneous dispersive systems using chemical methods involves inhibiting the decomposition of medicinal substances by binding or neutralizing chemical compounds that trigger the degradation of the drug substance. Stabilizers can either slow down or accelerate undesirable chemical reactions, adjust the pH of solutions, increase the solubility of the active ingredient, or maintain it in a suspended state. Medicinal substances in need of stabilization can be categorized into the following groups:

1) Solutions of salts derived from weak bases and strong acids;

2) Solutions of salts derived from strong bases and weak acids;

3) Solutions of easily oxidizable substances.

Stabilization of solutions of salts of weak bases and strong acids: This category encompasses solutions of salts of nitrogenous alkaloids and synthetic nitrogenous bases. In solutions of salts of very weak bases that are slightly soluble in water, a small increase in pH can cause the formation of a precipitate. This is evident in solutions of substances such as strychnine nitrate, papaverine hydrochloride, and dibazole. In instances of a significant increase in the pH of the solution (strongly alkaline environment), the release of strong free bases, like novocaine, is occasionally observed. Many of these can be stabilized by the addition of a 0.1 mol/L hydrochloric acid solution, which neutralizes the alkali released and shifts the pH of the solution towards the acidic side.

Stabilization of solutions of salts of weak acids and strong bases: In aqueous solutions, salts of weak acids and strong bases undergo hydrolysis easily, leading to a weakly alkaline medium. Consequently, this results in the formation of poorly soluble compounds, causing turbidity or precipitation in the solution. To minimize the hydrolysis reaction, a solution of 0.1 M sodium hydroxide or sodium bicarbonate is added.

Stabilization of solutions of easily oxidized substances: The presence of oxygen in dissolved form and in the gas space above the solution in the container is a primary cause of oxidation of active pharmaceutical ingredients (APIs) within solutions. To protect the APIs from the adverse effects of oxygen, stabilizers known as antioxidants are used. Oxidation inhibitors are classified as natural or synthetic based on their origin. Natural antioxidants are derived from various parts of plants, and most of the natural antioxidants in use belong to polyphenol derivatives. Based on solubility, antioxidants are categorized as either soluble in water or soluble in oils.

TEST QUESTIONS

Questions contain five answers and only one correct answer (example with an asterisk).

1. What quality indicators are used to regulate glass darts for ampoules?

A) Weight, color, and size

B) * Equiwall, straightness, standardized size, and washability of contaminants

C) Transparency, flexibility, and hardness

D) Temperature resistance, opacity, and shape

E) Chemical composition, density, and texture

2. Why is the use of tubes with the same diameter and wall thickness important in ampoule production?

A) To ensure the ampoules are transparent

B) To make the ampoules lightweight

C) * To standardize ampoules for consistent capacity

D) To improve the durability of the ampoules

E) To allow for faster production

3. Which method is most commonly used for washing glass darts during ampoule production?

A) Ultrasonic washing

B) * Chamber method

C) Thermal washing

D) Syringe washing

E) Chemical washing

4. What is the primary purpose of using polymer materials such as polyethylene, polypropylene, and polyvinyl chloride in the packaging of parenteral drugs?

A) To enhance the appearance of the drugs

B) To reduce production costs

C) To withstand sterilization conditions and maintain sterility

D) To make the packaging biodegradable

E) To improve drug solubility

5. What are the two main groups of depyrogenation methods?

A) Chemical and physical methods

B) Mechanical and thermal methods

C) Techniques to remove endotoxins and methods to destroy or inactivate endotoxins

D) Sterilization and disinfection

E) Enzymatic and ultrasonic methods

6. What is the primary reason for using ultrasonic washing in the cleaning of ampoules?

A) To reduce the washing time

B) To achieve highly effective cleaning

C) To enhance the color of the ampoules

D) To prevent glass breakage

E) To make the washing process more economical

7. In which type of equipment is the turbo-vacuum method used for internal washing of ampoules?

A) Ultrasonic washer

B) Turbo-vacuum apparatus

C) Syringe washer

D) Chamber washing unit

E) Dry-heat sterilizer

8. What is the typical temperature and duration for drying ampoules in a dry-heat oven?

A) 150-160°C for 10-15 minutes

B) 120-130°C for 15-20 minutes

C) 180°C for 30 minutes

D) 100°C for 25 minutes

E) 200°C for 60 minutes

9. Why is water considered the most widely used solvent for parenteral preparations?

A) It is inexpensive and readily available

B) It has high solvent capacity and physiological compatibility

C) It improves the taste of medications

D) It is easy to sterilize

E) It enhances the stability of active ingredients

10. What does pyrogenicity refer to in the context of parenteral drug administration?

A) The process of sterilizing the drug

B) The ability of the drug to prevent infection

C) The reaction of the body to pyrogens causing fever and other symptoms

D) The solubility of the drug in water

E) The chemical reaction of the drug with the container

Lesson No6

Topic: **Topic: Subtest. Seminar**

Didactic goals and motivation of the lesson: • Consolidate theoretical knowledge of the material on the topic, generalize knowledge on the methods of production of ampoule drugs, methods for testing their quality; to characterize the structure and principle of operation of machines and devices used in the production of injection solutions in ampoules, to know the nomenclature and technology of individual ampoule solutions, to be able to compare the advantages and disadvantages of existing methods, their preparation, to make a choice of rational methods of production.

THEORETICAL QUESTIONS

1. Characteristics of injectable medicines, requirements of the State Pharmacopoeia of Ukraine, I ed. to them.

2. Glass for injection solutions. Technological requirements. Quality testing.

1. Manufacture and preparation of a stack drot.
2. Manufacture of ampoules. Annealing of ampoules.

5. Opening of ampoules, washing and drying. Methods, equipment, comparative evaluation.

6. Water for injection, requirements of the State Pharmacopoeia of Ukraine, I ed. Equipment for industrial production of pyrogenicated and demineralized water.

7. Non-aqueous solvents and excipients used in the production of injectable solutions in ampoules.

8. Requirements for the conditions of production of ampoule injectables and their provision.

9. Ways to stabilize injectable drugs. Assortment and mechanisms of action of stabilizers, features of application. Preservatives in ampoule production.

10. Filtration Methods. Filter media, devices and installations.

11. Methods of filling ampoules with solutions, their comparative evaluation.

12. Ampoule of inert gases in the current. Sealing of ampoules without and with gas protection.

13. Sterilization methods in the production of ampoule injection solutions.

14. Characteristics of Methods of Quality Control of Ampoule Drugs. Rejection and regeneration of defective ampoules.

15. Marking, labeling and packaging of ampoules.

16. Ampulation of powders, nomenclature, requirements of the State Pharmacopoeia of Ukraine, I ed.

17. Nomenclature and technological schemes for the production of ampoule preparations of industrial manufacture. Examples, features, technology.

18. Polymeric materials in the manufacture of ampoules and vials. Syringe tubes. Production features.

PRACTICAL TASKS

1. 100 l of 37.8% solution of hexamethylenetetramine for ampoule was obtained. Bring the solution back to normal (40%). The specific gravity of a 40% solution is 1.090.

Answer: 3.188 kg.

2. 100 l of 41.3% solution of hexamethylenetetramine for ampoule was obtained. Bring the solution back to normal (40%). Calculate the amount of water required.

Answer: 3.25 liters of water.

3. 10 liters of 5.3% sodium ascorbinate solution for ampoule were obtained. Bring the solution to normal (5%).

Answer: 0.6 liters of water.

4. At what vacuum should the ampoules of 1.1 ml be filled, if at a vacuum of 498 mmHg. An ampoule filled with water weighs at RT. st. - , and the empty one - ? 2,32 г459 мм2,02 г1,12 г

Answer: 485 mmHg Art.

5. At what vacuum should the ampoules be filled but 5.3 ml, if the empty ampoule weighs 2.05 g, filled with water when the liquefaction of the mouth. st. - , and in case of rarefaction of RT. Art.-?615 mm 7,45 g 570 mm 7,15 g

Answer: 600 mmHg Art.

6. Make a working prescription for obtaining 20000 ampoules with a capacity of 1 ml of a 20% solution of camphor in oil.

Answer: Camphor 4,380 kg, peach oil - .15,910 l

Example of solving problem No. 1.

Strengthening of the prepared solution is carried out according to the formula:

$$X = V \bullet \frac{b - a}{100 \bullet \rho - b} = 100 \bullet \frac{40 - 37{,}8}{100 \bullet 1{,}090 - 40} = 3{,}188 \text{ KG}$$

Answer: To bring the solution to the norm, it is necessary to add 3.188 kg of hexamethylenetetramine.

Example of solving problem No. 3.

According to the mixing rule:

5,8 5

5

0 0,3

5 – 0,3

10 - x, x = 0,6 l of water

Example of solving problem No. 4.

1.Interpolation:

459 - 2,02

498 - 2.32

39 - 0,30

2. Weight of the contents of the ampoule when filled:

2,32-1,12=1,20 г.

3. Volume difference in filling:

1,20-1,10=0,10 мл.

4. Appropriate dilution to achieve a volume of 0.10:

0,30 - 39 мм рт. ст.

0,10 - x, x=13ммрт. ст.

5. Required vacuum to fill a 1.1 ml ampoule

498-13=485 mmHg Art.

Lesson No7

Topic: TABLETS-1

Didactic goals and motivation of the lesson:

To consolidate theoretical knowledge on the topic of the lesson, to be able to determine the physical, mechanical and technological properties of bulk materials (fractional composition, fluidity, bulk mass, etc.), to recommend the optimal technology of solid dosage forms based on the structural and mechanical properties of materials. Know the technological scheme for the production of tablets by direct pressing without and with the addition of excipients, be able to prepare tablets using this method on press.

THEORETICAL QUESTIONS

1. Physical, mechanical and technological properties of powdery materials, their importance in the production of solid dosage forms - powders, tablets, granules and others: shape and size of particles, fractional composition, fluidity (flowability), bulk (volumetric) mass or density, moisture content, compression ratio, compressibility. Their importance in the production of solid dosage forms - powders, tablets, granules, etc.
2. Tablets as a dosage form. Classification of tablets in accordance with the general article of the State Standard. Pharmacopoeia of Ukraine. Types and nomenclature of tablets.
3. The main hypotheses of tableting are: the theory of Academician Rebinder, capillary-colloidal, mechanical coupling, fusion, electrostatic.
4. Main types of tablet machines: rotary, crank (eccentric). Device of tablet machines, press tools. New RTM designs.

5. Direct pressing method. Advantages and disadvantages. Ways to improve the basic technological properties of powders for the purpose of direct compression. Nomenclature and production of tablets obtained by direct compression without the addition of excipients and with their addition.
6. Classification and assortment of excipients used in the production of tablets: fillers and diluents, binders, loosening, sliding and lubricating substances, stabilizers, dyes, prolongators, substances for creating shells.
7. Routes of administration of excipients. Mechanism of action. Nomenclature.

METHODOLOGY OF PRACTICAL WORK

A group of students is divided into teams of 3-4 people. Each team conducts a study of the technological properties of one of the proposed Powders, using 50.0 (100.0) material. 6 parameters of each of the powders are determined.

Determination of the shape and size of particles of medicinal powders is carried out as follows: the crushed powder under study is poured on the surface of the slide, then it is shaken by turning the glass by 180°C with a light tap on the glass. The dust of the powder remaining on the glass is quite sufficient for examination under a microscope. For each powder, at least 50 measurements are taken in the microscope field for the maximum and minimum dimensions of length and width. Then they calculate Average.

The shape of the particles is determined by the ratio of the average length of the particles to the average width. With this method, particles are conditionally divided into 3 main types: elongated - the ratio of length to width is more than 3:1, lamellar - the length exceeds the width and thickness, but not more than 3 times, equiaxial - have a shape close to isometric.

The fractional composition is determined according to the following method: 50.0 or 100.0 of the material is sifted through a standard set of sieves for 5 minutes,

and then the weight of each fraction and its percentage are determined. The results are displayed in the table:

Name of the substance	Fractional composition, %						
	+3	-3+2	-2+1	-1+0,5	-0,5+0	-0,25	V
1.							
2.							
3.							
4.							
5.							

The powder is considered homogeneous if one of the fractions is at least 75%.

3. Bulk mass (bulk density). A load of powder 50.0 (100.0) is poured into the upper hopper of the device with a working volume of 50 ml. The valve is slowly pulled out**,** the powder from the hopper is poured into the measuring glass. By inserting a valve into the device, the excess powder in the hopper is cut off, the hopper is removed, and the upper part of the gauge is wiped with gauze. The gauge with a gate valve is weighed on a tarrier scale with an accuracy of 0.1 g. The determination of the bulk mass is repeated at least 3 times. Based on the average data, the following is calculated:

$$K_H = \frac{P_1 - P_2}{V}$$, where is

P1 is the weight of the measuring stick with powder, g;

P2 is the weight of the gauge without powder, g;

V is the volume of the measuring stick, 50 cm^3.

The CL value is considered optimal if it is not less than 330 kg/m3.

4. The coefficient of compaction (compression) is determined in the following way: a weight of 0.55-0.75 g of the powder under study is poured into a matrix with a diameter of 11 to with a lower punch inserted into it. The height of powder filling in matrix H1 is determined with a caliper.13 мм Then the suspension is covered with an upper punch and at a pressure of 40 to 60 kgC/cm2, a tablet is obtained on a manual hydraulic press and its height H2 is measured. The formula is used to determine the compaction coefficient:

$$K_{Compression} = \frac{H_1}{H_2}$$

The lower the compression value, the less force is required to compress the tablet and then push it out of the matrix hole.

The results of the study are recorded in a summary table. The methodology for performing all parameters and the results of the study are drawn up in the form of a protocol. Based on the results of the study of technological properties, a conclusion is made about the rational technology of tableting the substances under study.

PRACTICAL TASKS

1. How much of the finished product can be obtained from 60 kg of licorice root extract containing 12% glycyrrhizic acid and 35% moisture to prepare a standard preparation (glycyrrhizic acid - 16%, moisture - 20%)?

Answer: 45 kg.

2. Calculate the amount of dry (anhydrous) diluent injected into 40 kg of licorice extract containing glycyrrhizic acid 22% and moisture 25% to obtain a thick extract with 15% glycyrrhizic acid.

Answer: 19.87 kg.

3. 50 kg of thick belladonna extract containing 2.2% alkaloids, moisture - 30% were obtained. How many kg of starch molasses (moisture content 30%) should be added and how much moisture should be evaporated in order to prepare a pharmacopoeia preparation with a tropane alkaloid content of 1.5% and a moisture content of 20%?

Answer: 33.81 kg of molasses, 10.47 liters of moisture.

4. Calculate the amount of finished product, thinner and moisture removed required to standardize 85 kg of semi-finished product of belladonna extract thick, containing alkaloids 1.95%, moisture 22%. As a diluent, dextrin with a moisture content of 6.8% is offered. The finished product should contain 1.5% alkaloids, 18% moisture.

Answer: see below.

5. From 100 kg of dandelion root containing 28% extractives, 33 kg of thick extract with a moisture content of 20% was obtained. Calculate output, spending, and Krash.. on extractives.

Answer: 94.3%, 5.7%, 1.061.

6. 53 kg of thick male fern extract with a 36% phylicin content was prepared. How much petroleum jelly should be added to bring the drug to normal (26.5%)? Answer: 19.0 kg.

7. It is necessary to bring to the standard (6% anthracene derivatives, humidity 4%) 50 kg of intermediate product of dry buckthorn extract containing anthraglycosides 11% and moisture 3%, using dextrin with a moisture content of 1.5%. How many kg of the finished product will be obtained, how much diluent and water should be introduced?

Answer: 91,667 kg, 40,102 kg, 1,565 L.

An example of solving a problem 4.

1. How much anhydrous diluent should be introduced into the semi-finished product.

$$X = \frac{P \bullet (a_o \bullet c_1 - a_1 \bullet c_0)}{100 \bullet c_0} = \frac{85 \bullet (82 \bullet 1{,}95 - 78 \bullet 1{,}5)}{100 \bullet 1{,}5} = 24{,}31 \text{ kg}$$

2. How much dextrin should I use for this?

93.2 kg of anhydrous water is contained in 100 kg of dextrin 24.31 kg of anhydrous water is contained in X kg

$$X = \frac{24{,}31 \bullet 100}{9{,}32} = 26{,}084 \text{ kg dextrin}$$

3. How much moisture should be introduced together with the diluent to bring the product to the specified moisture content?

$$V = \frac{P \bullet (a_o \bullet c_1 - 100 \bullet c_0 - (a_o \bullet c_1 + a_1 \bullet c_0))}{100 \bullet c_0} =$$

$$= \frac{85 \bullet (100 \bullet 1{,}95 - 100 \bullet 1{,}5 - 82 \bullet 1{,}95 + 78 \bullet 1{,}5)}{100 \bullet 1{,}5} = 1{,}13 \text{ kg}$$

4. How many kg of finished product will be obtained?

85+24,31+1,13=110,5 kg

5. How much moisture should be evaporated?

110,5 - (86+26,084)=-0,584 kg

An example of solving problem 7.

1. How much anhydrous dextrin is required for production?

$$X = \frac{50 \bullet (96 \bullet 11 - 97 \bullet 6)}{100 \bullet 6} = 39{,}5 \text{ kg}$$

2. How much dextrin does this correspond to (humidity 1.5%) available?

$$У = \frac{39{,}5 \bullet 100}{98{,}5} = 40{,}102 \text{ kg}$$

3. How much moisture should be introduced together with the diluent to bring the extract to the standard (specified anthracene derivatives content and moisture)?

$$V = \frac{50 \bullet (100 \bullet 11 - 100 \bullet 6 - (96 \bullet 11 - 97 \bullet 6))}{100 \bullet 6} = 2{,}167 \text{ kg}$$

4. What is the expected yield of the product?

50+39,5+2,167=91,667 kg

5. How much water should be added, taking into account the moisture content of dextrin?

91,667 - (50+40,102)=1,565 kg

SOME THEORETICAL ISSUES

Tablets are a solid dosage form containing one dose of one or more active ingredients, obtained by pressing a certain volume of particles. Most tablets are used orally. Some tablets are swallowed whole, some are pre-chewed, while others are

dissolved or dispersed in water before use or left in the mouth where the active ingredient is released.

Img. 11. Example images of solid oral dosage forms
(site:images.google.com)

Positive qualities of tablets:

− industrial production that ensures high productivity, purity and hygiene of the production of these dosage forms;

− accuracy of dosing of medicinal substances injected into tablets;

− portability of tablets, ensuring the convenience of their dispensing, storage and transportation;

− long-term preservation of medicinal substances in a compressed state;

− for substances that are not sufficiently stable – the possibility of applying protective coatings;

− the possibility of masking unpleasant organoleptic properties (taste, smell, coloring ability), which is achieved by applying coatings;

− combination of medicinal substances that are incompatible in terms of physical and chemical properties in other dosage forms;

− localization of the action of the drug substance in a certain part of the gastrointestinal tract – by applying coatings soluble in an acidic or alkaline environment;

− prolongation of the effect of medicinal substances (by applying certain coatings, using special technology);

− regulation of sequential absorption of several drug substances from a tablet at certain intervals (multilayer tablets);

− Prevention of errors in the dispensing and administration of medicines – by applying appropriate inscriptions on the surface of the tablets.

Tablets also have some disadvantages:

− the effect of drugs in tablets develops relatively slowly;

− tablets cannot be administered in case of vomiting and unconsciousness;

− during storage, tablets may thicken, which increases the disintegration time;

− tablets may contain excipients that cause some side effects (for example, talc irritates the gastric mucosa);

− Certain drugs (e.g., sodium or potassium bromide) form highly concentrated solutions in the dissolution zone, which can cause severe irritation of the mucous membranes (this disadvantage is eliminated by dissolving the tablets in a certain amount of water);

− Not all patients, especially children, can swallow pills freely.

Tablets can be categorized:

1) by composition: *simple (*single-component) and *complex* (multi-component);

2) according to the structure of the structure: *single-layer, multi-layer* (at least two layers) and *frame, without a shell (coating)* or *covered with a shell;*

3) by shape: round, oval, oblong (rectangular tablets with two opposite rounded edges), polygonal (triangular, quadrangular (square, rhomboid, trapezoidal), pentagonal, hexagonal), specific shape;

4) by purpose and method of use.

Film-coated tablets are divided according to the nature of the coating: *pelleted, film-coated and pressed-dry*.

Img. 12. Solid dosage form – tablets (site:images.google.com)

Single-layer tablets consist of a pressed mixture of drugs and excipients and are homogeneous throughout the dosage form.

In *multilayer tablets, the medicinal substances are arranged in layers. When chemically incompatible substances are used in multilayer tablets, their interaction is minimal.*

The size of the tablets ranges from 4 to 25 mm in diameter. Tablets with a diameter of more than 25 mm are called *briquettes*. Tablets with a diameter of more than 9 mm have one or two risks (applied perpendicular to each other) that allow the

tablet to be divided into two or four parts and thus vary the dosage of the drug substance.

The weight of tablets is usually 0.05-0.8 g, which is determined by the dosage of the drug substance and the amount of excipients in their composition.

Tablets must have a regular shape, be intact, without chipped edges, and their surface must be smooth and homogeneous. Tablets must have sufficient strength and must not crumble.

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

Oriblettae – tablets taken orally. Drugs are absorbed by the mucous membrane of the stomach or intestines. These tablets are taken orally with water.

Resoriblettae are tablets administered sublingually; the drugs are absorbed by the oral mucosa.

Implantablettae – tablets made aseptically are used for implantation. They are designed for gradual absorption of medicinal substances in order to prolong the therapeutic effect.

Injectablettae – tablets manufactured aseptically are used to produce injectable solutions of medicinal substances.

Solublettae are tablets used for the preparation of solutions for various pharmaceutical purposes.

Dulciblettae bacilli, boli, uretratoria, vagitoria – pressed urethral, vaginal and rectal dosage forms.

Oral tablets are classified as:

– uncoated tablets;

– film-coated tablets;

– effervescent tablets;

– soluble tablets;

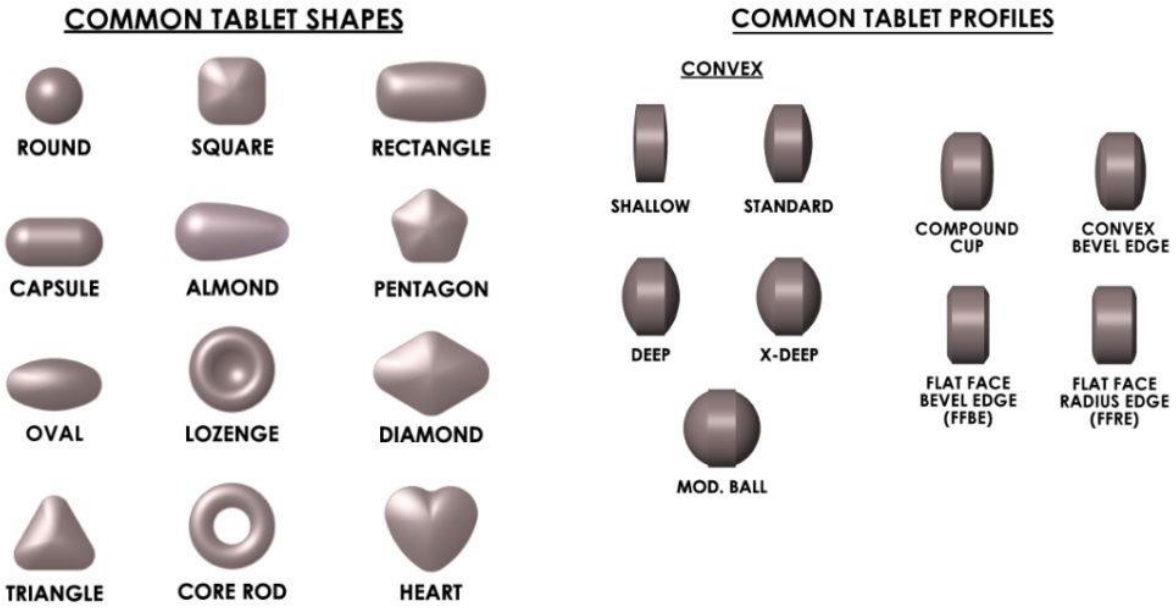
– dispersible tablets;

– enteric-soluble tablets;

– modified-release tablets;

– tablets for use in the oral cavity (oromucosal);

– oral lyophilisates.



Img. 13. Drug Tablet Design

(site:images.google.com)

Properties of powdered drug substances

The properties of the initial medicinal substances predetermine the rational method of obtaining tablets. Bulk substances in the form of powdered (particle size 0.2 mm) or granular (particle size from 0.2 to 3 mm) forms are used as starting materials, which have the following properties:

– physical – density, shape, size and nature of the particle surface, specific surface area of particles, adhesion forces (adhesion on the surface) and cohesion (adhesion of particles inside the body), surface activity, melting point, etc.;

– chemical – solubility, reactivity, etc.;

– technological (pharmaco-technological) – bulk volume and bulk density before shrinkage, shrinkability, volume and density after shrinkage, degree of

compaction, fluidity, moisture, fractional composition, dispersion, porosity, compressibility, etc.;

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

Physical and chemical properties

Particle shape and size. Powdered drug substances are coarsely dispersed systems and have particles of various shapes and sizes. Most of them are crystalline systems; the amorphous state is less common.

The physical properties of powders are determined by their specific contact surfaces and true density.

The specific surface is the total surface area occupied by the powdery substance, and ***the contact surface is*** the surface that is formed when powder particles come into contact with each other.

Wettability. The wettability of powdered medicinal substances refers to their ability to interact with various liquids (lyophilicity) and, above all, with water (hydrophilicity).

Process properties

The technological properties of powdered medicinal substances depend on their physicochemical properties.

Fractional (particle size) composition or percentage distribution of powder particles by size. It has a certain influence on the degree of its flowability, and, consequently, on the rhythmic operation of tablet machines, the stability of the mass of the resulting tablets, the accuracy of the dosage of the drug substance, as well as on the qualitative characteristics of tablets (appearance, disintegration, strength, etc.).

Img. 14. Sieves for testing distribution of powder particles by size (site:images.google.com)

The fastest and most convenient method for determining dispersion is sieve analysis. The technique of this analysis is to sift 100.0 g of the test powder through a set of sieves (hole diameter 2.0, 1.0, 0.5, 0.25 and 0.1 mm). The material is placed on a sieve with the largest holes (top) and the entire set of sieves is shaken (manually or on a vibrating unit) for 5 minutes, and then the weight of each fraction and its percentage are found.

Bulk volume (volume before shrinkage) – the volume of 100.0 g of powder poured without compaction.

Bulk density (density before shrinkage) is the weight of a unit volume of freely poured powder and depends on the density and moisture content of the substance, the shape and size of the particles, and their stacking.

The compaction coefficient is the ratio of the height of the powder in the matrix (H_1) to the height of the resulting tablet (H_2):

$$K_{\text{Compression}} = \frac{H_1}{H_2}$$

The determination is carried out using a matrix. The matrix channel is filled with powder and a pressing pressure of 120 MPa is carried out. The resulting tablet is pushed out with a punch and the height is measured.

The compressibility of powdered preparations is influenced by the shape of the particles, the ability of the latter to move and deform under the influence of pressure. Compaction is a significant technological factor; In particular, the larger it is, the more time is spent on pressing. At the same time, more effort is spent on pushing the tablet out of the depth of the matrix channel.

Main groups of excipients in the production of tablets

Excipients are subject to the following requirements: they must be chemically indifferent; should not have a negative effect on the patient's body, as well as on the quality of tablets during their preparation, transportation and storage.

Excipients (diluents) - starch, glucose, sucrose, basic magnesium carbonate, magnesium oxide, sodium chloride, sodium bicarbonate, kaolin, gelatin, microcrystalline cellulose, methylcellulose, sodium salt of carboxymethylcellulose, calcium carbonate, calcium phosphate disubstituted, glycine sorbitol, mannitol, pectin, etc.

Binders (for wet, structural and mixed granulation) - purified water, ethyl alcohol, starch paste, sugar syrup, solutions: carboxymethyl cellulose, sodium salt of carboxymethyl cellulose, oxypropyl methyl cellulose, oxyethyl cellulose, polyvinyl alcohol, polyvinylpyrrolidone.

Leavening – swelling: wheat, potato, corn, rice, pectin, gelatin, MC, sodium salt of carboxymethylcellulose, sodium-croscarmellose, sodium starch, glycolate.

Leavening agents – gas-forming: a mixture of sodium bicarbonate with citric or tartaric acid, citric acid with calcium carbonate, sodium glycine carbonate, etc.

Leavening agents - improving wettability and water permeability: Wheat, potato, corn, rice, sugar, glucose, tween-80 starch.

Anti-friction – sliding: starch, talc, polyethylene oxide-4000, aerosil, etc.

Anti-friction lubricants : stearic acid, calcium and magnesium stearate, gli ceryl behenate.

Anti-friction – anti-sticking: aerosil, starch, talc, macrogol 4000 or 6000, stearic acid, calcium and magnesium stearate, etc.

Film-formers: acetylphthalylcellulose, methylcellulose, oxypropyl methylcellulose, polyvylpyrrolidone, polyvinyl alcohol.

Flavor correctants : sugar, glucose, fructose, sucrose, xylitol, mannitol, sorbitol, aspartame, glycine, dulcine, lemon acid, cocoa, etc.

Odor correctants : essential oils, fruit juice concentrates, citral, menthol, vanillin, ethyl vanillin, fruit essences, etc.

Color correctants : indigo carmine, acid red 2C, tropeoline 00, tartrazine, eosin.

Plasticizers: glycerin, tween-80, petroleum jelly, oleic acid, macrogol 400, propylene glycol.

Prolongators: white wax, sunflower oil, cottonseed oil, monopalmitin, trilaurin.

Solvents: purified water, ethyl alcohol, acetone, chloroform, ammonia, hydrochloric acid, etc.

Direct pressing

The method of direct compression to obtain tablets has a number of advantages. It allows you to achieve high labor productivity, significantly reduce the time of the technological cycle due to the abolition of a number of operations and stages, eliminate the use of several equipment items, reduce production areas, reduce energy and labor costs, and significantly reduce the cost of tablets.

Direct compression is a combination of various technological methods that make it possible to improve the basic technological properties of the tableted material (fluidity and compressibility) and obtain tablets from it, bypassing the granulation stage

Direct compression of tablets is carried out:

1) by direct tabletting of bulk medicinal substances with good compressibility;

2) with the addition of auxiliary substances that improve the technological properties of the material;

3) forced feeding of tableted material from the feeding hopper of the tablet machine into the die;

4) with preliminary directional crystallization of the extruded material.

Particle size, particle strength, compressibility, fluidity, moisture and other properties of substances are of great importance for direct pressing. For example, for the production of sodium chloride tablets, the oblong shape of the particles is acceptable, and the round shape of this substance is almost impossible to compress. The best fluidity is observed in coarsely dispersed powders with an equiaxial particle shape and low porosity, such as lactose, phenylsalicylate, hexamethylenetetramine and other similar preparations. Therefore, such preparations can be compressed without prior granulation. Medicinal powders with a particle size of 0.5-1.0 mm, an angle of repose of less than 42º, a density after shrinkage of more than 330 kg/m3, and a porosity of less than 37% have proven to be the best.

TEST QUESTIONS

Questions contain five answers and only one correct answer (example with an asterisk).

1. Which of the following statements most accurately describes the pharmaceutical concept of tablets as a dosage form?

a) Tablets are liquid preparations containing multiple active ingredients

b) Tablets are solid dosage forms produced by chemical synthesis

c) Tablets are semi-solid formulations for topical application

d) * Tablets are solid dosage forms containing one or more active ingredients, obtained by compressing a volume of particles

e) Tablets are exclusively used for parenteral administration

2. In the context of tablet formulation, which of the following represents a key advantage in terms of physicochemical compatibility?

a) Enhanced bioavailability through particle size reduction

b) Improved stability due to anhydrous formulation

c) * Facilitation of combining otherwise incompatible substances

d) Increased solubility through crystal modification

e) Prolonged shelf-life due to moisture exclusion

3. Regarding the structural classification of tablets, which of the following types is not explicitly mentioned in the provided text?

a) Monolithic tablets

b) Bilayer tablets

c) Multilayer tablets

d) Compression-coated tablets

e) * Matrix tablets

4. Which of the following statements accurately describes a potential limitation of tablets related to excipient-induced adverse effects?

a) Decreased bioavailability due to first-pass metabolism

b) Potential for gastric mucosal irritation attributed to talc

c) Increased risk of dose dumping in modified-release formulations

d) Altered pharmacokinetics due to food-drug interactions

e) Enhanced degradation of active ingredients during storage

5. In the characterization of powdered medicinal substances, which of the following properties is not explicitly categorized in the provided text?

a) Physicochemical properties

b) Technological properties

c) Structural and mechanical properties

d) Biopharmaceutical properties

e) Chemical properties

6. How is the term "wettability" defined in the context of powdered medicinal substances?

a) The capacity of a powder to absorb atmospheric moisture

b) The ability of a substance to form a stable suspension in aqueous media

c) The propensity of particles to agglomerate in the presence of moisture

d) The tendency of a powder to interact with various liquids, particularly water

e) The rate at which a compressed tablet disintegrates in dissolution media

7. Which analytical technique is described for determining the particle size distribution of powdered substances in tablet formulation?

a) Laser diffraction spectroscopy

b) Dynamic light scattering

c) Sieve analysis

d) Coulter counter method

e) Optical microscopy with image analysis

8. Among the functional categories of tablet excipients, which class is specifically associated with enhancing wettability and water permeability?

a) Binding agents

b) Disintegrants

c) Glidants

d) Lubricants

e) Film-forming agents

9. Which of the following is not cited as an advantage of the direct compression method in tablet manufacturing?

a) Enhanced production efficiency

b) Reduced energy consumption

c) Minimized processing steps

d) Improved content uniformity

e) Decreased equipment requirements

10. According to the text, which combination of powder characteristics is considered optimal for direct compression tableting?

a) Particle size: 0.1-0.3 mm; angle of repose: > 50°; tapped density: < 200 kg/m³

b) Particle size: 0.5-1.0 mm; angle of repose: < 42°; tapped density: > 330 kg/m³

c) Particle size: 1.5-2.0 mm; angle of repose: 45°; tapped density: 250-300 kg/m³

d) Particle size: 2.0-3.0 mm; angle of repose: > 60°; tapped density: < 100 kg/m³

e) Particle size: 0.3-0.5 mm; angle of repose: 30-35°; tapped density: 400-450 kg/m³

Lesson No8

Topic: TABLETS - 2

Didactic goals and motivation of the lesson: to consolidate theoretical knowledge on the topic, to establish the relationship between compression pressure, mechanical strength and disintegration of tablets; Be able to determine the average weight, dosing accuracy, mechanical strength, abrasion and disintegration of tablets using appropriate devices. To study the technological features of trituration, sublingual, implantation tablets and tablets with poisonous, potent, coloring and volatile substances, as well as with extracts and essential oils. Know the methods of coating tablets with coating and technological schemes, be able to independently solve situational problems.

THEORETICAL QUESTIONS

1. Wet granulation, method characteristic and instrument.
2. Technological and instrumental schemes for the production of tablets using wet granulation. Nomenclature.
3. Dry granulation, briquetting. The concept of methods, the nomenclature of the excipients used
4. Structural granulation. Spheronization of granules. Characteristics and equipment.
5. Trituration, sublingual and implantation tablets. Features of the technology, nomenclature.
6. Tablet rejection. Basic parameters of tablet quality and methods of their division in accordance with the State Pharmacopoeia of Ukraine of the first edition.
7. Filling and packaging of tablets. Equipment and types of packaging materials.

8. Granules as a dosage form. HFC requirements for pellets, quality assessment. Technological process of pellet production. Nomenclature.

9. Purposes of coating tablets with coating Classification of coating types. Comparative evaluation of methods.

10. Pelleting. Process stages, equipment. Assortment of excipients.

11. Film coatings. Application methods. Classification, nomenclature of polymers and materials.

12. Extruded coatings. Excipients. Machines for double pressing.

13. Extended-release tablets Multilayer Current Technology. Skeletal (scaffold) tablets. Excipients for their production.

14. Drage. Micro dragees. Stages of production. Quality assessment.

METHODOLOGY OF PRACTICAL WORK

After a theoretical analysis of educational issues and instruction on safety when working with tablet machines, students prepare raw materials for the production of tablets by direct pressing.

To do this, each student prepares a fraction of raw materials (-2 + 1) of 10-12 g, combines them into teams and prepares 20 tablets at the KTM with the direct participation of the teacher. Prepared tablets are tested for dosing accuracy, average weight, mechanical crush strength, abrasion, disintegration, and appearance. The results are drawn up in the form of a regulation with a detailed description of the methods for testing the quality of tablets.

The results of the study of the quality of the obtained tablets are displayed on the board in the form of a graph. At the end of the session, the data is analysed and a conclusion is made about the optimal pressing pressure.

PRACTICAL TASKS

1. How many kg of phytin should be taken to prepare 50 kg of 0.25 g phytin tablets with an average weight of 0.275 g and $K_{cons.}$ = 1,028?

Answer: 46,727;

2. How many litres of 96% ethanol should I take to moisturize 75 kg of phytin powder if the amount of humectant should be 40% of the weight of the product?

Answer: 30L;

3.How much calcium stearate do I need to take to powder 120 kg of norsulfazole granulate? (Calcium stearate is the maximum allowable content.)

Answer: 1,212 kg;

4. Calculate the average weight of streptocide tablets of 0.25 g if 20% of excipients are introduced into the granulate.

Answer: 0.3 g;

5. Calculate the weight gain if 100 kg of diphenhydramine-lactose-starch mixture is moistened with 20 l of 10% starch paste and dried to a residual moisture content of 5%. K_{cons}.= 1,000.

Answer: 7 kg; •

6.Calculate the % of excipients in quinine hydrochloride tablets 0.25/0.3.

Answer: 20%;

7. What is the mass of dried granulate after moistening 50 kg with twenty litres of 3% methylcellulose solution and then drying to a residual moisture content of 3%?

Answer: 52.1 kg;

8. As a result of processing 50 kg of streptocide by moistening it with 15 liters of 3% methylcellulose, 49.5 kg of regranulate was obtained. How much streptocide and dry methylcellulose is in this granulate?

Weight: 49.055 kg, 0.4455 kg:

Example of solving problem No. 8.

1. How many kg of dry methylcellulose is in 15 litres of granulating liquid?

x=(3, 15): 100=0.45 kg

2. What is the total (theoretical) mass of streptocide and methylcellulose?

50 kg + 0.45 kg = 50.45 kg

3. How many kg of streptocide is contained in the resulting regranulate?

50.45 - 50 kg of streptocide

at 49.5 - x1,

$$x1 = \frac{49,5 \bullet 50}{50,45} = 49,058 \text{ kg}$$

4. What is the mass of methylcellulose contained in regranulate?

50.45 - 0.45 kg of methylcellulose

in 49.5 - x2,

$$x1 = \frac{49,5 \bullet 0,45}{50,45} = 0.442 \text{ kg}$$

5. The quantity of any of the components can also be determined by the difference. For example, the amount of methylcellulose can be determined:

49.5 kg - 49.058 kg = 0.442 kg.

SOME THEORETICAL ISSUES

Granulation is the process of transforming a powdery material into complexes of a certain size. Granulation is necessary to improve the fluidity of the tablet mass, which occurs as a result of a significant reduction in the surface area of the particles (due to the production of granules), as well as a reduction in friction that occurs between these particles during movement. Currently, the following granulation methods are used in the pharmaceutical industry:

1. *dry granulation*;
2. *wet granulation*;
3. *mixed granulation*;
4. *Structural granulation*.

The dry granulation method consists of mixing drugs and excipients, initially compacting them and then grinding them into coarse powder or granules. The resulting granules are sifted with sieves, powdered with anti-friction substances, and then pressed on tablet machines into tablets of a given weight and diameter, that is, secondary compaction is carried out.

The initial compaction of powders is carried out in two ways: briquetting and compaction.

Dry granulation is used when drug substances decompose in the presence of water or during drying at elevated temperatures, enter into chemical reaction reactions, or undergo physical changes (melting, softening, discoloration). Granulation by briquetting can also be used for medicinal substances with good compressibility, but insufficient fluidity.

The wet granulation method is used for powders that have poor fluidity and insufficient particle adhesion capacity. In both cases, solutions of binders are added to the mass to improve the adhesion between the particles. Wet granulation is a common type of granulation in the tablet industry and is carried out in ways such as: granulation by punching and granulation in a high-speed mixer-granulator.

Wet **granulation with punching** includes the following operations: mixing and moistening of powders; granulation of wet mass; drying of wet granules; production of dry granules; powdering of dry granules.

Mixing and moisturizing powders. Mixing of dry medicinal powders with excipients followed by moistening of the mixture with a solution of binders is carried out in mixers with rotating blades. The humectant is added to the mass in separate portions with continuous stirring, which is necessary to prevent the formation of lumps. With wet mixing of powders, the uniformity of their distribution is greatly improved, there is no separation of particles and stratification of the mass, and its plasticity is improved. The mixing of the moistened powders is accompanied by

some compaction of the mass due to air displacement, which makes it possible to obtain denser solid granules.

Granulation of wet mass. The wet mass is granulated on special pellet mills, the principle of operation of which is that the material is wiped by blades, spring rollers or other devices through a perforated cylinder or mesh. Pellet mills can be *vertical* and *horizontal*.

Wet punching granulation has a number of disadvantages:

– long-term exposure of medicinal and excipients to moisture;

– deterioration of disintegration and solubility of tablets;

– the use of a number of special machines and devices for each operation;

– Time and labor intensity of the process, since the transfer of the product from one piece of equipment to another, as a rule, is carried out manually;

– high losses of processed materials.

Drying of wet granules. There are different types of dryers for this purpose. Fluidized bed dryers are the most common. The principle of operation of dryers is to loosen the product with an air flow and bring it into a suspended state.

Production of dry granules and their powdering. In the process of drying the granules, they may stick together into separate lumps. In order to ensure a uniform fractional composition, the dried granules are passed through granulators with a mesh hole size of 1.5 mm, which largely ensures a constant weight of the tablets. After that, the granules are powdered in mixers with a rotating body, adding anti-friction substances, and transferred to the tableting stage.

Mixed granulation. In the production of tablets for some hydrophobic materials, which form a brittle mass after moistening and drying, mixed granulation is often used, which consists of mixing powders, moistening them with a solution of a binding agent in mixers, drying them to a lumpy mass in air dryers, followed by rubbing through the perforated plate of the granulator. The resulting dry granules are powdered and sent for tableting.

Structural granulation. With this method of granulation, there is a characteristic effect on the moistened material, which leads to the formation of rounded and, under certain conditions, sufficiently uniform in size. Currently, three types of granulation of this type are used in pharmaceutical production: in a dredging kettle; spray drying and fluid bed.

For ***granulation, a mixture of powders is loaded in the coating kettle*** and when it rotates at a speed of 30 rpm, it is moistened by supplying a solution of the binding agent through a nozzle. The powder particles stick together, are dried with warm air and, as a result of friction, acquire approximately the same spherical shape. At the end of the process, sliding substances are added to the granulate to be dried.

Spray drying granulation is advisable in cases of undesirable long-term contact of the granulated product with air (for example, in the production of antibiotics, enzymes, and products from raw materials of animal and plant origin).

Prepare a solution or suspension of the excipient and humidifier and feed them through nozzles in the form of small droplets into the spray dryer chamber. Drying is carried out by air at a temperature of 150ºC.

The sprayed particles have a large surface area, as a result of which there is an intensive mass and heat exchange. They lose moisture quickly and form spherical porous granules ranging in size from 10 to 70 μm in just a few seconds.

Granulation in a fluidized bed. For the granulation of tablet mixtures in order to prepare them for tableting in the pharmaceutical industry, fluidization of the material is widely used, in which the processed powder and then the resulting granulate are constantly in motion. The main processes – mixing the components, moistening the mixture with a binding solution, granulation and drying of the granulate – take place in one unit. Fluid bed granulation is carried out in two ways:

– by spraying a solution or suspension containing excipients and medicinal substances in a fluidized system into small spherical nuclei;

– by spraying a solution of binders on powdery substances in a fluidized state.

Factors Influencing the Bioavailability of Drug Substances from Tablets.

The method of preparation of dosage forms affects the stability of the drug, the rate of its release from the dosage form, the intensity of absorption, and ultimately the therapeutic efficacy. For example, the degree of preservation of a number of medicinal substances in finished dosage forms depends on the choice of granulation method for the production of tablets. In this regard, wet granulation is especially undesirable in the preparation of tablets containing antibiotics and other substances, since it leads to the decomposition of the preparations.

1. Granulation conditions have a great influence on the disintegration of tablets. Humidifiers often used in industry, such as starch paste and gelatin solutions, are not optimal for many preparations, as they increase their disintegration time.
2. Compression affects the rate of release of the drug, which in turn can disrupt the absorption process at the absorption sites.
3. One of the methods for improving the biopharmaceutical properties of tablets is to create them on the basis of complexes for the inclusion of cyclodextrins with medicinal substances.

Tablet Compression Machine (also referred to as Tablet press machine, tablet making machine, tablet machine, or tablet punching machine) is a mechanical device that is used to compress the granules or mixture of API and excipients to uniform and predetermined size, shape, and weight of tablets for research, pilot-scale, and full production.

Types of tablet compression machines:

- Single punch Tablet Compression Machine /Single station/Eccentric tablet press machine;
- Multi punches Tablet Compression Machine/ Multi-station/ Rotary presses.

Tablet compression machine parts:

Hopper. The hopper holds and supplies the granules/powder mixture (API and excipient) to the feeder system. It is the input point of powder mix or granules to tablet press for compression of tablets. Granules or powder mix may feed manually or using automated systems.

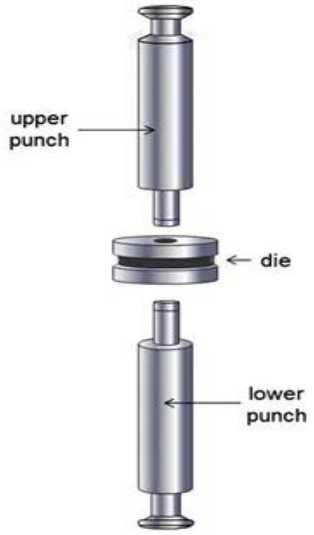
Img. 15. The hopper

(site:pharmaeducation.net)

Feeder System or Feed Frame. The Feeder System helps to force the feed of the granules into the die cavity, especially during faster rotation. It also mixes the granules and inhibits the separation of granules. Feeder System is also called a force feeder.

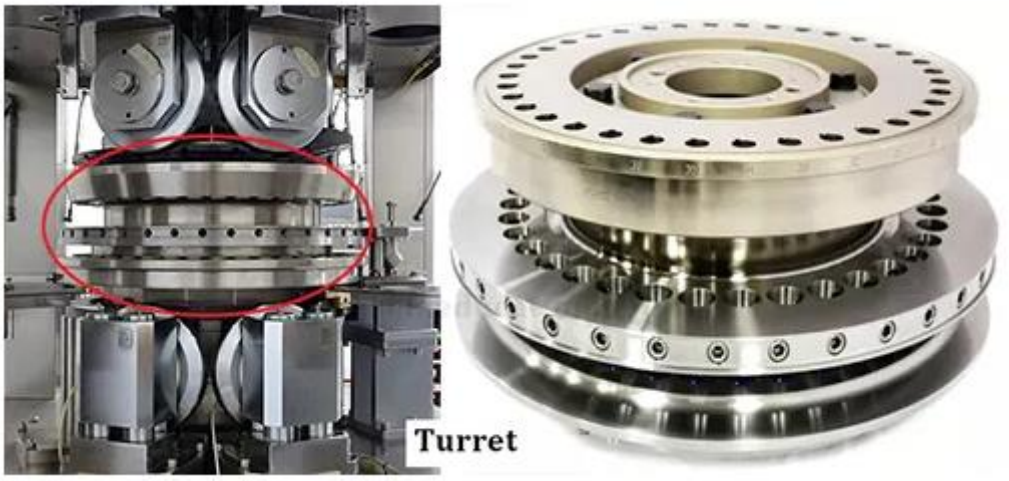
Img. 16. Feeder System
(site:pharmaeducation.net)

Punch. Two punches (upper and lower) compress the granules/powder mix in the die bore. The lower punch moves upward and the upper punch moves downward and compresses the tablet within the die cavity. Then the upper punch moves upward and the lower punch moves upward.



Img. 17. The punchs
(site:pharmaeducation.net)

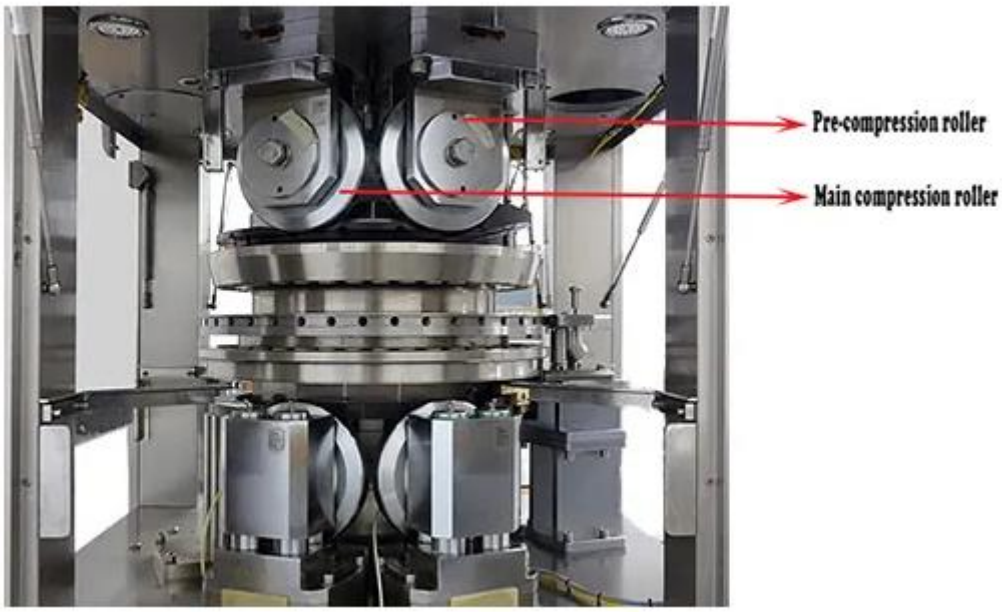
Turret. The turret hosts the die as well as upper and lower punches on its holes and ensures the position of the die bore and two punches (lower and upper) for the tablet compression process. The turret is the heart-like part of the tablet press machine.



Img. 18. The Turret
(site:pharmaeducation.net)

Tablet Weight Controller. This is used to adjust the volume of the granules to be compressed and so determines the weight of the tablet with the help of different movements of the cam systems, material will flow into the die cavity depending on the position of the punches.

Main compression roller: It exerts sufficient compression force to compress the granules into tablets. The rollers stay stable with no vibration during the entire compression process to ensure consistent thickness and size of the tablets.



Img. The main compression roller

(site:pharmaeducation.net)

Discharge chute. Guides the compressed tablets to a collection drum *or* bin.

Img. 19. Discharge chute

(site:pharmaeducation.net)

Advantages of Single Punch tablet compression machine:

1. Rational and small.

2. Easy to operate.
3. Easy to clean.
4. Ideal for new tablet development and small-batch production.
5. Due to single a set of punches, less chance of weight variation.
6. Less noise production.
7. Minimal spare part requirements.
8. Operate by both motor and manually.

Advantages of Multi-station/Rotary presses:

- High-speed operation.
- Robust design and high productivity.
- High overall equipment effectiveness.
- Minimal product loss.
- Low noise level in operation.
- Compact machine with space-saving design.
- Ease washable and high containment technology.
- High safety system.
- Modern Rotary presses may control digitally.
- Cost-effective.
- Optimized lubrication system.

Rotary tablet machines are widely used by the pharmaceutical industry in the production of tablets. Unlike impact machines, rotary tablet machines have a large number of dies and punches.

Coating tablets. The goal:

1) protection of tablets from mechanical impact (impacts, abrasion, etc.);

2) protection against environmental influences (light, moisture, oxygen and carbon dioxide in the air);

(3) protection against the staining power of medicinal substances contained in tablets (e.g., activated charcoal tablets);

4) protection of the medicinal substances contained in the tablets from the acidic reaction of gastric juice;

5) protection of the mucous membrane of the mouth, esophagus and stomach from the irritating effect of drugs;

6) masking the unpleasant taste and smell of medicinal substances contained in tablets;

7) localization of the therapeutic effect of drugs in a certain part of the gastrointestinal tract;

8) prevention of disorders of digestion processes in the stomach, which are possible during the neutralization of gastric juice by drugs of the main nature;

9) prolongation of the therapeutic effect of medicinal substances in tablets;

10) overcoming the incompatibility of different substances in one tablet by introducing them into the composition of the shell and the core;

11) improvement of the presentation of tablets and the convenience of their use.

Types of excipients that are used to coat tablets:

- ✓ *adhesives* that ensure adhesion of coating materials to the core and to each other (sugar syrup, polyvinylpyrrolidone, carboxymethylcellulose, methylcellulose, oxypropyl methylcellulose, ethyl cellulose);
- ✓ *structural substances that* create scaffolds (sugar, magnesium oxide, calcium oxide, talc, magnesium carbonate);
- ✓ *plasticizers* that give coatings plasticity properties (vegetable oils, methylcellulose, polyvinylpyrrolidone, carboxymethylcellulose, twins, 1,2-propylene glycol, diethyl phthalate, triacetylglycerol (triacetin), etc.);
- ✓ *hydrophobic agents* that make coatings moisture-resistant (aerosil, shellac, polyacrylic resins, zein);

- ✓ *dyes* used to improve the appearance or to designate a therapeutic group of substances (tropeoline 00, tartrazine, acid red 2C, indigo carmine, etc.);
- ✓ *corrigants* that give the coating a pleasant taste (sugar, citric acid, cocoa, vanillin, etc.).

Tablet coatings, depending on their composition and method of application, are divided into the following groups:

1. Pelleted coatings (application of sugar coating).
2. Film Coatings

Tablet Quality Control

According to the requirements of HFCs, quality control of finished tablets is carried out according to the following indicators*:*

- description (organoleptic properties);
- identification; average weight of the tablet and homogeneity of dosage units or homogeneity of mass and homogeneity of the content of the active ingredient;
- abrasion; resistance to crushing; disintegration; dissolution; determination of the amount of talc;
- loss in mass on drying or water content;
- concomitant impurities; residual quantities of organic solvents (when used in technology); micro-biological purity;
- Quantification of active ingredients.

TEST QUESTIONS

Questions contain five answers and only one correct answer (example with an asterisk).

1. Which of the following statements most accurately describes the primary purpose of granulation in tablet formulation?

a) To increase the solubility of active pharmaceutical ingredients

b) To enhance the chemical stability of the formulation

c) * To improve the fluidity of the tablet mass and reduce inter-particle friction

d) To increase the bioavailability of the drug substance

e) To modify the release profile of the active ingredient

2. In the context of pharmaceutical manufacturing, which granulation method is most appropriate for substances that are sensitive to moisture or elevated temperatures?

a) Wet granulation

b) * Dry granulation

c) Mixed granulation

d) Structural granulation

e) Spray drying granulation

3. What is the primary disadvantage associated with wet punching granulation in tablet production?

a) Increased tablet disintegration time

b) Reduced bioavailability of the active ingredient

c) * Prolonged exposure of ingredients to moisture

d) Increased production costs

e) Limited applicability to hydrophobic materials

4. Which of the following granulation techniques is most suitable for heat-sensitive materials such as antibiotics and enzymes?

a) Wet granulation with punching

b) Dry granulation by briquetting

c) Mixed granulation

d) Spray drying granulation

e) Structural granulation in a dredging kettle

5. In the context of tablet compression machinery, what is the primary function of the turret?

a) To control the weight of tablets

b) To feed granules into the die cavity

c) To host the die and punches and ensure their proper positioning

d) To exert compression force on the granules

e) To guide compressed tablets to the collection area

6. Which type of tablet compression machine is most suitable for high-speed, large-scale production in the pharmaceutical industry?

a) Single punch eccentric press

b) Multi-station rotary press

c) Hydraulic press

d) Pneumatic press

e) Manual tablet press

7. What is the primary purpose of applying a coating to tablets?

a) To increase the tablet's hardness

b) To enhance the drug's bioavailability

c) To protect the tablet from environmental influences and mask unpleasant tastes

d) To increase the dissolution rate of the active ingredient

e) To reduce the tablet's size for easier swallowing

8. Which of the following excipients is primarily used as a plasticizer in tablet coatings?

a) Sugar

b) Magnesium oxide

c) Aerosil

d) Triacetylglycerol (triacetin)

e) Tartrazine

9. According to the text, which of the following is NOT a standard quality control parameter for finished tablets as per regulatory requirements?

a) Average weight and homogeneity of dosage units

b) Disintegration time

c) Dissolution profile

d) Hardness and friability

e) Particle size distribution of the granules

10. Which granulation method involves the formation of rounded, uniform-sized particles through characteristic effects on moistened material?

a) Dry granulation

b) Wet granulation

c) Mixed granulation

d) Structural granulation

e) Direct compression

Lesson No9

Topic: Topic: Subtest. Seminar

Didactic goals and motivation of the lesson:

Consolidate the theoretical material on the topics: "Tablets, granules, dragees". To summarize knowledge on the methods of granulation, drying, pressing, and coating of dosage forms in the production of tablets, dragees, granules and quality assessment of solid dosage forms. To characterize the structure and principles of operation of machines and devices used in the production of these dosage forms. Expand knowledge of the modern nomenclature of drugs, their composition, type of packaging, storage method, and application in practice. To compare methods of preparation of preparations with different technological and pharmacological properties.

THEORETICAL QUESTIONS

1. Tablets as a dosage form. Classification and nomenclature of tablets. Requirements of the State Pharmacopoeia of Ukraine of the first edition for tablets. Assessment of the quality of tablets.
2. Selection of the optimal scheme for the production of tablets taking into account the technological, volumetric and physical and mechanical properties of medicinal substances.
3. Production of tablets by direct pressing. Possibilities and Prospects of the Direct Pressing Method.
4. Granulation, purpose, methods. Wet granulation. Dry granulation. Features of the equipment. Structural granulation. Types of structural granulation. Spheronization of granules.

5. Excipients, classification. Assortment, characteristics and mechanism of action. Adhesives and anti-friction substances. Methods of administration. Mechanism of their action. Loosening excipients. Classification, assortment, methods of administration. Diluents, colorants and other excipients. Problems of prolongation of action and stabilization of drug substances in tablets.

6. The essence of the pressing process according to modern ideas of physical and chemical mechanics of disperse systems.

7. Modern hypotheses of compression of medicinal substances.

8. Types, structure, and comparative evaluation of tablet machines.

9. Coating of tablets and granules with coatings. Purpose, methods, characteristics and assortment of materials and groups of coatings. Pelleting. Essence, stages of production, nomenclature. Film coating. Methods of application. Materials for chemically soluble coatings. Pressed coatings. Tablet presses for double pressing.

10. Rejection (quality assessment) of tablets. Filling and packaging of tablets. Types of packaging, materials and equipment used.

11 Achievements of the staff of the department in the creation and improvement of the technology of tablet dosage forms.

12. Granules. Production schemes. Nomenclature. Pellet quality assessment.

13. Dragee. Production scheme. Nomenclature. Assessment of the quality of dragees.

14. Spansuls. Characteristics. Technological scheme of receipt. Prospects.

15. Biopharmaceutical aspects of the production of solid dosage forms under conditions of serial production.

PRACTICAL TASKS

1. Calculate the amount of talc in 0.3 g and 0.5 g quinine hydrochloride tablets with an average weight of 0.36 g and 0.6 g, respectively.

Answer: 0.0108 g, 0.018 g.

2. How much excipients should be added to 20 kg of granulate to obtain tablets of 0.5 g of analgin with an average weight of 0.55 g?

Answer: 2 kg.

3. How much talc can be added to 15 kg of granulate used to press 0.5 g sulfadimezin tablets with an average tablet weight of 0.55 g?

Answer: 0.495 kg.

4. Calculate the amount of talc, calcium stearate and starch for powdering 150.0 g granules in the manufacture of streptocide tablets of 0.3.g with an average weight of 0.33 g.

Answer: 4.95 g talc, 1.65 g calcium stearate, 8.4 g starch.

5. Calculate the amount of starch for the production of 10 tablets of 0.5 g of norsulfazole with an average weight of 0.575 g, if talc in the finished tablets should be 2%.

Answer: 0.635 g.

Example of solving problem No. 4.

1. How many excipients (in %) are used for the production of streptocide tablets?

0.3g - 100%

(0,33 – 0,3) - x, x=10%

2. The total amount of powdering excipients is 150.0 g granules:

150,0 - 100%

y - 10%, y = 15 г

3. Amount of talc:

(150 г + 15 г) - 100%

X - 3% x = 4.95 g

4. Amount of Talc Stearate:

(150 г + 15 г) - 100%

y - 1%, y = 1,65 г

5. The amount of starch is found by the difference:

15 g - (4.95 g + 1.65 g) = 8.4 g

RECOMMENDED LITERATURE

Regulatory

1. Державна Фармакопея України: у 3 т. Державне підприємство "Український науковий фармакопейний центр якості лікарських засобів". – 2 вид. - Харків: Державне підприємство "Український науковий фармакопейний центр якості лікарських засобів". 2014. - Т.1. - 1128 с.: - Т.2. - 724 с.: - Т.3. - 732
2. European Pharmacopoeia 8.0 [8th edition] / European Directorate for the Quality of Medicines & HealthCare. – Strasbourg, 2013. – 3638 p.
3. Good manufacturing practices for pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report. Geneva, World Health Organization, 2022, Annex 1 (WHO Technical Report Series, No. 823).

Basic

1. Pharmaceutical Formulation. The Science and Technology of Dosage Forms. e-book / ed. by Geoffrey D. Tovey. – The Royal Society of Chemistry, 2019. 409 p.
2. Loyd V. Allen Jr. The Art, Science, and Technology of Pharmaceutical Compounding, 6th edition. – Washington, D.C. : APhA, 2020. – 699 p.
3. https://pharmaeducation.net/tablet-compression-machine/

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