MINISTRY OF HEALTH OF THE REPUBLIC OF UZBEKISTAN

CENTER FOR DEVELOPMENT OF MEDICAL EDUCATION

TASHKENT PHARMACEUTICAL INSTITUTE

“PRODUCTION OF MEDICINAL PREPARATIONS”

Methodical manual for laboratory lessons

for the students of the third course faculty “Industrial pharmacy”

Part I

Tashkent - 2015

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Part I

Tashkent - 2015

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INTRODUCTION

Industrial production of medicinal preparations became the choiceless method of mass provision with available medical aid for population of industrially developed countries. Share decreasing of individual production of medicinal preparations according to physicians' prescribing naturally increases the role of industrial provision with available medicinal means the population of any country. Extract preparations are the most spread medicinal means that is why mastering the principles, technologies and study the equipment for production, quality control of these medicinal forms are always topical when training specialists.

Educational material is given according to logical structure of the theme: objective of the lesson, ability and skills, which must be acquired after doing the tasks, information material, control questions to find out the students' initial level of knowledge and methodical recommendations for carrying out practical tasks. For consolidation students' knowledge on each theme control questions which can be used in conduction seminars are given.

In this section in detail are given theoretical extraction processes, description and principal nomenclature of the produced tinctures and extracts, methods of their preparing, basic methods of purification, technological and instrument production schemes.

In appendix there are general pharmacopoeia articles, technological and instrument production schemes of medicinal forms of industrial production, tests for self-control, creative tasks for students.

List of abbreviations used in the manual:

BAS – biologically-active substances;

AW – auxiliary work

Ct – control technological;

Cc – control chemical;

MS – medicinal substances;

MPRM – medicinal plant raw material;

PW – stages of processing wastes;

TP – technological process;

PLS – stage of packaging, labeling, shipping of finished product.

THEME: INTRODUCTION. NTD. POWDERS AND THEIR INDUSTRIAL PRODUCTION. TECHNOLOGY OF PREPARING CHILDREN'S POWDER

Objective: To get acquainted with terminology and production of finished medicinal preparations (FMP), with structure of state organs and standardization services, and also with rules of their packing and labeling. To study the technology for preparing powders and gatherings, the principle and device of grinding, sieving and stirring mechanisms, filtering classification; to learn composing material balance, technological production schemes.

Importance of theme: Subject of production medicinal preparations gives knowledge about rational production of medicinal preparations. In order to produce finished medicinal preparations normative-technical documentation should be studied (SP, PA, TPA, laboratory, experimental-industrial regulations, technological industrial regulations, TC, SectSt, SSt) confirmed in determined order. NTD must provide quality improvement and effectiveness of medicinal preparations.

Administrative bodies when producing finished medicinal forms: 1. SJSC "Uzfarmsanoat"; 2. SJSC "Dori-darmon"; to get acquainted with 3. State administration of quality control of medicinal preparations SAQCMP which has worthy role in organizing technology of preparing and standardization medicinal forms.

Normative documentation - are documents setting rules, general principles or descriptions, regarding various types of activities or their results.

NTD for medicinal preparations, medicinal plant raw material and items of medical equipment is divided into the following categories:

1. Technological and technical regulations.
2. State pharmacopoeia (SP)
3. Pharmacopoeial articles (PA)
4. Provisional pharmacopoeial articles (PPA)
5. State standards (SSt)
6. Sectoral standards (SectSt)
7. Technical conditions (TC)
8. Leading normative document (LD) - instructions, methodical recommendations and etc.
9. Industrial and technological instructions.

For conduction of this practical lesson pedagogic technological method *TRAINING «MILL»* is used

№	**Normative documents needed for production finished medicinal forms**	**Normative documents**
1	PA	
2	PPA	
3	SP	
4	SSt	
5	TC	
6	SectSt	
7	Regulations	
8	Decree of social institute	
9	КСТ	
10	Licence	
11	Pension book	
12	Decrees of SanC	
13	Registration	
14	ISO, GMP rules	

Situational tasks:

1. Should the enterprise in production of medicinal preparations meet the requirements of ISO, GMP?

2. If the enterprise doesn't meet the requirements of SanC can it produce medicinal preparations?

3. Is it possible to produce medicinal preparations with the help of industrial regulations?

Control and theoretical questions:

1. Tell about the subject of medicinal preparations production (PMP) and its connection with other pharmaceutical subjects.

2. What kinds of regulations do you know? Production regulations and its sections.

3. Tell about PMP sections and give information about general objectives.

4. What standard do SP, TPA, PA conform to?

5. Give brief information about the history of PMP subject and the people who contributed to its development.

6. Administration bodies in production of medicinal preparations.

7. What kinds of pharmaceutical plants produce medicinal preparation in our republic?

8. The main role of technical control department in production enterprises and its obligations.

9. What NTD are required in production of FMP?

11. Composing and confirmation of laboratory regulations?

12. Main standards set for FMP.

13. Main principles of GMP.

14. Production structure of GMP.

15. What is validation?

16. Grinding in pharmaceutical production. Types of grinding. Degree of grinding.

17. What devices are used in grinding of plant raw material? Describe principles of their work.

18. What are advantages and disadvantages of ball mills?

19. How does the grinding process depend on physical-mechanical properties of raw material?

20. Sieving. Sieving classification of grinded raw material.

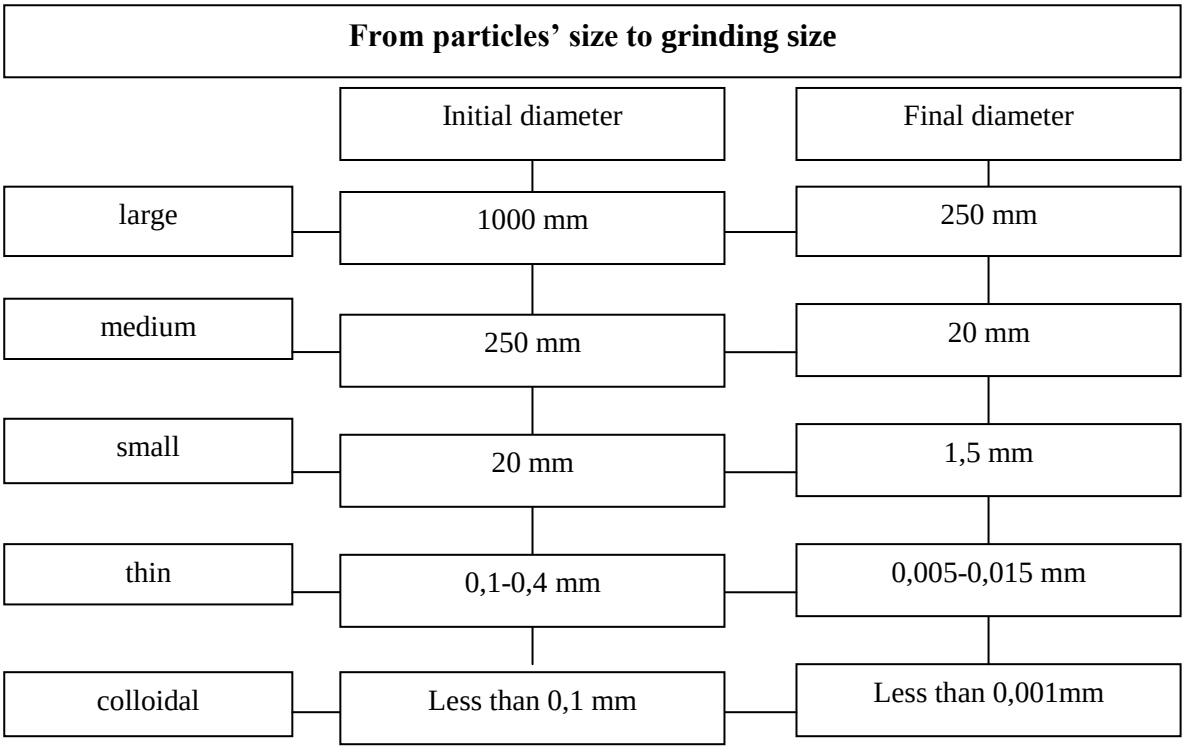
21. Materials and types of sieve clothes.

22. What types of mixers do you know?

23. Prepare 100 kg of powder of licorice root ($К_{cost}$=1,001).

24. Quality control of powders and gatherings.

For conduction this practical lesson the pedagogical technological method "Think, reflect on, find out" is used



Powders – solid medicinal form for internal and external application, having different flowability degree. Production of powders in plants is concentrated in powder-milling section, consists of grinding, sieving, stirring and standardization.

Pharmaceutical enterprises produce in the form of powders the following preparations: salt Karlovy Vary synthetic, halmanine, powder of licorice root complex, children's powder.

Grinding process is widely used in pharmaceutical industry with various purposes. Grinding can be the auxiliary process for provision further dissolution, extraction, drying and etc., which course faster and more complete, the larger the surface of participating in

them solid substances. Grinded material in this case plays the role of semi-product, as it is used by the enterprise for preparing solutions, tinctures, extracts, tablets and etc.

Grinding can be the basic process for preparing the marketable product (powders and medicinal gatherings) with definite particles' size, in this case the technological scheme of preparing grinded product consists of several step-by-step technological stages: grinding of material; sieving; mixing (in preparing complex powders and gatherings).

GRINDING is a process of decreasing particles' size by mechanical effect. In the result of grinding the specific surface of particles increases that allows significantly increase the speed of chemical and diffusive processes, dosage accuracy of MP, and in some cases intensify pharmacological activity of MP.

In technological practice grinding is characterized – by grinding degree of the substance.

Grinding degree (i) is called diameter relation of material part before grinding (D) to diameter of particles obtained after grinding (d), i.e.

$$i = \frac{D}{d}$$

When conducting grinding process the requirements of State pharmacopeia or SSt to particles' size of grinded material are taken into consideration. Depending on the size of initial material and the size of grinded material conditionally are distinguished the following types of grinding:

	i	D,mm	d,mm
Large (crushing)	2-6	1000-200	250-40
Medium (crushing)	6-10	250-50	40-10
Fine (crushing)	10-50	50-25	10-1
Thin (crushing)	50-100	25-3	1-0,4
Colloidal (размол)	100-10000	0,2-0,1	Up to 0,001

In pharmaceutical practice medium large, fine, minute and the finest grinding are widely applied. To grinding can be subjected solid substances of mineral and organic origin. Depending on structure all solid substances are divided into 2 groups: amorphous and crystal. From technological point of view to these categories should be added the third one – materials with cellular structure (plant and animal raw material).

Grinding machines can be classified according to different features:

- **purpose**: prior or final grinding;

-**method of grinding material:** cutting (herb-cutters, root-cutters), squashing and abrasive (rollers, chaser mills, millstones, excelsior; percussion-centrifugal mills (hammer mill, cross-beating, disintegrator, dismembrator), percussion-abrasive (ball and rod-shaped mills; machines of ultrafine grinding (vibromills, colloidal and jet mills),

- **grinding degree of material** (grinders of large, medium and fine grinding, mills of fine and colloidal grinding), type of working instrument (disk, ball, cutler, rotor machines and etc.).

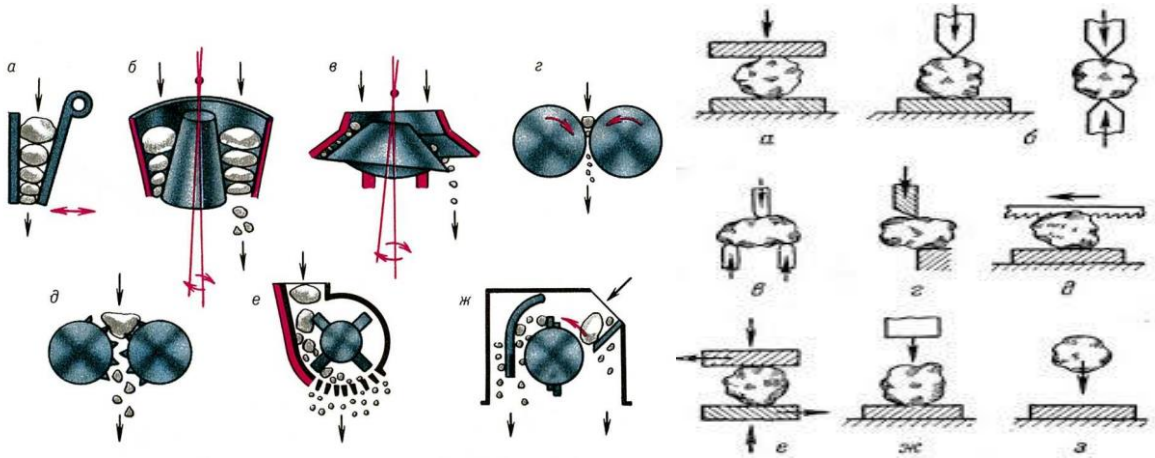


Fig.1,2. Grinding methods

SIEVING. Grinded materials are always heterogeneous on particles' size. By this reason it is necessary to separate larger and smaller particles from the basic mass. This process is called - sieving, sifting or sieve classification and is carried out by means of sieves. In the result of sieving the initial material is divided into 2 fractions: sieving (material, passed through shorts) and sifting (kept on sieve).

The main part of sieving machines are sieve cloths which are divided into wattled, punched, fire grate. Form of net's holes can be square, round, right-angled, that depends on method of preparing nettings and material, which they are made of.

Woven sieves are prepared by weaving thin fibers or wires. Natural silk, synthetic materials (fosta nylon, lavsan), special sorts of corrosion-resistant steel, brass (alloy of copper and zinc), phosphorous bronze are used. Cloths of woven sieves are made observing specified ration between width of holes and thickness of threads according to so called «formula of sieves»: width of net holes - 6/n; thickness of threads - 4/n, where n – number of threads, related to 1 cm of sieve cloth.

Ratio of constant numbers 6 and 4 to the number of threads gives the possibility to

determine width of holes and thickness of threads. According to this formula width of net's holes must be by 1,5 times larger than thickness of thread (6:4). Woven sieves are relatively cheap, but not enough durable. Their net is easily stretched, threads are moved, holes' size is changed. To increase durability silk woven sieves in some cases are supported with metallic bearing. Metallic wire nets are pressed in places of crossing threads or made them of shaped bent wires.

Punched, piercing nets are metallic plates with frequent round, oval or square holes. Punched nets are distinguished by high durability. Such sieves are widely used in industry, but they have enough large holes – not less than 0.3 mm.

Fire grates sieves are combination of metallic (cast-iron, steel) shaped plates. In spite of extreme durability, sieves are applied not often, as they are differed by low productivity.

In industrial conditions are used mechanical constructions of sieves: rotation, swinging, vibration.

Rotation sieves are drums of cylindrical, conical or polyhedral form (reels), walls of those are made of net or punched metallic plates. Cylindrical drum sieve rotates on roller and fixed slightly with a bend to horizontal line (under the angle of 4-7°). In order to remove dispersion of material the drum is put into coat. Sieve surface of the drum consists of sections. Each section – is a flat detachable sieve with enlarging during the course material by holes' size. Advantage of rotation sieves is the possibility to differentiate material to several fractions with different particles size. In spite of simplicity of construction and service rotation sieves are applied relatively rarely in connection with small productivity per unit of sieve surface, and net holes are easily filled, as material is not shaken.

Swinging sieves are applied for sieving plant material. They are flat swinging box in elastic support fixed with a bend under the angle of 7-14° to horizontal line, with vibration number of 60-400 turn/min and amplitude of 5-225 mm. Swinging movement is created by elbow roller, conrod-crank-type or eccentric mechanisms. Productivity is not high, and net holes are easily filled, as movement of material is smooth in horizontal surface.

Vibration sieves are similar to swinging, but they have larger frequency of rotations (1800 num/min and more) and low amplitudes (0.3-5 mm). Such sieves are widely used in pharmaceutical industry. Their large productivity is explained by the fact that, at high frequency of sieve rotations its holes are not filled with material, thanks to persistent tossing in the net.

According to construction there are 3 types of vibration rolls depending on vibration device: electromagnetic, gyration, inertial.

MIXING of powder-like products and also mixing of vaporous materials is applied in technology of preparing most MF and carried out in special mixers. Mixers are classified according to process of mixing (convection or diffusive), structural feature (drum mixers with rotation case and paddles), method of influencing on mixture (gravitational, centrifugal), type of mixing process (periodic or persistent) and other features.

MATERIAL BALANCE

According to the law of the conservation of mass of substances the amount (mass) of initial materials, taken for production of galenic or finished preparation must be equal to the amount (mass) of the obtained materials (finished product + by-products + wastes). This condition can be expressed by the following equation:

$$g_1=g_2+g_3+g_4,$$

where, g_1- initial materials; g_2-finished product; g_3- by-products; g_4- wastes.

But in practice the amount of obtained materials is always less than the amount of initial ones. It is explained by the fact that there are material losses in any production.

$$g_1 = (g_2+g_3+g_4) + g_5,$$

where, g_5- material losses, kg.

This equation is called the equation of material balance. *Material balance* is the correlation between the amount of initial materials, finished product, by-products, wastes and material losses. Material balance can be presented not only in the form of algebraical equation but in tables of income and cost of materials. In the income part of balance it is given the amount of material introduced into production, and in the cost part – the amount

of obtained materials and losses. In the total the income and cost parts of the balance must compose the same sum. Material balance can be composed: a) for one stage or operation; бfor the unit of finished product (for 1000 or 100 kg).

Task

1. To crush 250 g of sugar in the ball mill and compose material balance for this stage; to calculate the percent of discharge, technological losses and cost coefficient.

2. To sieve grinded sugar. To compose material balance counting wastes at this stage. To calculate the percent of discharge, technological losses and cost coefficient.

3. To compose the total material balance.

4. To carry out sieve analysis of grinded sugar and ascertain fractional η composition (2; 1; 0.5 and 0.25mm) in grams and percent.

Grinding. 250 g of sugar is charged in the cylinder of ball mill, which has balls inside (fig.1), charging hatch of the drum is tightly closed with a cover. The mill is switched on for 1,5-2 hours. After 2-3 min (after dust settling) the cover of ball mill is opened and grinded sugar is poured out to the sheet of clean paper, weighed and compose material balance for this stage:

$$g_1 = g_2 + g_5$$

where g_1 - amount of initial material, charged into the mill, g;

g_2 - amount of grinded material, discharged out of the mill, g;

g_5 - losses, g.

$$\eta\% = \frac{g_2}{g_1} \cdot 100 \quad , \quad \sum_{\text{йўқотиш}} \% = \frac{g_5}{g_1} \cdot 100 \quad , \quad K_{\text{сарф}} = \frac{g_1}{g_2} \quad ,$$

Where η- percent of output, %,

$\sum_{loss}$ - technological expense in %,

K_{cost} - cost coefficient.

Working out material balance. Weighed grinded sugar is poured out to the sieve with diameter of pores of 0.25 mm, which is connected with the bottom (receiver), when

closed with cover and sieved up to residue of minimal amount of powder on the sieve. Then separately is weighed the sieved sugar and residual on the sieve. It is necessary to clean the sieve and receiver from powder with a brush. Then material balance is composed for sifting stage:

$$g_2 = (g^I_2 + g_3) + g^I_5$$

where, g_2 - amount of grinded sugar (g), taken for sifting;

g^I_2 - amount of grinded sugar (g), passed through the sieve;

g_3 - amount of sugar (g), left on the sieve;

g^I_5 - losses (g) during sifting.

$$\eta\% = \frac{(g^I_2 + g_3)}{g_2} \cdot 100 \ , \quad \sum_{\text{йўқотиш}} \% = \frac{g^I_5}{g_2} \cdot 100 \ , \quad K_{\text{сарф}} = \frac{g_2}{(g^I_2 + g_3)}$$

General material balance (considering income):

$$g_1 = (g^I_2 + g_3) + (g_5 + g^I_5)$$

$$\eta\% = \frac{g^I_2}{(g_1 - g^I_3)} \cdot 100 \ , \quad \sum_{\text{йўқотиш}} \% = \frac{(g_5 + g^I_5)}{(g_1 - g_3)} \cdot 100 \ ,$$

$$K_{\text{сарф}} = \frac{(g_1 - g_3)}{g^I_2} \ ,$$

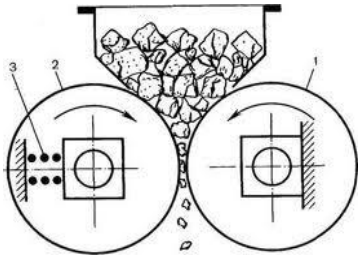


Рис.3. Disk mill

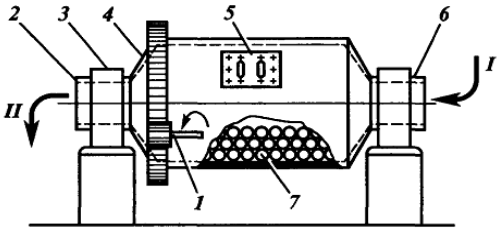


Рис.4. Ball mill

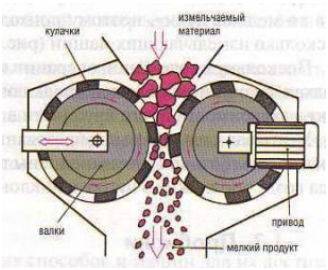


Рис. 5. Roller crusher

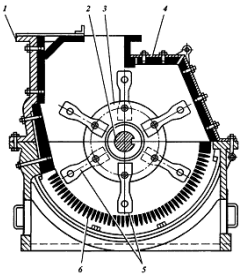


Рис.6. Hammer crusher

Laboratory work -1

PA 42-1615-81. SALT KARLOVY VARY SYNTHETIC (SAL. CAROLINUM FACTITIUM)

Description of finished product. White powder, dissolved in 10 parts of water.

Packing. In cups and polyethylene packets by 125 g, and natural geyser salt (Czech republic) - by 100 g.

Storage. In well stopped up cups and polyethylene packets in a dry cool place.

Application. Laxative and choleretic remedy. As laxative it is administered for adults by 1 tablespoon, for children (2-6 years) - by 1 teaspoon in ½ glass of water воды of room temperature, taken on an empty stomach.

As choleretic remedy it is administered by 1 teaspoon in a glass of water at temperature of 40-50^0 30-40 min before a meal. For taking bath synthetic Karlovy Vary water is prepared calculating 6 g of salt to 1 l of water.

Task

1. To prepare 20 g of synthetic Karlovy Vary salt.
2. To draw the scheme of technological process.
3. To conduct the analysis of finished product.
4. To make material balance according to production stages.

Composition: sodium sulfate dried 44 g, sodium hydrocarbonate 36 g, sodium chloride 18 g, potassium sulfate 2 g.

Table 1

Description of initial raw material

Number of pharmacopoeia article	Technical or trade name of raw material	Content, %	Quality
SP X, art. 439	Sodium sulfate	Not less than 99,0	According to SP
SP X, art. 430	Sodium hydrocarbonate	Not less than 99,0	-«-
SP X, art. 426	Sodium chloride	Not less than 99,5	-«-
SP X, art. 382	Potassium sulfate	Not less than 99,5	-«-

TECHNOLOGICAL PROCESS

Grinding of ingredients and their mixing is produced directly in coffee grinder «Straum» SSt 5.1581-72 (Fig.2) or in tissue grinder MRTU-42-1505-63 (Fig. 3).

For preparing (grinding and mixing) the calculated amount of ingredients is placed into the apparatus, closed with cover and switched on for 12 sec. Then coffee grinder is switched off and after 40 sec. cover is opened, the contents are poured out to the sheet of paper. Coffee grinder is cleaned with a brush. The obtained powder is weighed and filtered through the sieve with pores diameter of 0,2 mm, mixed again, standardized and prepacked.

When applied tissue grinder (for work convenience with small amount of grinded material on the bottom of the vessel the plexiglass plate for knives is fixed) the amount of grinded material not less than 15 g is placed into the apparatus cup, closed with cover and switched on. At that in the beginning the apparatus is switched on for 4000 rot/min, then for 8000 rot/min. Grinding time is 2-3 min. After that the process is the same as working with coffee grinder.

Fig.7. Islamgulov's apparatus

Fig. 8. Coffee grinder

ANALYSIS OF FINISHED PRODUCT

Authenticity. Hydrocarbonates are determined by rapid excretion of carbonic gas after adding diluted acid.

Sulphates are determined by formation of white sediment with solution of barium chloride.

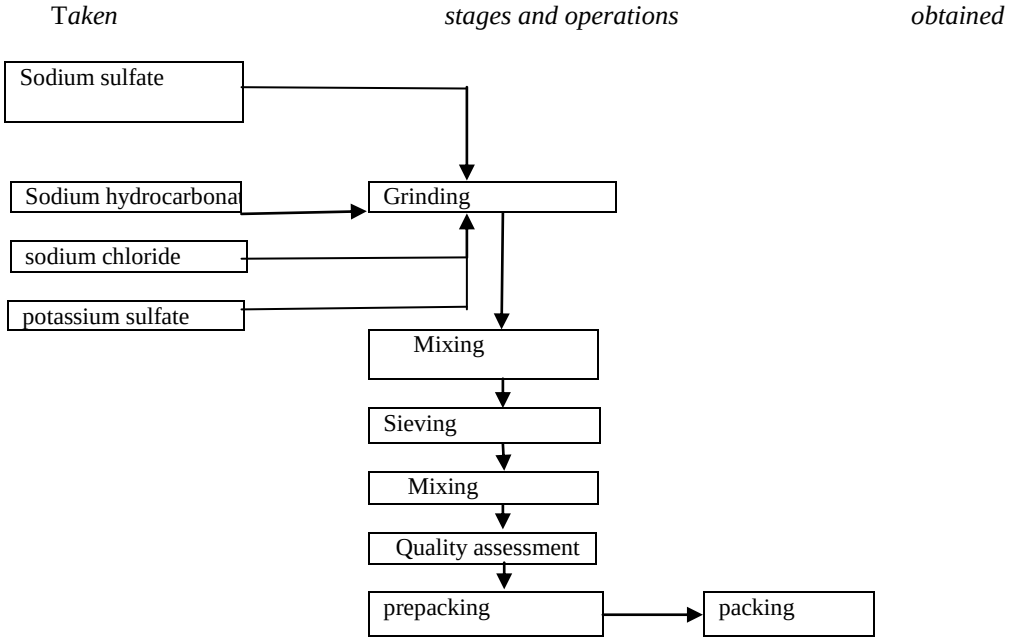
Chlorides are determined by formation of white clotted sediment with solution of silver nitrate in nitric-acid medium.

Ions of potassium are determined by formation of light golden-yellow sediment with solution of sodium cobalt nitrite.

Ions of sodium are determined by coloration of colorless flame into yellow color.

Purity. Heavy metals should be not more than 0.0005%; arsenic – not more than 0.0002%.

SCHEME OF TECHNOLOGICAL PROCESS



MAKING MATERIAL BALANCE

1. To determine output, losses, consumed coefficient and make material balance according to stages and general (see work №1).

2. To make formulation for preparing 10 kg of Karlovy Vary synthetic salt in industrial conditions.

Laboratory work - 2

PA 42-279-72. Halmanine (GALMANINUM)

Description of finished product. White or pink- fatty by touch powder. When rubbing in hands there must not be grains, clots.

Packing. In cardboard boxes by 50 g.

Storage. In dry place.

Application. Antiseptic applied as powder in foot hyperhidrosis.

Task

1. To Prepare 20 g of halmanine.
2. To draw the scheme of technological process.
3. To conduct the analysis of finished product.
4. To make material balance according to production stages.

Composition: salicylic acid 2 g, zinc oxide 10 g, talc 44 g, starch 44 g.

Table 2

Description of initial raw material

Number of pharmacop article and SSt	Technical or trade name of material	Content, %	Quality
SP X, art. 21	Salicylic acid	Not less than 99,5	According to SP
SP X, art. 736	Zinc oxide	Not less than 99,0	-«-
SSt 879-52	talc	-	Medical extra
SSt 7699-66	starch	Not less than 90,0	According to SSt

TECHNOLOGICAL PROCESS

Preparation is conducted in coffee grinder or precutter of tissues according to technology described in work №2.

SCHEME OF TECHNOLOGICAL PROCESS

See laboratory work №1.

ANALYSIS OF FINISHED PRODUCT

Authenticity. Alcoholic extraction of preparation with solution of iron oxide chloride forms violet coloring (salicylic acid).

Preparation with iodine solution forms dark-blue color (starch).

Preparation is treated with hydrochloric acid and to the extracted is added potassium ferricyanide; white sediment is formed.

MAKING MATERIAL BALANCE

1. Determine output, losses, consumed coefficient and make material balance according to stages and general (see work №1).
2. Make formulation for preparing 10 kg of halmanine in industrial conditions.

Laboratory work №3

PREPARATION AND STUDY OF CHILDREN'S POWDER (ASPERSIO PUERILIS)

Description of finished product. White powder.

Packing. Preparation is packed in cardboard boxes by 50 g.

Storage. In place protected from light.

Application. Externally, as drying agent in skin diseases.

Task

1. To prepare 10 g of children's powder.
2. To draw the scheme of technological process.
3. To conduct the analysis of finished product.
4. To make material balance according to production stages.

Composition: zinc oxide 10 g, talc 80 g, starch 10 g.

TECHNOLOGICAL PROCESS

Ingredients which are in the composition weighed beforehand according to working formulation. Then they are grinded each separately, filtered through the sieve with pores diameter of 0.1 mm, then weighed again. Zinc oxide is rubbed through the sieve horny plate, as it sticks to the cloth.

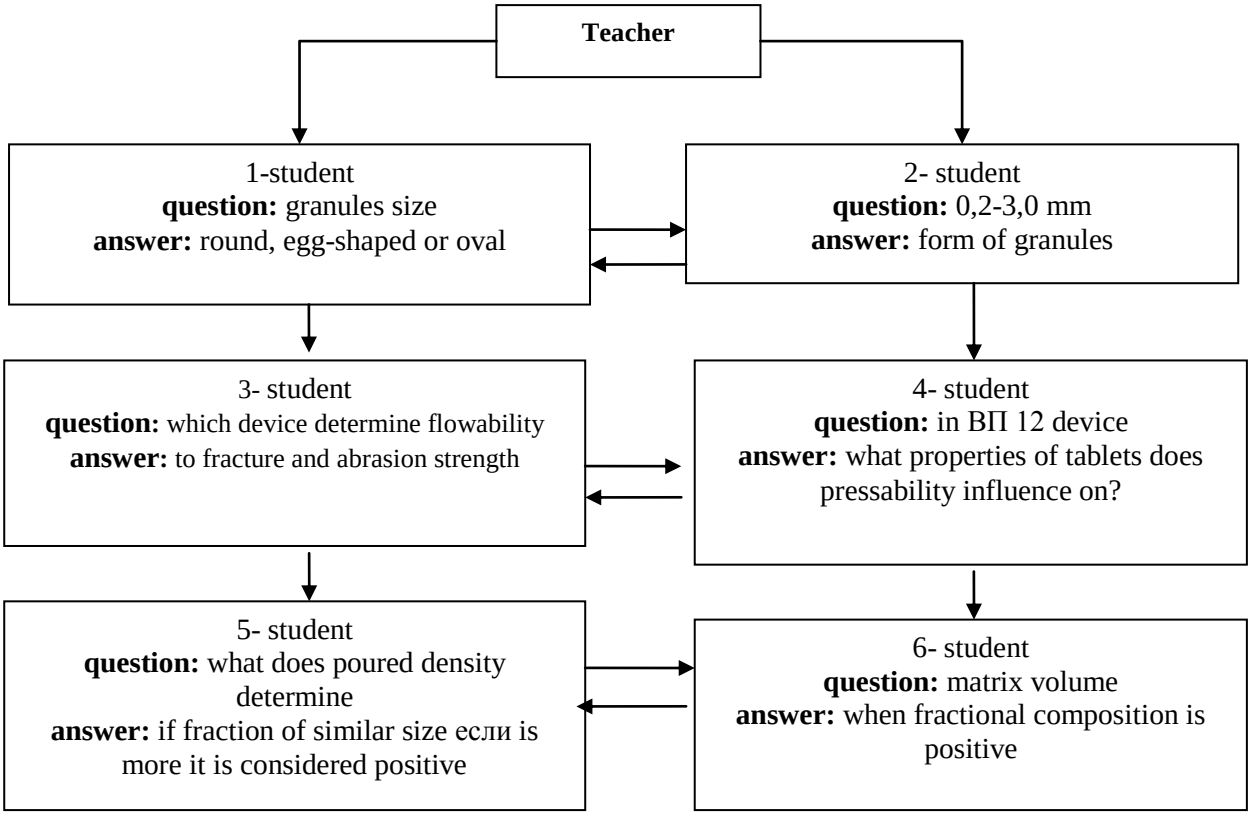
Ingredients weighed for preparing «finished product» are mixed in the mixer with sigma-like paddles according to the rule of mixing powders; i.e. charging is started with the ingredient, which is more according to formulation. After mixing up to homogeneous composition powder is sieved and mixed again.

THEME: GRANULES AND THEIR PRODUCTION. TECHNOLOGY OF PREPARING BLEMAREN GRANULES

Objective: To give definition for granule as medicinal form, their nomenclature and classification. To get acquainted with particular technology of preparing granules and their quality assessment.

Importance. Granules are not only finished medicinal preparations (FMP) but also they are intermediate material in technology of tablet making. That is why methods for obtaining granules have big importance for production.

For teaching this practical lesson pedagogical technological method "I give you, you give me" is used



Situation tasks.

1. When assessed granules quality, small fractions were more than ascertained requirement.

2. When granules of urodanium dissolved in water gases of CO_2 didn't appear.

3. In the process of preparing plantaglucide granules the mass became adhesive.

4. Granules were not disintegrated during the time according to SP XI.

5. In finished granules in composition of medicinal substances deviations were ±15%.

Theoretical questions.

1. Determination of granules and its importance in tablet making.

2. What methods of granulation are there?

3. Give examples of the most modern granulation methods.

4. Granulation in fluidization conditions.

5. Composition and particular technology of urodanium granules.

6. Composition, technology and application of plantaglucide granules.

7. Make working formulation for 50 kg of urodanium granules. ($К_{cost}$= 1,02).

8. Particular technology for preparing urodanium granules.

9. Spheres of granules' use.

10. Importance of briquetting method.

11. Why in preparing urodanium granules 96% ethyl alcohol is used?

12. Assessment of granules quality.

Granule – is a medicinal form in grains (granules) of round, cylindrical or irregular form for internal use. Granulating increases stability of preparations, improves their flowability, that considerably facilitates their dosage.

Granules have bioactive and auxiliary substances. As auxiliary substances are applied sugar, milk sugar, sodium hydrocarbonate, vinic acid, calcium phosphate twice-substituted, starch, talc, dextrin, glucose, sugar syrup, alcohol, water, colouring agents and etc.

Test on good quality of granules. They should be homogeneous according to colouring. Granules size (determined by sieve analysis) should be 0.2-3 mm. Amount of small and larger granules shouldn't exceed in total 5%. Permissible deviations in composition of medicinal substances in granules shouldn't exceed ±10%. Talc amount shouldn't exceed 3%.

Determination of disintegration. Into conic flask with capacity of 100 ml is placed 0.5 g of granules, added 50 ml of water, with temperature of 37^0C. Flask is slightly rocked with speed of 1-2 times per a second, in the process granules must be disintegrated or dissolved within not more than15 min.

Laboratory work-1

PA 42-627-72. Urodanium (URODANUM)

Description of finished product. Granules of white color with saltish-acidic taste, they are dissolved in water with excretion of carbonic acid.

Packing. In polyethylene packets or glass cups screwing cover by 100 g.

Storage. In well В хорошо stopped up cups in dry place.

Application. In podagra, renal and urinary stones and chronic polyarthritis by 1 teaspoon per ½ glass of water 3-4 times a day (dissolve before use). Application is based on the fact that salts of piperasine and lithium form with urinary acid relatively easily soluble salts and promote their excretion from the body.

Task

1. To prepare 20 g of urodanum granules.
2. To draw the scheme of technological process.
3. To conduct the analysis of finished product.
4. To make material balance according to production stages.

Composition: piperasine 2.5 g, lithium benzoate 2 g, hexamethylenetetramine 3 g, sodium benzoate 2.5g, sodium phosphate twice-substituted waterless 10 g, sodium hydrocarbonate 37.5 g, vinic acid 35.6 g, sugar 1.9 g, ethyl alcohol 96% 30,1 ml.

Table 3

Description of initial raw material

Number of pharmacopoeia article and SSt	Technical or trade name of raw material	Content, %	Quality
PA 42-619-72	Piperasine phosphate	99,0	According to PA
SP X, art. 328	Hexamethylenetetramine	99,0	According to PA
SP X, art. 424	Sodium benzoate	99,0	-«-
SP X, art. 319	Sodium phosphate dried	Not less than 75,0,0	-«-
	Sodium hydrocarbonate		-«-
SP X, ст. 430	Ethyl alcohol	99,0	
SSt 5962-67	sugar	Not less than 96,2	According to SSt
PA 42-77-72	lithium benzoate	99,8	According to PA
PA42-372-72	vinic acid	-	-«-
SectSt НКПП-424		-	According to SectSt

TECHNOLOGICAL PROCESS

All ingredients, beforehand grinded and sifted through the sieve with diameter of pores of 0.2 mm (sieve №32), are place into coffee grinder, closed with cover and switched on for 12 sec, then the content is transferred into porcelain cup, coffee grinder is cleaned with brush and the mixture is moistened with 96% alcohol. Mass should be not very wet and friable. It is granulated through the sieve with diameter of

pores 3 mm. Wet granules are laid out by thin layer on the sheet of oil paper and dried in drying cabinet at temperature of 35-40^{0}C up to the optimal (3%) residual moisture. After drying they are passed through the sieve again with diameter of pores of 1.5-2 mm. Granules are standardized and delivered as finished product in a cup with screwing cover.

Note. Amount of vinic acid is taken more than according to stechiometric calculation for leading the reaction up to the end in dissolving preparation and for giving acidic taste.

ANALYSIS OF FINISHED PRODUCT

Authenticity. The solution is treated with ether, the ether is evaporated, to the residue is added a solution of sodium hydroxide and solution of ferric chloride oxide - sediment of light yellow color is appeared (benzoate ion).

Lithium is determined by appearance of yellow color from toron solution.

To the solution of preparation after removing formaldehyde Dragendorf reagent is added - sediment of red color is appeared (piperasine).

Test on good quality of granules. In the obtained granules appearance, disintegration and deviations in content of active substances are determined (see Granules).

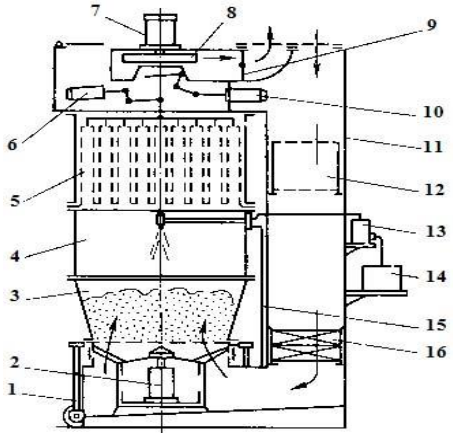


Fig. **9.** Principal scheme of apparatus Liquefied layer of granulation (СГ-30)

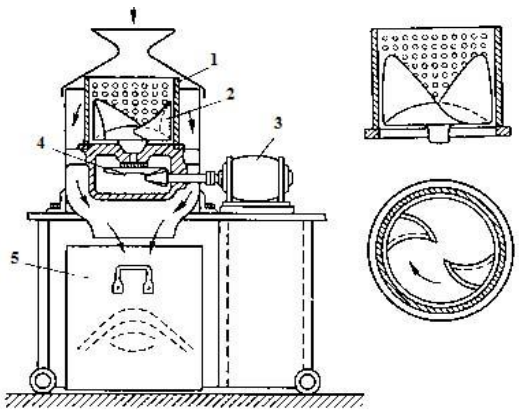
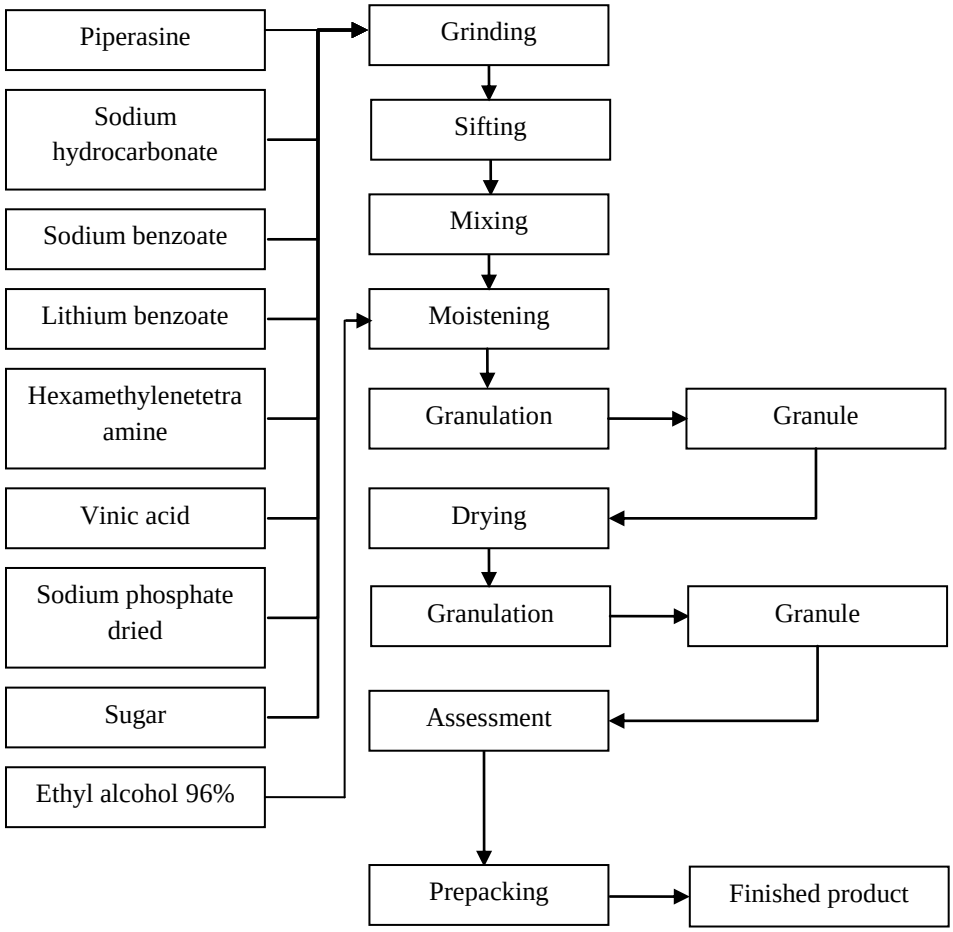


Fig.10. Granulator vertical with pseudo-

SCHEME OF TECHNOLOGICAL PROCESS



Laboratory work - 2

PA 42-266-72. GRANULES OF PLANTAGLUCIDE

(GRANULAE PLANTAGLUCIDI)

Description of finished product. Preparation is in the form of granules with size of 0.2-3 mm of dark-grey color, sweet taste, soluble in water forming turbid liquid.

Packing. By 50 g in glass bottles with screwing plastic covers.

Storage. In well stopped up cups in dry place.

Application. It has anti-inflammatory and spasmolytic properties, slightly increases secretion of gastric juice. It is prescribed internally by ½ teaspoon 2-3 times a day 20-30 min before meals. Before taking the preparation is dissolved in ¼ glass of warm water.

Task

1. To prepare 20 g of plantaglucide granules.
2. To draw the scheme of technological process.
3. To conduct the analysis of finished product.
4. To make material balance according to production stages.

Composition: plantaglucide 50 g, sugar 50 g, ethyl alcohol 70% - sufficient amount.

Table 4

Description of initial raw material

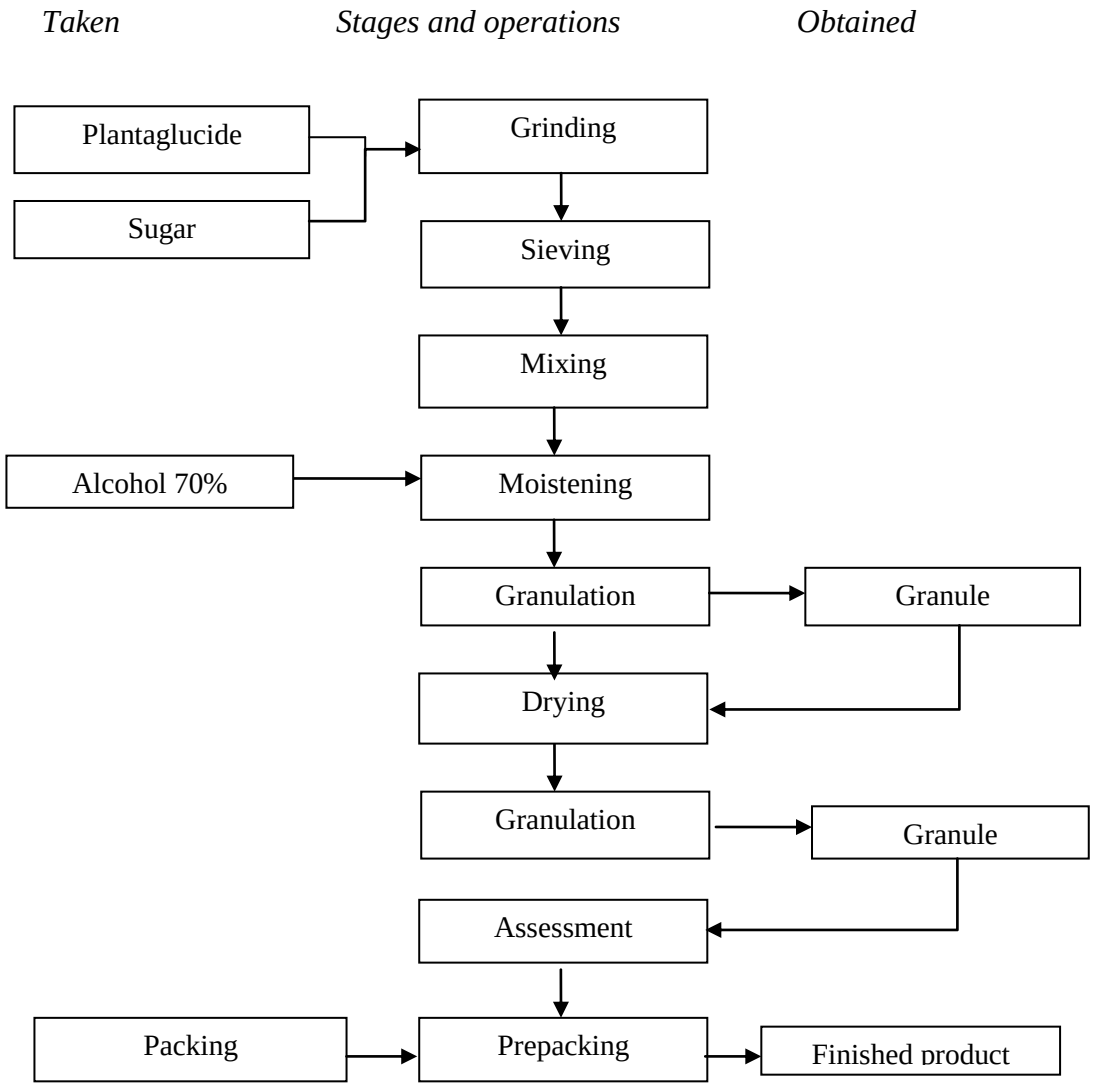
Number of pharmacopoeia article and SSt	Technical or trade name raw material	Content, %	Quality
PA 42-790-73	Plantaglucide	-	According to PA
PA 42-77-72	Sugar	99,8	-«-
SSt 5962-67	Ethyl alcohol	Not less than 96,2	According to SSt

TECHNOLOGICAL PROCESS

All ingredients previously ground and sieved through a screen with openings 0.2 mm in diameter (sieve №32), are placed in a coffee mill, close with a lid and comprise grid for 12 seconds, then the contents are transferred to a porcelain cup, a coffee grinder is cleaned with brush and mixture is moistened with 70 % alcohol. The mass should not be too wet and not too crumbly. It is granulated through a sieve with holes diameter of 3 mm.

The wet granules are spread in a thin layer on a sheet of parchment paper, and dried in an oven at a temperature of 40-60^{0}C. After drying they are again passed through a sieve with holes diameter of 1.5-3mm. The granules standardized and delivered as a finished product in a jar with a screw cap.

SCHEME OF TECHNOLOGICAL PROCESS



ANALYSIS OF FINISHED PRODUCT

Authenticity. In preparation the presence of polysaccharides is determined after acidic hydrolysis by the method of paper chromatography.

When added to a preparation solution of ammonium oxalate, a white sediment is formed (calcium).

Test on good quality of granules. In the obtained granules appearance, disintegration and deviations in content of active substances are determined (see Section 2 Granules).

Laboratory work - 2

BLEMAREN GRANULES

(GRANULAE BLEMARENUM)

Description of finished product. Preparation is in the form of granules with size of 0.2-3 mm, of white color, coarse-grained, with slight odour.

Packing. By 200 g in plastic bottles or polyethelene packets in a set with measured spoon of 3 g, clamp for packet, indicated paper or control calendar.

Storage. In well stopped up cups in dry place.

Application. Preparation is applied in urilithiasis. Before taking granules are dissolved in 200 ml of liquid. Daily dose is 6-18g.

Task

1. To prepare 20 g of blemaren granules.
2. To draw the scheme of technological process.
3. To conduct the analysis of finished product.
4. To make material balance according to production stages.

Composition: lemon acid 39.9 g, potassium hydrocarbonate 32.25 g, sodium citrate 27.85 g -100 g

TECHNOLOGICAL PROCESS

All ingredients previously ground and sieved through a screen with openings 0.2 mm in diameter (sieve №32), are placed in a coffee mill, close with a lid and comprise grid for 12 seconds, then the contents are transferred to a porcelain cup, a coffee grinder is cleaned with brush and mixture is moistened with 70 % alcohol. The mass should not be too wet and not too crumbly. It is granulated through a sieve with holes diameter of 3 mm.

The wet granules are spread in a thin layer on a sheet of parchment paper, and dried in an oven at a temperature of 40-60^{0}C. After drying they are again passed through a sieve with holes diameter of 1.5-3mm. The granules standardized and delivered as a finished product in a jar with a screw cap.

SCHEME OF TECHNOLOGICAL PROCESS

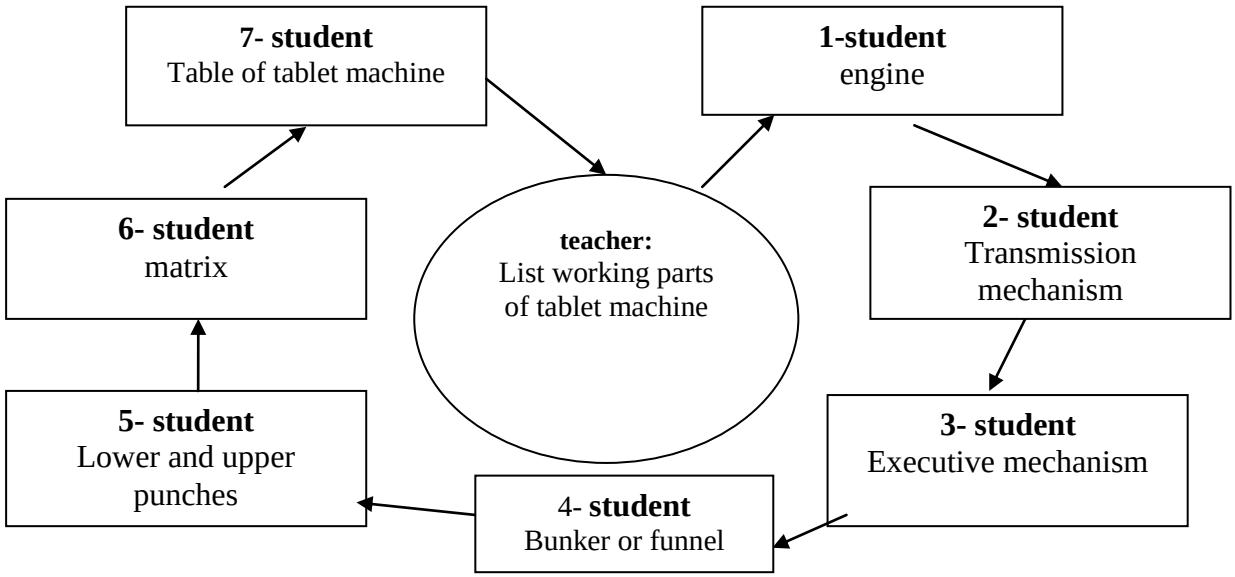
Schemes of technological process see in laboratory works №1 and №2.

THEME: TABLETS AND TABLETTING MACHINES. SETTING AND PRINCIPLES OF WORK OF TABLETTING MACHINES.

Objective. Tablets are not only among the solid but also among the manufactured finished drugs in their performance have a leading position. The main reason for this is technology, packaging, storage, and applications of high performance, and also tablets have significant advantages over other drugs. High performance of tablets is associated with a tablet machine and their working parts.

Importance. Today, the tablet has a significant place among other finished medicines, so the expansion of production, the introduction of new formulations and tablet technology, as well as the study of working arrangements, such as adjusting the volume and strength of the matrix and pressure strength of tablet machines provide high performance and long-term performance.

For conduction this practical lesson pedagogical technological method "Boomerang" is applied



Theoretical questions and situation tasks

1. The role and place of tablets in the pharmaceutical service

2. The forms of tablets and their meaning

3. The advantages and disadvantages of tablets as medicament

4. Why in manufacture of tablets excipients are used?

5. Tablet machines and their classification

6. Explain the advantages and disadvantages of eccentric and rotary tablet machines

7. Calculate the capacity for 1 hour impactor machines matrix with three holes

8. How much time is required for the tabletting of 50 kg of mass by 0.5 g of percussive type machine with two matrix holes?

9. Calculate the specific pressing pressure when tablets of 9 mm diameter, 10 atmospheres gauge reading.

10. What indication pressure gauge must be to press tablets with d = 11 mm, so that the specific pressure corresponds to 1.200 g/cm3?

Fig.12. Tablet forms

Tablets - solid dosage MF obtained by compressing drugs, a mixture of drugs and excipients, or by forming special mass and intended for internal, external, sublingual or parenteral administration. When administered tablets washed down with water, sometimes pre-dissolved in the water.

According to a method for preparing tablets are divided into 2 types: compressed (compression method - the vast majority) and trituration (molding - 1-2%, nitroglycerin).

Currently, the tablets make about 80% of total MF.

Description. Round shape with a flat or biconvex end surface. The size is from 3 to 25mm in diameter. Tablets with a diameter> 25 mm are called briquettes. Tablets with a diameter> 9mm have one or two + risks for division into two or four parts in order to vary the dosage of the drug. Tablet weight of 0.05 to 0.6 g is determined by the dose of medicinal substance.

Administration:

1) orally, absorbed by mucosa of the stomach or intestines;

2) sublingual - absorbed by mucous membranes of the oral cavity;

3) aseptically prepared and used for the preparation of injection solutions, or used for implantation;

4) for the preparation of solutions for mouthwashes, douches, etc.;

5) Pressed urethral, vaginal and rectal MF.

As other MF, tablets have their (+) and (-). To positive (+) properties of tablets are related such as:

a) full mechanization of the production process, delivering high performance, cleanliness and hygiene of tablets;

b) the accuracy of dosing of drugs;

c) portable tablet allows you to quickly release the necessary big MP and facilitates the work of pharmacies transportation and storage;

d) drugs prolonged preservation in the compressed state;

e) masking of unpleasant organoleptic properties (taste, smell). It is achieved by applying coats of sugar; cocoa; chocolate;

f) the possibility of a combination of drugs that are incompatible in their physical and chemical properties in other forms.;

g) localization of MP action. This property is achieved by applying a special composition shells soluble in acid (stomach) or alkaline (intestine) environment;

h) the prolongation of the action of drugs;

i) regulation of sequential absorption of several drugs from the tablet at certain intervals - the creation of multi-layer tablets;

j) error warning when delivered and taken medication achieved pressing off on the

tablet inscriptions.

In addition, the tablets are not free from some (completely avoidable) drawbacks:

a) when storing the tablets may lose their disintegration and cemented or, on the contrary, be destroyed;

b) into the body with pills are administered substances that do not have therapeutic value, sometimes causing some side effects (eg., talc irritates mucous membrane);

c) individual MP (NaBr and KBr) form in dissolution zone highly concentrated solutions, which can cause severe irritation of the mucous membranes. To eliminate this drawback, the tablets before taking are comminuted and dissolved in a certain amount of water;

g) not all patients, especially children, can easily swallow tablets.

Main requirements for tablets and theoretical base of tabletting.

There are 3 main requirements for tablets:

1) dosing accuracy - homogeneity (uniformity) of the distribution of the active substance in a tablet; as well as the correct weight of the tablet;

2) mechanical strength. The hardness, brittleness, fragility characterize the quality of the tablets. Tablets must be strong enough to remain intact when mechanical impacts during packaging, transport and storage.

3) Disintegration - the ability to disintegrate or dissolve in the terms regulated by NTD.

Today tablets are compressed on a tablet machine such as hammer type (eccentric) and rotational (revolving).

Fig.13. Rotation tablet machine (RTM) **Fig. 14.** Eccentric tablet machine

Laboratory work - 1

MECHANISM AND PRINCIPLE OF WORK OF TABLET MACHINES. ASCERTAINING PARAMETERS OF PRESSING PROCESS

Task

1. Introduction and principle of the impact-type tablet machine.
2. To determine the necessary parameters of compaction process (compression force and ejection of the tablets from the mold

Required devices and auxiliary materials for laboratory works:

1. Hydropress
2. Tablet percussive type machine
3. The form, the upper and lower punches (9 and 12 mm)
4. Tapered cylinder (to eject a tablet)
5. Sodium chloride
6. Potassium bromide
7. sieve with a hole diameter of 1000 microns
8. Micrometer
9. Scales and weights, mica
10. Paper Capsules

TECHNOLOGICAL PROCESS

Mechanism of tablet machines. Tablet machine (press) consist of three main parts: the engine, transmission and enforcement mechanisms. The actuator of shoe-eccentric (percussive) machine is a combination of the matrix, the upper and lower punches, the hopper (loading funnel).

Matrix is a steel cylindrical member having one or more the same polished cylindrical holes parallel to each other and to the axis of the matrix. With the help of the locking screw matrix is fixed in a cylindrical nest of the fixed metal countertop. The upper end surface of the matrix must coincide with the countertop surface without interfering with the movement of the hopper.

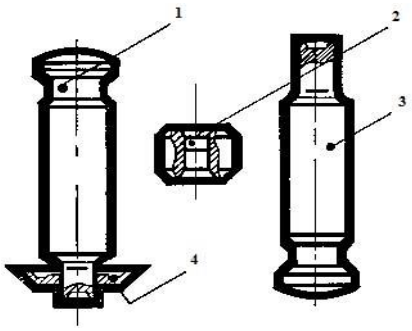


Fig. 15. Punch

Fig.16. Punches and matrix

Lower punch is a single or group metal cylindrical piston with a smooth polished flat or slightly concave operative end surface forming the bottom of the hole matrix. Mechanism of lower punch provides a periodic reciprocating movement of the lower punch within the matrix at a predetermined interval.

Higher punch is a single group or metal cylindrical piston with a smooth polished flat or slightly concave operative end surface. When moving down the upper punch enters the channel matrix and compresses the latter being in the starting material. Press tools must be made of steel CVH (SSt 5950-73) and X12M (SSt 5950-73), and other hard metals. The hardness of the forming punch must be 54-58 HRC, forming part of the matrix - HRC 58-62.

Bunker is a rigid funnel serving as a container for the pressed granulate. It is mixed in a special ledge fastened to the machine bed. In tablet machines hopper or bunker consists of 2 parts: unmoving (storing mass) and moving (transferring weight to the matrix).

Adjusting the volume of the matrix channel. In the matrix channel, filled with granulate flush with the edge of the matrix, must be placed the correct dose of the pressed material. On hand weights is carefully weighed the desired dose of the granulate and poured it into the matrix of the channel at the lowest position of the lower punch.

Adjusting the upper punch. When you have finished the adjustment of the lower punch and filled the matrix channel with desired dose of the granulate flywheel is gently rotated by hand and compressed the tablets. If the tablets are too friable or not pressed,

then the upper die should be set to a lower level. If the machine shaft does not rotate or rotates with difficulty, and the tablet will turn too hard and does not break within the prescribed period, then the upper punch is too low and needs to be slightly lifted.

Determination of the necessary settings of the pressing process. Considering that on tablet machines there are no devices that detect the pressing force, the required compression mode is set manually by means of a hydraulic press and corresponding die-mold.

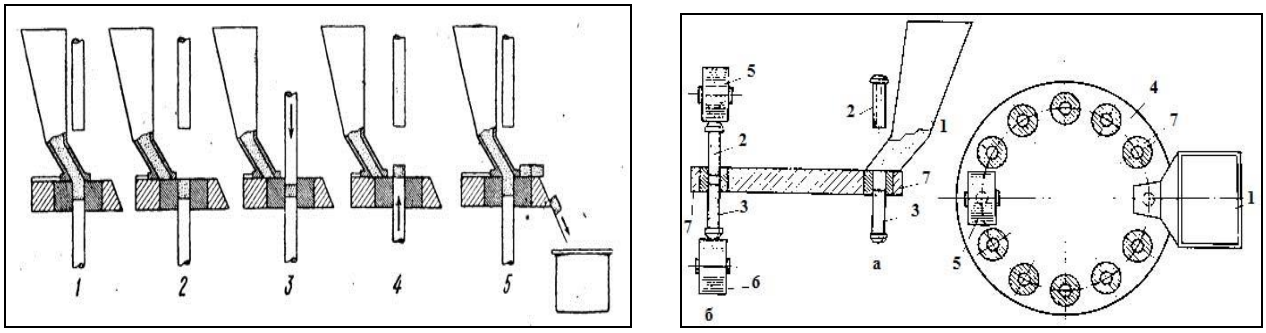


Fig.17. Scheme of tablet process

Adjusting a pressing pressure. For this purpose at hand weights is usually weighed 0.3-0.5 g of mass, brought it carefully into a matrix on the lower punch, then the upper punch is inserted, the entire mold is mounted on the middle of a hydraulic piston and by its gradual pumping pressure is exerted. Upon reaching the desired pressure, marked on the pressure gauge, the lubricator valve is opened and removed the mold.

To obtain tablets that satisfy the requirements of the SP XI by standard sizes (weight, diameter, height, shape), pressing is usually carried out at a specific pressure of 80-300 MPa, but in most cases the pressure is 200 MPa. The pressure force depends on the physico-chemical and technological properties of compressible materials. For example, for potassium bromide pressure of 160 MPa at a weight of 0.5 g, 9 mm diameter matrix is enough. Calculations are made according to the formula:

$$P_{прессования} = \frac{P_{ман} * 26{,}4}{S_{таб.}},$$

Where P_{man} – manometer readout, atm;

26,4 - plunger area of this hydro-press, cm^2;

S_{tab} – surface of tablet, cm^2 equal to pr^2;

(r-radius of tablets, π=3,14).

Consequently, the pressing is needed to produce as long as the pressure gauge reaches the digits 40. The height of the resulting tablets should be 30-40% of its diameter, that is, must comply with SS 64-7-170-75.

Force ejection is calculated by the following formula:

$$Рвытал = \frac{P_{ман.} * 26{,}4}{S},$$

where, S_{lat} - lateral surface of tablet cm^2, equal to (2prh).

(r-radius of tablet in mm; h- height of tablet in mm; π=3,14).

Fig.**18**. Hydropress for pressing

THEME: DETERMINATION OF TECHNOLOGICAL PROPERTIES OF PRESSED MASS

Objective. To determine the technological properties of the pressed mass, to organize activities to improve the technological properties of the pressed poor masses.

Importance. Pressed mass which showed positive performance has a great opportunity to obtain from them high-quality tablets. Therefore, to achieve satisfactory results in determination of technological properties of the pressed mass is an important role in the tablet technology.

Theoretical questions

1. The purpose to determine the technological properties of the pressed mass.
2. What are the quality indicators related to the technological properties of the pressed mass?
3. What are the measures to obtain tablets from poor pressed weight?
4. Fractional composition of the pressed mass, and the purpose of its determination?5.

With the use of what equipment is determined the free-flowing of compressible mass and its value?

6. The main value of the determination of the shape of the particles and its role in the preparation of tablets?

7. The bulk density of the pressed mass, and its definition?

8. Pressed mass, and its definition?

9. Packing factor and purpose of its definition?

10. Porosity, permeability of the pressed mass, and their meaning.

12. How does the compression ratio affects the workflow of tablet machine?

13. Methods for determining the residual moisture content and its value.

Situation tasks.

1. In tablets has happened cracking and breakage, so pressing was difficult.

2. The flowability of the pressed mass is positive, but the strength of tablets after compression has shown that it is unsatisfactory.

3. While pressing the mass was sticking to the mold and pushing it out of the mold has led to some difficulties.

4. Compressibility of the mass is poor.

5. The flowability of the mass is poor.

6. The bulk density of the mass is poor.

For conduction this practical lesson pedagogical technological method "Boomerang" is applied

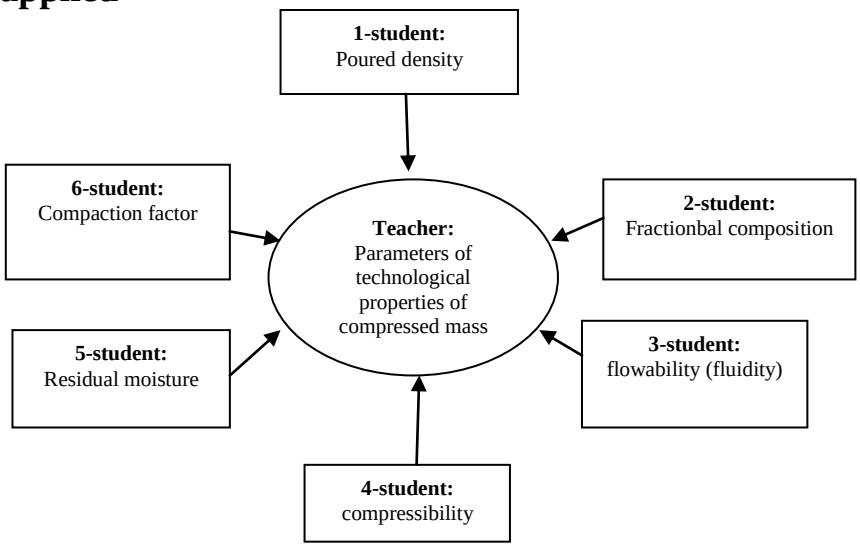


Table 5

Fraction composition

Fraction content, %					
+3,0 mcm	-3,0 +2,0 mcm	-2,0 +1,0 mcm	-1,0 +0,5mcm	-0,5 +0,25mcm	-0,25mcm
3,0	9,0	10,0	13,0	25,0	40,0

Technological properties include fractional composition, bulk density, porosity, compressibility and fluidity. The determination of these properties is produced in two names of tablet mass. And one of them - sugary, and the second - any tablet mass.

Flowability density - is the ratio of freely filled up mass of substance in 1g to unit volume in cm3. It characterizes the bulk properties of powders, which are important in the calculation of the channel matrix and forecasting the stability of tablets mass. The bulk density is determined in a cylinder with a certain diameter of the holes (can be used for this purpose the matrix of tablet machine). In the latter case, the matrix is put on a sheet of parchment paper on a flat surface, filled with the mass and easy tapped on the wall matrix up to a constant volume. The top of the mass is removed by carrying out a surface line of the matrix. The matrix is removed and its content is

weighed and then dividing the weight of the mass per volume of the matrix the bulk density is determined.

Fig. 19. Vibrosieves

Fig.20. Detector of flowability density

Determination of flowability (fluidity). The flowability of the mass is determined by detecting the passage of time of the mass 200 g through glass funnel with outlet diameter of 11 mm. The funnel is set in Electrovibrator "Erweka" with an oscillation frequency of 1 to 350 min (Figure 3). The flowability of powders is associated with several factors: the size, or the size and structure of the granules, the form of the structure of substances, compaction factor, residual moisture, etc. If the powder particles have a smooth surface, the same size and normally the residual humidity, the flowability of the powders will have beneficial properties. This ensures high-quality of production tablets. If the residual moisture of powders or pressed mass is more than normal and the difference between the groups is very large, then to such powders are added auxiliary substances and for improving the flowability are added anti-friction material to change the flowability in a positive way.

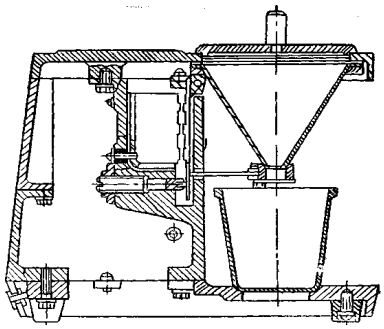


Fig. **21**. Device for determination flowability of powders

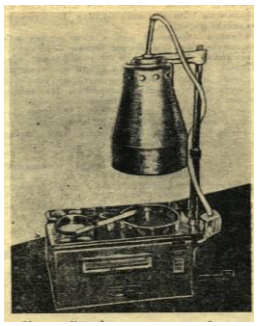


Fig. 22. Moisture gauge of «Kett» brand

Determination of compressibility. Compressibility sometimes is determined by dividing the mass of the tablet at its height. Compressibility - the ability of the particles to mutual attraction and adhesion under pressure. On degree of manifestation of this ability depends the strength and stability of the tablets after depressurization. The drugs that are

part of the tablets have different individual moldability. When drug substance particles have various shapes, as well as limiting the residual moisture it is not required high pressure for compression. The larger the given pressure, the stronger becomes the tablet, and this adversely affects the strength and disintegration of the tablet.

Residual moisture. Residual moisture is important when compressed tablet material. If the residual moisture is above the limit, then the mass will not be filled evenly and it is needed to add anti-friction material, as compressible mass will stick to the punch and die of tablet machine. This adversely affects the quality of the tablets. Appearance of the tablet is unsatisfactory, disintegration and ejection force from the tablet matrix is difficult. If the residual moisture is less than the limit, the mass is difficult to pressing, for pressing large pressure is needed and this leads to rapid aging of tablet machine. The tablet strength to abrasion and fracture is also reduced, this leads to breakage of tablets edge. Therefore, compressible mass should be dried to the desired limit and to select an optimal residual moisture is required. For each drug substance is selected residual moisture in its structure, and this is due to its natural origin. Residual moisture is determined by research.

Laboratory work - 1

DETERMINATION OF TECHNOLOGICAL PROPERTIES OF COMPRESSED MASS

Task

1. To determine the fractional composition of the pressed mass
2. To determine the flowability (fluidity) of pressed mass
3. To determine the bulk density of the pressed mass
4. To determine the compressibility of tablet (compressible) mass
5. To determine compaction factor of pressed mass

Required devices and auxiliary materials for laboratory works:

1. VP-12A devices and 545 AK-3
2. Manual hydraulic press
3. A set of sieves (2000, 1000, 500, 250, 150, 125 and 80 microns)

4. The matrix of 25 mm diameter holes
5. The matrix of 25 mm diameter and punches holes
6. Tapered cylinder
7. The device for determining the strength of the tablets on a break
8. The vibrating device of "Erweka" brand
9. Scales and weights
10. Parchment paper
11. Micrometer, ruler and mica
12. The pressed mass

TECHNOLOGICAL PROCESS

1. **Determination of fractional composition of pressed mass.** Fractional composition is determined by sieving a mass of 100 g through a set of sieves with different diameters (2000, 1000, 500, 250, 150, 125 and 80 microns).

Fractional analysis is performed as follows: 100 g of tested pressed mass (tablet mass) is filled into a set of screens, tightly capped, set on the number of vibratory oscillations 350 in 1 min. For complete fractionation of particles 5 minutes is enough. After their expiration (controlled by stopwatch) the set of sieves is kept for 1 minute for settling of dust particles, the cover is then opened, the contents of each sieve is transferred to a sheet of parchment paper and weighed on scales manual. What is left on the surface of the sieve is recorded (+), passed through a sieve recorded with value (-). Fractional composition is represented with microns, in%.

2. **Determination of looseness (flowability) of compressed mass**. The flowability of the mass is determined by detecting the passage of time of 200 g mass through the glass funnel with outlet diameter of 11 mm. The funnel is set in Electrovibrator "Erweka" with an oscillation frequency of 1 to 350 minutes or by VP-12 instrument. For this compressible mass is fed through the funnel and vibrated for 20 seconds for compaction, and then open the lower portion of the funnel and recorded time of the pulp with a stopwatch. For the first objective account of the results the mass few times is passed

through the funnel, and then fixed the time of its passage. Flowability rate is expressed in kg /s or the flowability coefficient (K) according to the equation:

$$V_{fl} = \frac{m}{t-20},$$

where, Vfl- flowability of pressed mass, kg/s, g/s· $10^{-3,}$

m- weight of pressed mass charged into funnel, kg or g,

t- time of passing pressed mass, sec,

20- time for compaction of pressed mass, sec.

Determination is carried out at least 5 times and registers the average result.

3. Determination of flowability density. Poured density - is the weight ratio of free poured mass in 1 g of substance per unit volume in cm^3. It characterizes the bulk properties of powders, which are important in the calculation of the channel matrix and forecasting tablet stability. The bulk density is determined by free filling the powder in the defined volume (e.g., a beaker) cylinder, matrix of tablet machine or apparatus 545 AC-3. Matrix is put on a sheet of parchment paper on a flat surface, filled with the mass and tapped easy on the wall matrix up to a constant volume. Top of the mass is removed by carrying out a surface line of the matrix. The matrix is removed and the contents are weighed and then dividing the weight of mass per volume of the matrix the bulk density is determined. Moreover, to obtain objective results a certain five-time replication is produced and from values of average results bulk density of the tested mass is calculated. The bulk density is calculated by the formula:

$$\rho = \frac{m}{V},$$

where, ρ- poured density, kg/m^3;

m- weight of pressed mass inside the matrix, g,

V- volume of matrix (πr2h).

4. Determination of pressing ability. Compressibility is determined by dividing the mass of the tablet by the height (the determination is produced in the matrix with diameter hole of 11 mm at a pressure of 1200 kg /cm2 and a weighed portion of 0.5 g) to

which on manual scales 0.5g of investigated mass is placed into a matrix, supported on the lower left-hand punch. Then, the upper punch is delivered. The entire mold is put in the middle of the surface of the plunger of hydraulic press and pressed to the desired specific pressure, marked on the pressure gauge. The mold is then removed from the press, the upper punch is removed and the tablet is ejected by lower punch on the same hydraulic press. To prevent destruction of the surface of tablets to the surface of matrix channel metal cylinder or cone with a larger diameter than the diameter of matrix hole is put. The resulting pellet is weighed on a torsion balance, the height is measured with a micrometer, and the compressibility is calculated by the formula:

$$К_{press} = \frac{m}{h},$$

where, $К_{press}$ – compressibility,

m - tablet mass, g,

h - tablet height, cm.

After determining the compressibility tablet strength to breaking is determined and expressed in Newtons (N).

Determination of compaction factor (pressing). Compaction factor (pressing) - is determined in a matrix with holes diameter of 11 mm and a height of 22.3 mm at a pressure of 1200 kg/cm2 in 0,5 g weighed portion by dividing the height of powder in the matrix before pressing (h1) to a height of the resulting tablets (h2) , i.e

$$К_{com.} = \frac{h_1}{h_2}$$

where, $К_{com.}$ – compaction factor

h_1 – height of the mass before pressing, mm,

h_2 – tablet height, mm.

For example, amidopyrine content in matrix channel is 1.24 g. Therefore, if 1.24 g takes the height of 22,3 mm, then 0.5 g – 9 mm (h_1), i.e.

22,3 -1,24

X – 0,5 X= 9 mm.

The height of obtained tablets is h_2 =4,45 mm.

Pressing coefficient is $K_{com.} = \frac{h_1}{h_2} = \frac{9}{4,45} = 2$

Determination results of technological properties of pressed mass

№	Studied indicators, единица измерня мкм, %	Results	
		Granules of plantaglucide	Granules of urodan
1	Fractional composition: + 1000 - 1000 + 500 - 500 + 315 - 315 + 250 - 250 + 100 - 100 + 50 - 50		
2	Flowability, kg/s*10^{-3}		
3	Poured density, kg/m^3		
4	Compressibility, H		
5	Compaction factor		
6	Residual moisture, (70^0C), %		

Tests

1. The ability of powder mass to pour from the funnel capacity, or "flow" under their own weight and to ensure uniform filling of the matrix channel is called:

A) Fluidity

B) compressibility

C) granulation

D) pelleting

2. Specify the technological properties of the tablet mass, which mainly depends on the accuracy of dosing in the production of the tablets:

A) The flowability

B) Relative density

C) compression ratio

3. What is the "bulk density"?

A) The ratio of tablet mass to its height

B) The ratio of powder height in the matrix to the height of tablet

C) The ratio of the mass to the volume of freely poured material

4. Select the device which determines the fractional composition of dry materials:

A) The device is 545-P-AC-3

B) Microscope with micrometric ruler

C) Device SP-12A

D) The standard set of sieves

5. Specify, with the help of what device determines the flowability of powders and granules is determined:

A) Device SP-12-A

B) The standard set of sieves

C) Microscope with micrometric grid

D) Device 545-P-AC-3

6. Select from the offered properties those that relate to the physical and chemical properties of powders (granules)?

A) Porosity

B) Solubility

C) Bulk weight

D) The power of expulsion

7. The granulometric distribution of particles of pressed material refers to the technological properties and is denoted by the term:

A) The flowability

B) Bulk density

C) Porosity

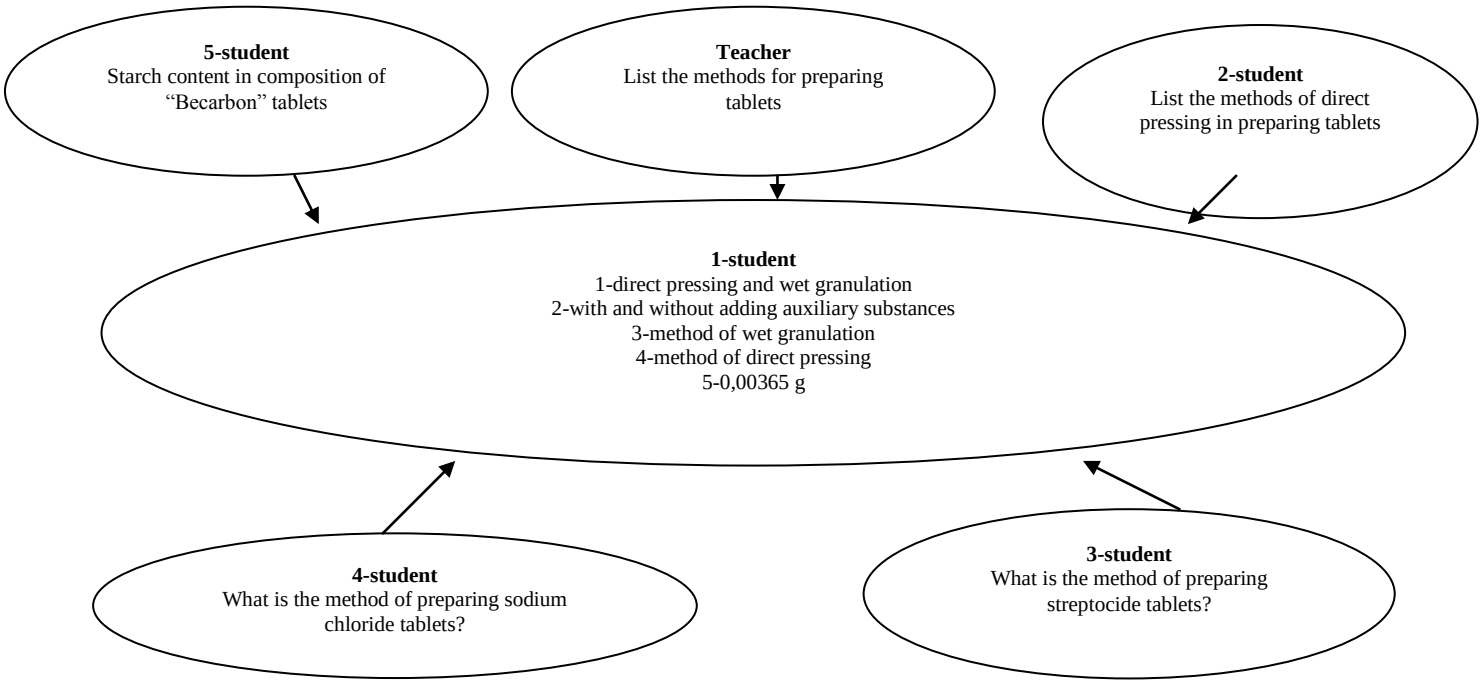
D) The fractional composition

THEME: PREPARATION TECHNOLOGY OF FERAMID TABLETS BY THE METHODS OF DIRECT PRESSING AND WET GRANULATION. AUXILIARY SUBSTANCES

Objective: To date, in tablets technology, there are two methods for obtaining tablets: Preparation of tablets by wet granulation and direct compression. Features of making tablets by direct compression and wet granulation, as well as which types are used and the choice of optimal content of excipients in tabletting.

Importance: From tablets technology results that direct compression process allows eliminating 3-4 technological steps and thus has the advantage over pre-granulation tabletting powders. Tablets prepared by this method have a number of advantages in terms of economy and also from the standpoint of drug bioavailability. However, despite the apparent advantages direct compression is introduced slowly into production. This is because for the productive work of tablet machines compressible material must have optimal processability (flowability, moldability and moisture etc.). Therefore, today auxiliaries and processes have a major role in the production of tablets by wet granulation.

For conduction practical lessons pedagogical technology «Hot potato» is applied



Control questions and situation tasks

1. Create a working recipe according to SP X for 0.5 g tablets of sulfademisine №10 10,000 packages (Kcost = 1.003).

A) Given that for moistening 100g of sulfademisine 5.61 g of 5% starch paste is consumed, calculate how many grams of binding and disintegrating agents you will need.

2. What conditions are necessary for the production of tablets by direct compression? 3. The classification of excipients and their amount according to SP X.

4. What are the pressing theories there?

5. Create a working recipe according to SP X for 0.9 g of sodium chloride tablets №10 10,000 packages (Kcost = 1.003).

6. Calculate the RTM-41 productivity for 1 hour, with 1 matrix hole and rotation number 42 per 1 min.

7. How much time is required for the tabletting of 50 kg of mass by 0.5 g on shock-type machine with two matrix holes?

8. How much time is required for tabletting of 20 kg of mass by 0.3 g per RTM-41 with 1 matrix hole and rotation number of 42 per 1 min?

9. List the most common form of crystalline powders and their importance in tablet technology.

10. Calculate the required amount of excipients to produce 1000 pieces of tablets amidopirine 0.5 g

11. List the methods and conditions for direct compression of tablets.

12. Give the definition of fillers. Classification and characterization.

13. Give the definition of a binder. Classification and characterization.

14. Give the definition of disintegrating agents. Classification and characterization.

15. What is the effect of disintegrating agents?

16. Give the definition of lubricants (anti-friction agents). Classification and characterization.

Laboratory work - 1

TABLETS OF SODIUM CHLORIDE 0.9 g

(Tabulettae Natrii chloridi 0.9)

Description of finished product. Tablets of white color, salty taste. Sodium chloride should be 0.86-0.94 g, calculating for the average tablet mass.

Packing. In glass cups.

Storage. In well stopped cups in dry place.

Application. For preparing isotonic and hypertensive solutions. Isotonic solution is used both subcutaneously, intravenously and in the form of enema as deintoxication agent. Hypertensive solutions (3-5-10%) are used externally in the form of compresses and washes in treatment of purulent wounds. Sodium chloride solutions are also used for baths, rubbing-down, rinsing.

Task

1. To prepare 25 tablets of sodium chloride by direct pressing.
2. To draw the scheme of technological process.
3. To conduct the analysis of finished product.

Composition: sodium chloride – 0.9 g.

Devices and auxiliary substances

1. Tablet impact type machine.
2. Tablet form (matrix) with 12 mm diameter and punches.
3. Drying oven.
4. Sieve with a hole diameter of 1000 microns
5. Scales, weights, paper, mica, porcelain cup
6. Calcium stearate
7. Cotton wool and gauze
8. 100 ml flat-bottomed flask
9. The dried sodium chloride
10. Hydraulic press

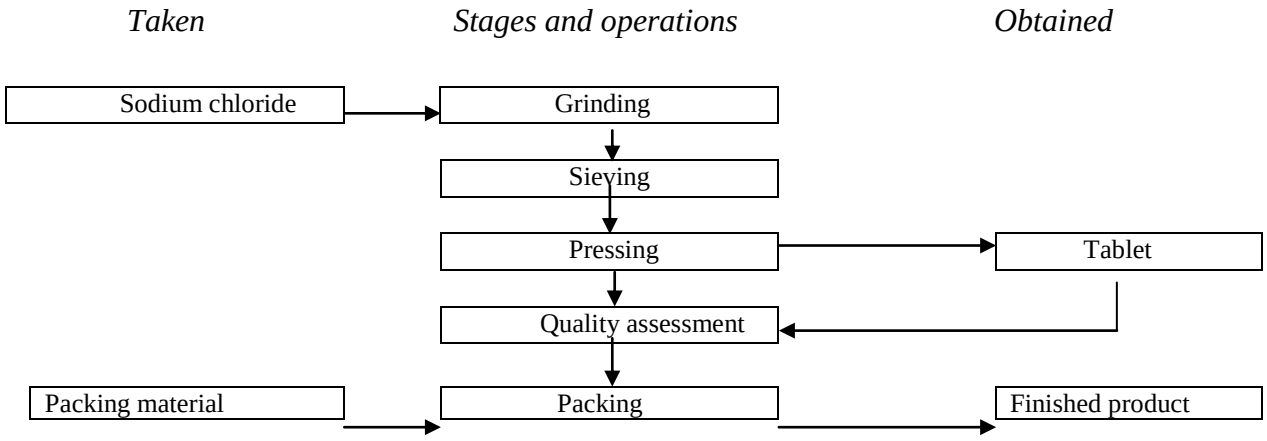
11. Purified water

12. Dishes for the packaging of the finished product

TECHNOLOGICAL PROCESS

Beforehand dried and grinded sodium chloride is sifted through the sieve with holes diameter of 1 mm, weighed 25 g and pressed in tablet machine of percussive type by 0.9 g with diameter of matrix holes 13 mm.

SCHEME OF TECHNOLOGICAL PROCESS



ANALYSIS OF FINISHED PRODUCT

Authenticity. Preparation solution in acetous medium with solution zinc-uranyl-acetate forms yellow crystalline sediment (sodium).

Preparation solution in nitric acid medium with solution of silver nitrate forms white clotted sediment soluble in ammonia solution (chlorides).

Quantity determination. Argentometry method. Indicator – solution of potassium chromate. Sodium chloride should be 0.86-0.94 g, calculating for the average mass of one tablet.

Test for good quality of tablets. In prepared tablets the appearance, average mass, declination from average mass, solubility, strength are determined.

Laboratory work - 2

FERAMIDE TABLETS 0.12 g

(Tabulettae Ferramidi 0.12)

Description of finished product. Tablets of maize-yellow color, metallic taste. Soluble in water.

Packing. By 0.1 g in single dose packings.

Storage. In well stopped packings in dry place.

Application. It restores iron deficiency in the organism, stimulates erythrogenesis. Post haemorrhoidal anemia of various origin.

Task

1. To prepare 25 tablets of feramide by direct pressing.
2. To draw the scheme of technological process.
3. To conduct the analysis of finished product.

Composition: feramide – 0.1 g, potato starch-0.0188 g, calcium stearate- 0.00012 g. Average mass-0.12 g.

TECHNOLOGICAL PROCESS

See laboratory work №1.

SCHEME OF TECHNOLOGICAL PROCESS

See laboratory work №1.

Laboratory work - 2

STREPTOCIDE TABLETS 0.3 g

(Tabulettae Streptocidi 0.3)

Description of finished product. Tablets of white color, with diameter of 9 mm, cylindrical form, flat or with edging or convexo-convex form, tablets height 2.7-3.6 mm. One tablet must contain 0.285-0.315 g of streptocide.

Packing. In convolutes and cups.

Storage. Letter B.

Application. For treatment of cerebrospinal meningitis, erysipelas, quinsy, cystitis, colitis, for prevention and treatment of traumatic infection. Administered by 2 tablets 5-6 times a day.

Task

1. To prepare 25 tablets of streptocide
2. To draw the scheme of technological process
3. To conduct analysis of finished product

Composition: streptocide – 0.3 g, auxiliary substances – sufficient amount.

According to the regulation of the production of the Tashkent Chemical and Pharmaceutical Plant, benign streptocide tablets conforming to the requirements of SP X, are produced using 10% of excipients. As a lubricant is used 1% calcium stearate (0.0033 g), binding and loosening - 9% potato starch (0.0267 g). From these data constitute one tablet recipe:

Streptocide - 0.3 g

Starch – 0.0267 g

Calcium stearate – 0.0033 g

Average mass 0.33 g.

TECHNOLOGICAL PROCESS

Previously pulverized, sifted through a sieve with holes of 0.16 mm diameter calculated amount of streptocide is mixed with a solution of 7% starch paste (100 g of dry powder is consumed 13-16 g of starch paste) in a porcelain cup or twin blade sigma-like laboratory type mixer to obtain a homogeneous moist mass. Its spread in a thin layer on a sheet of parchment paper, and dried in an oven at a temperature of 40-50ºC to optimal residual moisture (1.5%). The dried mass is passed through a granulator - sieve with a hole diameter of 1-2 mm. Mass is weighed, dusted in a porcelain dish with a pre-sieved through a sieve with 0.1 mm diameter holes calcium stearate and the remaining amount of starch (calculated from the total amount of the

used amount is subtracted as a binder). Powdered granules are compressed on a percussive type tablet machine by 0.33 g with diameter of matrix holes of 9 mm. Moreover, first by hand, and after obtaining satisfactory results - automatically.

ANALYSIS OF FINISHED PRODUCT

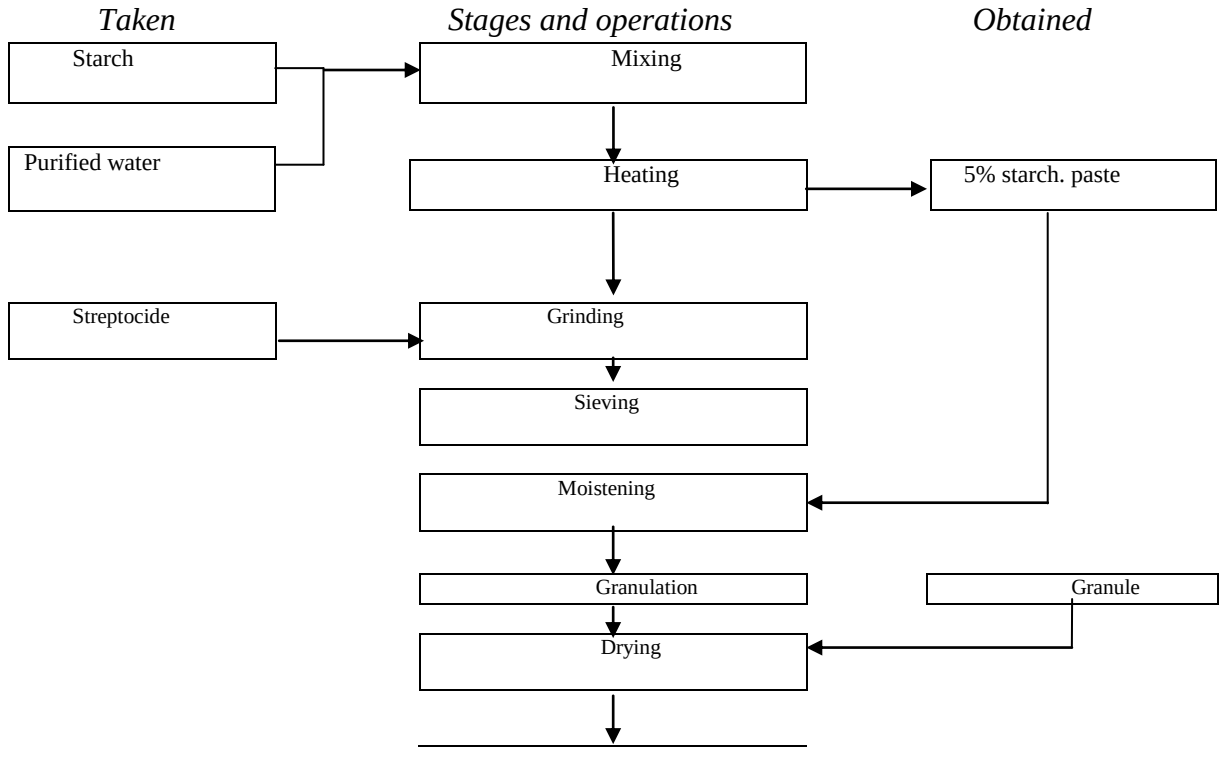
Authenticity. The drug is treated with acetone and extract is evaporated to dryness. The residue is dissolved in water, acidified with hydrochloric acid, added titrite and sodium alkaline solution of β - naphthol, there appears cherry-red color or an orange-red sediment (streptocide).

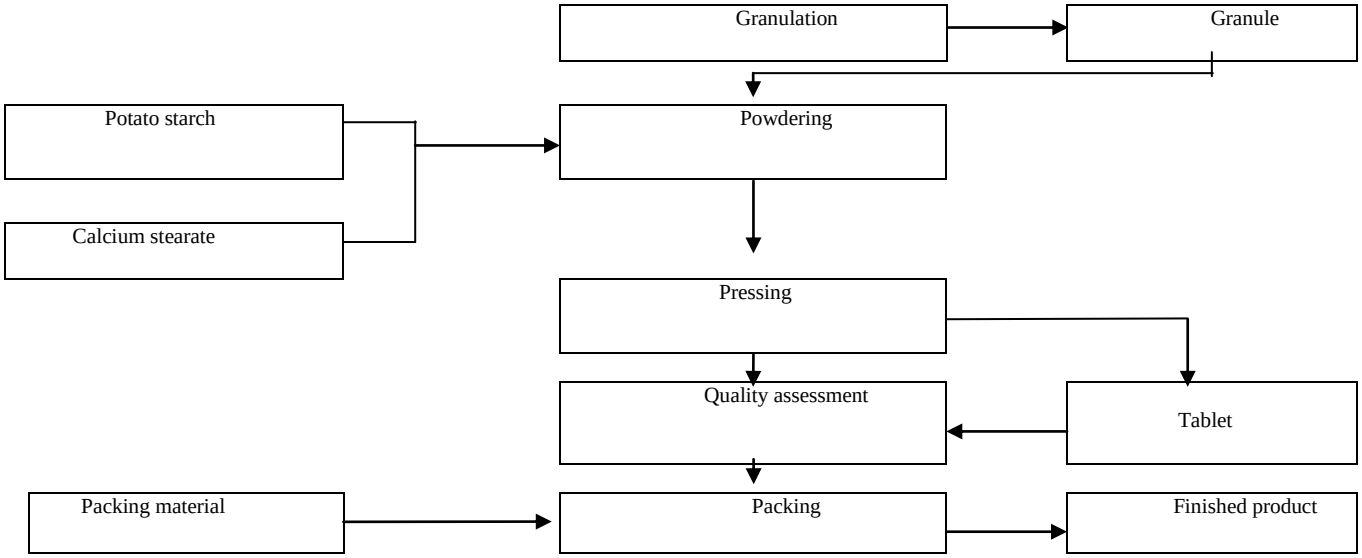
By heating the drug in a dry test tube on the burner's flame is formed alloy of violet-blue color, there is a smell of ammonia and aniline (unlike other sulfa drugs).

Quantitative determination. By nitritometric method. One tablet should contain 0.285-0.3 g of streptocide, calculating for average mass.

Test for good quality of tablets. In the prepared tablets appearance, dimension types, average mass, declinations from average mass, disintegration and strength are determined.

SCHEME OF TECHNOLOGICAL PROCESS





THEME: TABLET COVERING.TRITURATION TABLETS

Objective. To get acquainted with the methods for coating tablets, with coating excipients, as well as evaluation of quality of tablets, coated tablets.

Importance. Protection of tablets from extreme environmental factors, masking the unpleasant taste and odor contained in tablets of drugs, protection of the mucous membrane of the esophagus and stomach, prolongation of the therapeutic effect of drugs, overcoming the incompatibility of different substances in one tablet, by introducing them into the membrane and the core is of great practical and economic importance.

Situation tasks.

1. When film forming were used such excipients as purified water, starch, wheat flour and MCC.

2. After panning on the surface of tablets cracks appeared.

3. 0.1, 0.2 and 0.3 g tablets after пofilm-formation their average mass was 0.2, 0.22 and 0.309 g.

Theoretical questions.

1. In what cases tablets are covered with coat?

2. Technological pattern of coating tablets by pressing. In what machine is carried out compression method?

3. Technology of preparation of tablets coating by panning.

4. Technology of preparation of tablets coating by film formation method.

5. What are the auxiliaries used for coating tablets?

6. How does the mass of the tablet's coat is controlled by "fluidization" method?

Coating pursues the following objectives: to give tablets beautiful appearance, to increase their mechanical strength, to hide unpleasant taste, smell, protect from the environment (light, moisture, atmospheric oxygen), locate or prolong the effect of the drug, to protect the mucous membranes of the esophagus and stomach from the destructive action of the drug. A coating applied to a tablet can be divided into 3 groups: sugar-coated, film and molded.

Mass of a tablet, coated by pelleting should not exceed twice the mass of the tablet taken. When coating with a film the mass of the coat should not exceed 3% of the tablet, and at coating by pressing method coat is 50-100% by weight of the tablet.

Film coatings.

They are created on tablets by applying a solution of a film-forming material, followed by removal of the solvent. This forms a thin (0.05 - 0.2 mm) on the surface of the tablet coat. Film coatings based on solubility are divided into the following groups: water soluble, soluble in gastric juice, soluble and insoluble in the intestines coatings. ***Watersoluble coatings*** protect against mechanical damage, but do not protect against exposure to moisture in the air. The water soluble coats form PVP, MC, oxypropylenemethylcellulose, Na CMC, etc. applied in the form of water-ethanol or aqueous solutions.

Coatings, soluble in gastric juice. These are films, which protect the tablet from the effect of moisture, but do not prevent their rapid degradation in the stomach (for 10-30min). These include polymers having in the molecule basic substituents mainly amino groups for example, diethylaminomethylcellulose, benzilaminocellulose, paraaminobenzoates of sugars and cellulose acetate, etc. For coating are used solutions of these substances in organic solvents. Ethanol, isopropanol, acetone.

Coatings, soluble in the intestine. They localize the drug in the intestine, prolonging its action. For obtaining coatings acetylphthalylC, methaphthalylC, polyvinylacetate phthalate, phthalates of dextrin, lactose, mannitol, sorbitol, shellac (natural HMC). For obtaining film these substances are used as solutions in ethanol and isopropanol, ethyl acetate, toluene and other solvents. CPI (Saint - Petersburg) has developed a tablet coating technology by water-ammonia solution of shellac and acetylphthalylC. To improve the mechanical properties of the films a plasticizer is added thereto.

Insoluble coatings – films with microporous structure. They are solutions of ethylC and acetylC in ethanol, isopropanol, acetone, toluene, chloroform, ethyl acetate and others. With the addition of plasticizers. The mechanism of drug release: digestive juices quickly penetrate the pores of insoluble coat and dissolve medicinal substance or cause it to swell. In the first case, the drug diffuses through the film in the reverse direction, the second - break of coat occurs, after which the drug substance is released in the usual manner.

Forced on coatings.

Forced on coatings - are dry coatings applied to the tablet by pressing on special machines (RTM-41D), which are a combination of the two machines: a rotary - conventional tablet pressing and special - to obtain on them pressed coating. On the first rotor are compressed tablets that are sent to the transmitting device to the second rotor, to matrix of which coating solution is applied and finally the tablet is compressed. The main causes of hindering wider application of this method are lower characteristics of coatings as compared with films and a less attractive packaging.

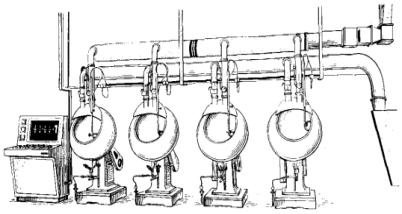


Fig. 24. Dragee pot

Laboratory work -1

COATING TABLETS BY PRESSING METHOD

Task

1. To prepare 100 g of granulate for the coating of tablets.
2. To perform covering with coat 10 model tablet by compression method.
3. To draw a diagram of the process.

4. To make a determination of purity of tablets.

5. To cover the tablet by compression method the next available coat composition is recommended: glucose, sugar, starch 33 g, 1 g of calcium stearate, food dyes (amaranth) - a sufficient number.

Table 1

Description of initial raw material

Number of pharmacopoeial article and SSt	Technological or trade name of raw material	Content, %	Quality
SP X, art. 331	Glucose	100,0	According to SP
PA 42-77-72	Sugar	99,8	-«-
SSt 6-99-98	Starch	90,0	Extra medical
TC 609-65-59-70	Calcium stearate	99,0	

TECHNOLOGICAL PROCESS

Glucose, sugar, starch, calcium stearate, are separately preliminarily crushed, sifted through a sieve with holes diameter of 0.1 mm and mixed in a porcelain dish. The resulting mixture of powders is moistened with 10% starch paste containing 0.1% amaranth dye solution. Typically, per 100 g of powder is consumed 10-13 g of starch paste. The mass is well mixed until a uniform coloration, spread in a thin layer on a sheet of parchment paper and dried at 50-60ºC to optimal residual moisture. The dried mass is granulated through a sieve with a holes diameter of 1 mm, the resulting granules are used for coating of tablets by compression methods.

Covering of model tablets by compression method is produced on a manual hydraulic press at a pressing force of 1600-2000 kg/cm². Readout of pressure gauge is calculated using the formula:

$$P_{man.} = \frac{P_{press.} \cdot 26,4}{\pi r^2},$$

where $P_{man.}$- readout of pressure gauge, atm,

26,4- plunger area cm^2,

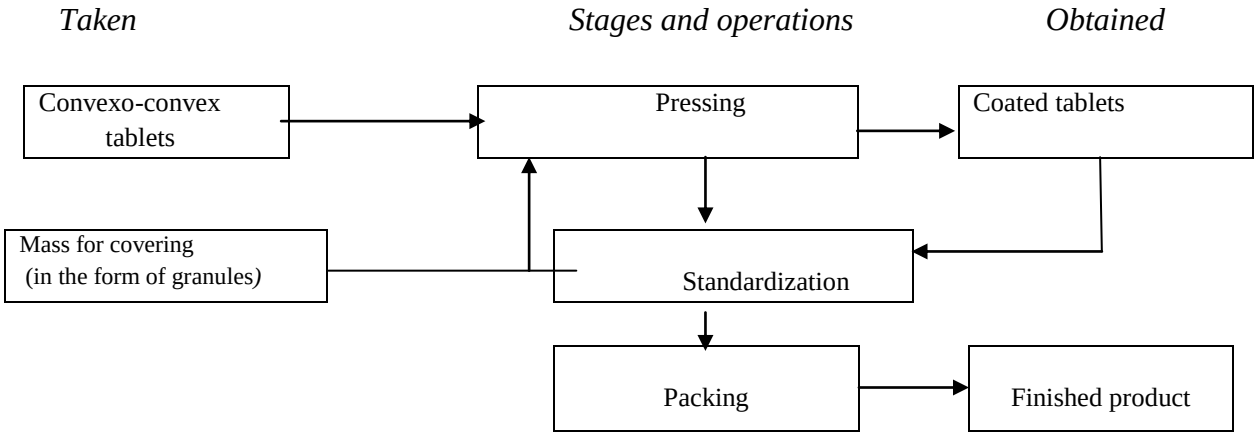
$P_{press.}$- pressing power, kg/cm^2.

The mass of biconvex tablets is pre-determined on manual scales accurately to 0.01 g. Then the finished granulate is weighed in an amount of 100% by weight of the tablet.

A half of the weighed granulate is poured into the corresponding matrix with concave lower punch, the tablet is placed on it and it is poured onto the other half of the granulate. The diameter of the matrix should be 2 mm greater than the diameter of the tablets covered. The upper concave punch is inserted and compressed on a hydraulic press at a calculated pressure (Rman). Then removed the upper punch, put on a matrix cone-stand and on the same hydraulic press pushed the tablet.

Test for good quality of tablets. In the obtained covered tablets the appearance, average mass and disintegration are determined (see. work Tablets.)

SCHEME OF TECHNOLOGICAL PROCESS



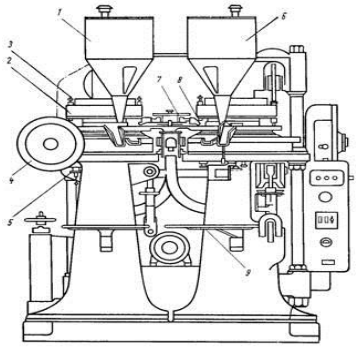


Fig.25. "Drycota" Tablet machine

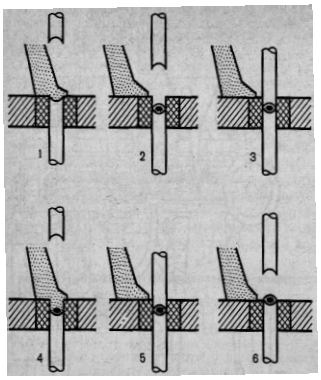


Fig.26. Pressing method

Laboratory work - 2

COATING TABLETS BY FILM-FORMATION METHOD

Task

1. To prepare 100 ml of solution for coating tablets.
2. To perform a coating by film forming method in a coating pan.

3. To draw a diagram of the process.

4. To make a determination of purity of the resulting tablets.

For coating enteric tablets by film forming method is used 5% acetylphthalyl solution in an organic solvent with the addition of plasticizers of following composition:

Acetylphthalylcellulose -5.0 g

Vaseline oil -1.0 g

Amaranth (dye) -0.2 g

TECHNOLOGICAL PROCESS

5.0 g of acetylphthalylcellulose is dissolved in a small amount of an alcohol mixture with chloroform (1: 4) tinted with amaranth then added 1.0 g of liquid paraffin and liquid volume is adjusted to 100 ml with solvent mixture. The resulting liquid is used to coat tablets by film forming method.

The coating is produced in the coating pan of "Erweka" firm. For this purpose 1000 pieces of biconvex model tablets screened out dust, weighed, placed in a coating pan. With continued rotation of the boiler tablets are sprayed by spraying with a solution of film-formation. After uniform wetting of tablets spraying is stopped and pot is rotated until complete volatilization of the solvent. This operation is repeated as long as the mass of the film will not be 3% by weight of the tablet.

The mass of the coat is calculated using the following formula:

$M_{film.} = \frac{m_1 - m_2}{n}$, where,

$m_{film.}$- film mass, g,

m_1 - tablets mass after covering, g,

m_2 - tablets mass before covering, g,

n- tablets number.

The thickness of the film is calculated using the following formula:

$$L = \frac{m_{film}}{\rho \cdot S},$$

where, L- film thickness, mm;

m_{film} - film mass, g;

ρ – film density, g/cm^3;

S- tablets surface, cm^2.

Test for good quality of tablets. In the obtained covered tablets the appearance, average mass and disintegration are determined (see. work Tablets.)

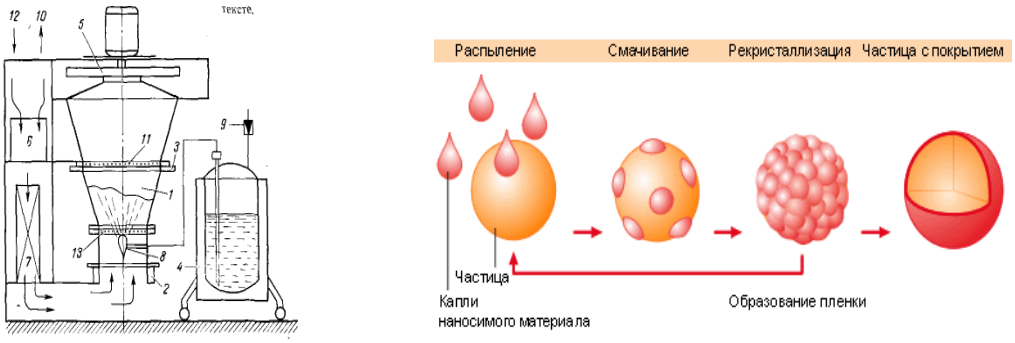


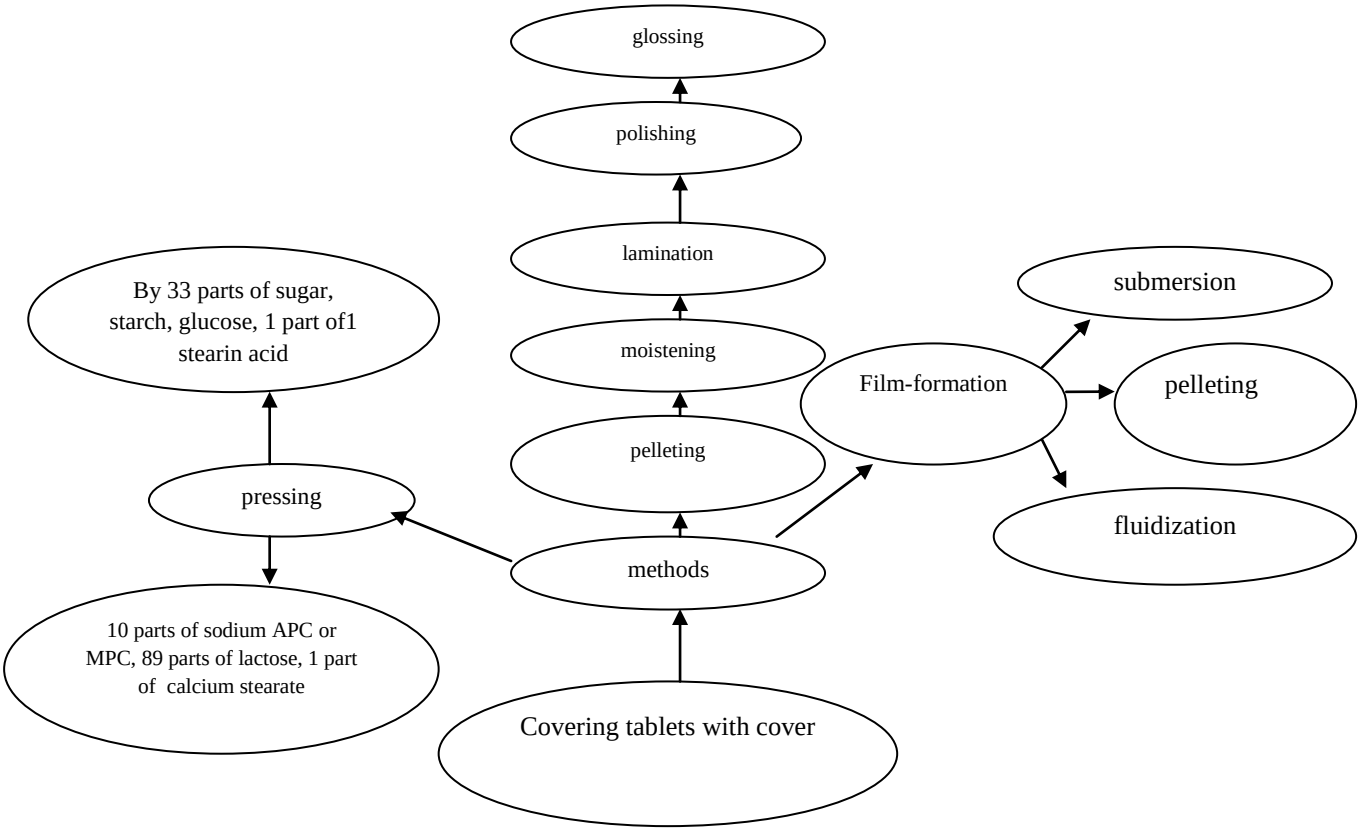
Fig.27. Covering of tablets by film-formation method

TRITURATION TABLETS
(TABULETTAE TRITURATIONES)

Objective. To master the characteristic features of preparation technology and quality assessment of micro-tablets.

Importance. Trituration tablets are made in cases where the use of pressure for some reason is undesirable or dosage of drug is small, and the addition of large amounts of auxiliary substances is impractical. These tablets are reasonable to be manufactured in cases where tablets are required to quickly and easily soluble in water, since they do not require antifriction material which are water insoluble compounds. Therefore, the production of such tablets is not only of tehnological but economical importance.

For conduction practical lessons pedagogical technology «Cluster» is applied



Situation tasks.

1. Microtablets were compressed in the RTM-12 tablet machine with a diameter of 8 mm.

2. To prepare 1 micro-tablet the mass of the drug is about 1 g

3. When preparing microtablets auxiliaries are not added.

4. When preparing the mass stuck to the mold and the edges of the tablet were not smooth.

Theoretical questions.

1. In what cases it is necessary to produce micro-tablets?

2. By what criteria is evaluated the quality of trituration tablets?

3. Give examples of Trituration tablets.

4. Composition of zinc sulfate microtablet.

5. Select the composition for the preparation of micro-tablets with riboflavin and ascorbic acid (for 100 000 pieces of micro-tablets).

Trituration tablets are called pills formed from the hydrated mass by rubbing it in a special mold, followed by drying. In contrast, with compressed, trituration tablets don't not undergo the action of pressure: clutch of particles of these tablets is carried out only by autohesion during drying, so trituration tablets have less strength than molded. Trituration tablets are made in cases where the use of pressure is undesirable or impossible. This may occur when the drug dose is low, and the addition of large amounts of auxiliary substances is impractical. To produce such tablets due to the small size (d = 1-2 mm) is technically difficult to tablet machine. Trituration tablets are manufactured when the addition effect may cause a change in the drug substance. For example, in the preparation of nitroglycerin tablets explosion can occur when using the addition. And trituration tablets is advisable to prepare in cases where necessary the tablets quickly and easily dissolving in water. For their manufacture are not needed glidants that are insoluble compounds. Trituration tablets are porous and fragile, and therefore they dissolve rapidly upon contact with liquid, which is useful in the production of tablets for injection and eye drops.

As excipients for trituration tablets lactose, sucrose, glucose, kaolin, $CaCO_3$ are used. When receiving the powder mixture is moistened to 50-70% alcohol until a plastic mass, which then is rubbed with a spatula on a plate - matrix placed on the glass. Then, using pistons punch wet tablets are ejected from the matrix and dried in the air or in an oven at a temperature of 30-40ºC. In another method, drying of tablets is carried out directly in the plates and through the punches are pushed already dried tablets. Their weight is of 0.05 g.

Trituration tablets are standardized according to the content of the active substances and the physical and mechanical characteristics. For trituration tablets deviation from the average weight ± 20% is permissible.

Trituration tablets include tablets of nitroglycerin, zinc sulfate, zinc sulfate with boric acid, ascorbic acid, riboflavin, and others.

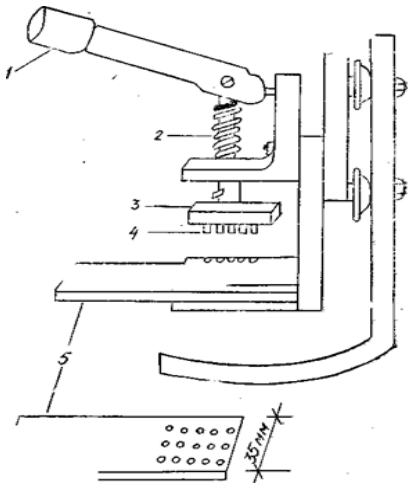


Fig.27. Punch for obtaining microtablets

Laboratory work - 3

TABLETS OF ZINC SULFATE 0.0003 g

(TABULETTAE ZINCI SULFATIS 0.0003)

Description of finished product. Tablets of white color, odourless, with weight of 0.03 g, diameter 3 mm.

Content of zinc sulphate in 1 tablet should be 0.00028-0.00032 g.

Packing. By 20 pieces in glass tubes, poured over with paraffin.

Storage. Letter B.

Application. In ophthalmic practice instead of zinc sulfate solution as an antiseptic and astringent. Applied under the eyelid.

Task

1. To prepare 100 zinc sulfate tablets including 20% of loss.
2. To draw a diagram of the process.
3. To analyze the finished product.

Composition of 1 tablet: zinc sulphate 0.0003 g, milk sugar and alcohol 50%- sufficient amount.

According to the rules of production, the average weight of one tablet should be 0.03 g, therefore the lactose, accounting for 0.0297.

As the binder is used 50% alcohol, and per each 0.16 g of dry substance 0.02 ml of 50% alcohol is taken.

Given the loss of these ingredients, it is recommended to take 20% more than required for the calculation. Accordingly, the recipe is constituted for one tablet:

Zinc sulphate - 0.00036 g

Lactose -0.03664 g

Alcohol 50% sufficient amount

Average mass -0,03 g

Table 3

Description of initial raw material

Number of pharmacopoei article and SSt	Technical or trade name Raw material	Contents, %	Quality
SP X, art. 753	Zinc sulphate	99,5-101,5	According to SP
SP X, art. 589	Milk sugar	99,3	-«-
SSt 5962-67	Ethyl alcohol	Not less than 96,2	According to SSt

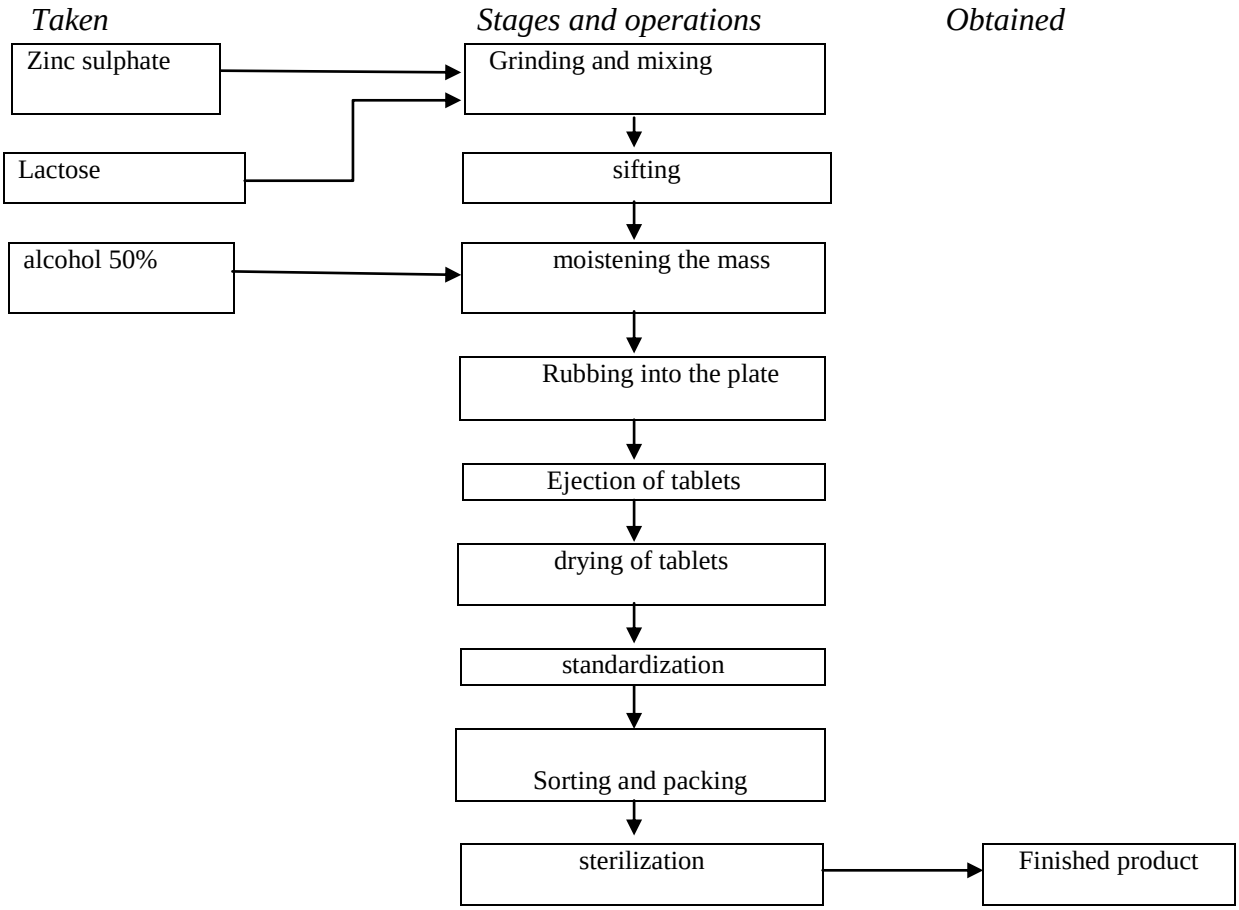
TECHNOLOGICAL PROCESS

For the preparation of micro-tablets, we recommend portable machine formed on the basis of manufactured by industry punch (Fig.).

Operation is as follows: in a sterile porcelain dish is triturated 0.11 g of lactose and the mixture is sifted through a sieve with a hole diameter of 0.16 mm. The mixture is moistened with 1.35 ml of 50% alcohol and the wet mass through a plexiglass or plastic spatula is rubbed into holes (matrix) of the plate. When this plate is put on a flat surface or a plate without holes. The plate-matrix is inserted into the groove of the punch and the handle is lowered the upper punch for pressing the mass-expulsion of the matrices. Thus tablets are arrived at the receiver, they are collected, dried on a sheet of parchment paper at 55-60ºC. The resulting tablets are sorted and stacked after standardization in glass tubes and sterilized at 100º C for 1.5 hours.

Note. Since zinc sulfate tablets are used instead of eye drops, then at preparing all kinds of personal hygiene and asepsis types are observed: treated mortar pestles, machine, and spatula with 96% alcohol.

SCHEME OF TECHNOLOGICAL PROCESS



ANALYSIS OF FINISHED PRODUCT

Authenticity. Zinc is determined by sodium sulfide solution on white sediment. Sulphates with barium chloride reagent in nitric medium form turbidity or sediment. Lactose forms a brownish-red sediment when heated with Feling's liquid.

Quantitative determination. Zinc Sulphate is determined by trilonometric method in an alkaline medium. It should be 0.00028-0.00032 g of zinc sulfate per 1 tablet.

Test for good quality of tablets. In the obtained tablets the appearance, dimension types, average mass and disintegration are determined.

Solubility. On warmed watch glass is poured 0.05 ml of isotonic sodium chloride solution, heated to 40ºC, and placed one tablet.

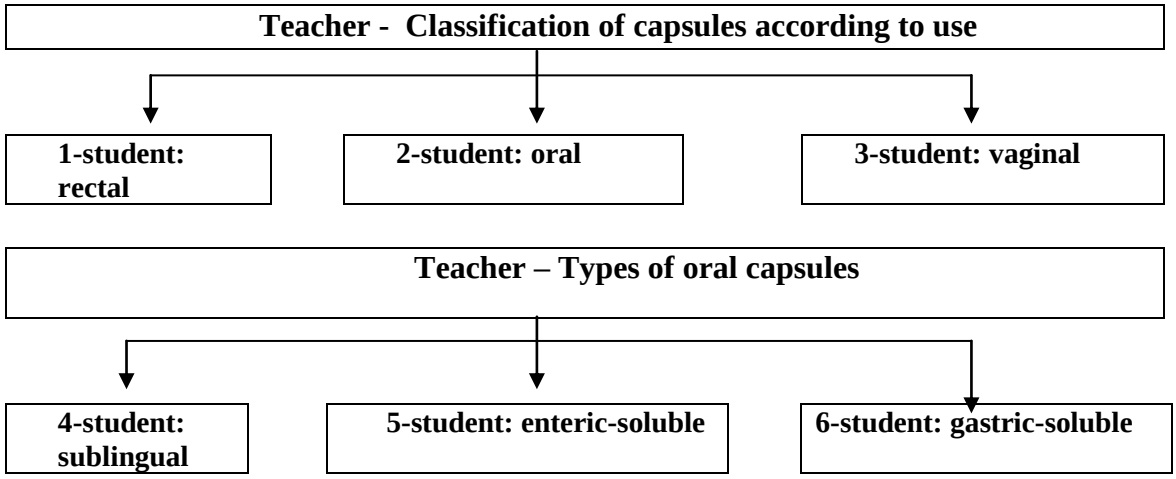
Under gentle shaking with a glass rod tablet should be dissolved within 2-3 minutes.

THEME: CAPSULES AND THEIR PRODUCTION.TECHNOLOGY FOR PREPARING «FERASK» CAPSULES

Objective. To study the technology of solid and soft capsules and their mixture with drugs or excipients, methods of filling capsules using liquid, thick solutions or powders.

Importance. Due to a number of advantages capsules as a medicament (full automation, high bioavailability due to preservation of physicochemical and pharmacological properties of drugs) is different from other drugs (tablets, ointments, syrups, injections, etc.). When looking at the capsule manufacturing medicaments for today they take the third place after injection solutions and tablets. There are forecasts that the production of capsules, will take the first place in the future.

For conduction practical lessons pedagogical technology «Quick game» is used



Situation tasks.

1. When shaking a hard gelatine capsule filled with drug substance the sound can be heard.
2. When examining hard gelatine capsules with the naked eye cracks were detected.
3. It has been found - soft gelatine capsules in size differ from each other.
4. Explain why gelatine capsules of the following composition and size meets or does not meet the requirements.

Number	000	00	0	1	2	3	4	5
Average volume of capsule, ml	1,37	0,95	0,68	0,5	0,37	0,3	0,21	0,3

Components	Soft	Semisoft	Semisolid
Gelatine	41,1	43,5	47,6
Glycerine	30,1	24,6	17,5
Water	28,8	31,9	34,9

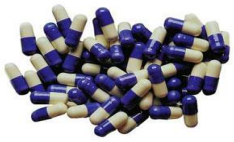
Fig. 28. Capsule contents

Theoretical questions.

1. Capsules. Definition, characteristics and classification.
2. Advantages and disadvantages of capsules.
3. The composition of hard gelatine capsules
4. Non hard gelatine capsules
5. Technology of hard gelatine capsules
6. What are the stages of preparing hard gelatine capsules?
7. Composition of soft gelatine capsules
8. Technology of preparation soft gelatine capsules
9. Methods of filling capsules
10. Pearls, medules and spansules, microcapsules.
11. Microdragees and tubatines.
12. What dosage forms can be prepared from the microcapsules?

TESTS

1. List solid medicinal forms.



a) dragees, suppositories, powders;

b) tablets, powders, ointments;

c) capsule, granule, tablet, dragee;

d) powders, capsule, tincture.

2. What are the types of using capsules?

a) Orally, injection, vaginally;

b) rectally, vaginally, sublingually;

c) vaginally, rectally, orally;

d) subcutaneously, orally, topically

3. What types are divided capsules into on composition?

a) 2

b) 6

c) 9

d) 5

4. What ingredients do gelatin capsules consist of?

a) gelatine, glycerin, water;

b) Gelatine, starch, glycerol;

c) Glycerine, water, magnesium oxide;

d) talc, gelatine, water.

5. Methods of preparing capsules?

a) dipping in a solution, pressing, pelleting;

b) Drop, wet granulation;

c) dipping in a solution, pressing;

d) dipping in a solution, pressing, drop.

6. To which forms are pearls and tubatines related to?

a) solid;

b) soft;

c) liquid;

d) dry;

7. Indicate disadvantages of capsules.

a) Precise dosing;

b) masking the unpleasant smell and taste;

c) Dissolution at a specific location of the body;

d) breeding ground for microorganisms.

8. In what capacity gelatine capsules are packed?

a) Plastic jars;

b) Glass containers;

c) The blister packaging

d) in a cardboard box.

9. How long should the capsule be disintegrated?

a) 15 min;

b) 25 min;

c) 30 min;

d) 20 min.

10. What scientists have made a great contribution to the development of capsules?

a) Mot and Deublan;

b) Rettinger.

c) Borzunov E.E.

d) Gandel.

Capsules – is a dosage form comprising the drug enclosed in the coat.

The main advantages of this formulation are:

1. Protection of the drug from the effect of light, moisture, atmospheric oxygen.
2. Accuracy of dispensing of drugs.
3. Masking the unpleasant taste, odor of medicines.
4. Ease of taking dyes.
5. Protection of the gastric mucosa from the irritating effects of certain drugs.

6. Slow release of drugs, thereby ensuring prolongation of their therapeutic effect and decreased toxicity.

7. The high bioavailability due to the absence of ballast excipients.

8. The ability to localize the drug release in the intestine.

9. Almost complete mechanization and automation of production.

The disadvantage of capsule is a hygroscopicity of gelatine coat of capsules and the impossibility of their filling with materials dissolving the coat.

There are 2 types of gelatinous capsules:

1. Solid, consisting of body and cover, freely entering into one another.

2. Soft with whole coat.

Solid capsules are intended for dosing of bulk powders and granular substances. They are available in eight sizes depending on their capacity.

Soft gelatinous capsules generally have spherical, egg-shaped, oblong or cylindrica forml with hemispherical ends, with a capacity of up to 1.5 ml. They encapsulate medicinal liquid and pasty substances. Capsules with a capacity of 0.1-0.2 ml, filled with oily liquids, sometimes called the pearsl. Capsules with a long neck - tubatines, from which it is easy to squeeze out the contents, cutting off the tip of the neck.

2. Technological production scheme.

Preparing of capsules consists of several stages:

1. Preparing gelatinous mass.
2. Capsules formation.
3. Filling.
4. Covering.
5. Quality assessment.

Stage of forming and filling capsules may be combined, and the step of coating may be omitted.

Preparation gelatinous mass. For mass production of gelatine mass are used gelatine, water, plasticizer, the ratio of which depends on the type of capsule produced. To provide elasticity of capsules to a gelatine mass are added plasticizers (glycerol,

sorbitol, poliyethylenesorbit with oxyethylene, hexantropol). The amount of plasticizer (usually glycerol) is determined by properties of the coat and for solid capsules is up to 0.3%, for soft up to 20-25%.

The composition of gelatinous mass can include:

- To ensure antimicrobial stability - preservatives (potassium metabisulfite, benzoic acid, sodium benzoate, salicylic acid, nipagine, nipazol).
- For coloring - dyes (titanium dioxide, acid red 2C, tropeolin 00 and others.).
- To make the taste - sugar.
- For obtaining acid-resistant capsules - film formers (ethyl cellulose, cellulose acetate, cellulose acetate phthalate).

The quality of the capsules is determined by the technology of obtaining gelatine mass and the method used to produce membranes.

Gelatine mass is prepared in a reactor with a steam jacket and anchor stirrer. **Depending on the type of capsules (manufacturing method) obtaining a gelatinous mass can occur in two ways:**

1. With the swelling of gelatine, it is used in high concentrations. Most often, the capsule is obtained by pressing.
2. Without swelling of gelatine.

Formation of the capsule is carried out by three methods:

1. The method of "immersion";
2. The drop method;
3. The method of compression;

By immersion method are obtained both soft and solid capsules in the capsule machines. The method is based on the use of metal molds (olive, rods), lubricated with vegetable or mineral oils.

In the manufacture of solid capsules metal cores of two sizes of cylindrical shape are fixed to the frame, dipped in a gelatinous mass, rotating, first rising and dried at a temperature of 26-27ºC, 45-50% humidity, then at a temperature of 18ºC, humidity of 70-75%. This temperature range provides the necessary physical and chemical properties.

Strongly dried capsules - hard and brittle, the excess moisture in the coat leads to the bacterial decomposition of gelatine.

Finished capsule halves are cut at the base and served on recruitment and filling.

Soft capsules are prepared by similar techniques, but the formation of the coat is conducted at a cooling and subsequent drying. Empty soft capsules are laid on special stands up and holes filled with liquid drug substances using a piston type dispenser further the opening is sealed with drop of gelatinous mass or heating.

Drip method allows to obtain spherical seamless capsules at the Dutch company machine «Globex Mark» simultaneous filling with a liquid drug substance or dosage form (solution, suspension, emulsion).

The method provides high precision of dosing, hygienic production, economical consumption of gelatine mass. The relative disadvantage is requiring use of solutions of medicinal substances of similar density and viscosity to the oil (e.g., oil solutions of vitamins A, D, E, K, nitroglycerin, validol, fish oil).

Method of pressing (stamping) is used to obtain soft capsules with a transverse seam on the machines, which are horizontal capsular press.

Formation of capsules is made of gelatine mass. The method consists of placing of previously prepared thin gelatine sheet on metal plate having a recess in the form of a capsule half (matrix). Matrices are heated with hot water of temperature 45-55ºC, at the expense the gelatine ribbon is softened and lines the cells. Into the resulting groove is fed solid or liquid medicinal substance, whereupon another hot gelatine sheet using the second plate closes the capsule, wherein sealing their edges.

The disadvantage of these machines is their low productivity. More productive is a **drum capsule press of Scherer**. The principle of operation is similar to a horizontal drum press.

High-performance machine also has a **SSC-1 of «Leiner» company** (England). This unit also refers to the drum presses and how it works is similar to the press of Scherer. The difference is that the formation of the gelatine ribbon enters the production cycle of automated line.

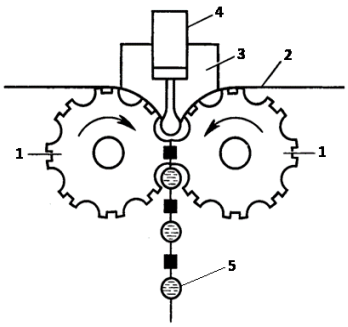


Fig.29. Pressing method

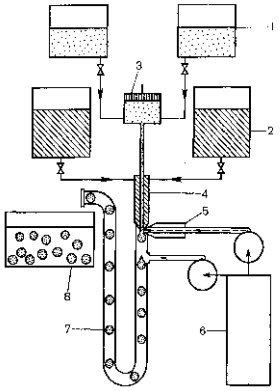


Fig.30. Dripping method

Filling of capsules. This step is essential for soft and solid capsules, produced by immersion, because drip and stamping methods involve filling in the step of forming the capsule coats.

Filling of solid capsules is carried out on semi-automatic and automatic machines of companies: Eli Lilli, R. Sherer (USA), «Hofliger und Karg» (Germany). The most advanced machines differ with high productivity and precision dosing of + 2-5%. After filling in order to avoid coming off the cap the capsules are hermetically sealed with submelting tape of gelatine or PVS solution on devices for filling or special units of "Diaf" company (Denmark).

Soft capsules are filled with the drug through a syringe using a dispenser and sealed. Further capsules are transferred to the grinding and coating.

Coating. Stage of coating capsules is used primarily to localize the drug release in the intestine in order to protect the gastric mucosa from the irritating effects of certain drugs.

Currently, coating of solid capsules is carried out with 5 % acetylphthalyl solution (APC) in a mixture of acetone and alcohol (3:1), or APC is added in an amount of 30 % of gelatine mass. For obtaining enteric-coated capsules by drop method the most suitable gelatine solutions with the addition of 15-30 % APC, providing resistance to an acidic solution of pepsin for 3 hours.

As coatings for prolonging action of drug it is possible to use a mixture of hydroxypropylmethylcellulose phthalate and dibutyl phthalate.

Film coatings are also used for cosmetic purpose to give glitter, reduce transparency for moisture resistant capsules, increasing tightness. For this are used stearic acid, polyvinyl acetate, acetylated monoglycerides, and others.

At all stages of the process are revealed defects of capsules and they are regenerated. Thus, soft capsules with a liquid medicinal substance are cut and placed in a centrifuge. Separated drug substance is filtered and analyzed. The capsule coats are washed and used to prepare the gelatine mass.

Quality assessment of capsules

Standardization of capsules is carried out according to the SP XI edition, issue 2 on the following parameters: average weight, dosing homogeneity, disintegration and dissolution.

To determine the average mass 20 unopened capsules are weighed, determined the average mass of one capsule. Each capsule is then weighed separately and found the average deviation from the mass, which must not exceed 10%.

Thereafter, the capsules are opened, the contents removed. Soft capsules after release of the drug substance are washed with a volatile solvent and dried. Then, each coat is weighed and the average mass of capsule contents is determined. The deviation in the weight should not exceed 10%.

Test for dosing homogeneity is performed for capsules containing 0.05 g or less of the drug substance under article "Tablets" or articles of partial instructions.

Determination of disintegration is carried out in accordance with annex 3 to the article "Tablets" on the device "rotation" basket. If there are no other indications in partial articles then the disintegration time should not exceed 20 minutes.

Dissolution of capsules is determined according to the article «Tablets» or indications of partial articles on the device "rotation" basket.

Quantitative determination and other indications are determined according to partial articles.

4. Packing and storage of capsules

For the packaging of the capsules glass or plastic bottles, jars are used. It can also be used the blisters with cells of PVC heat-sealed with aluminum foil.

The capsules should be kept in conditions providing their stability within a specified expiration date, if necessary - in a cool place.

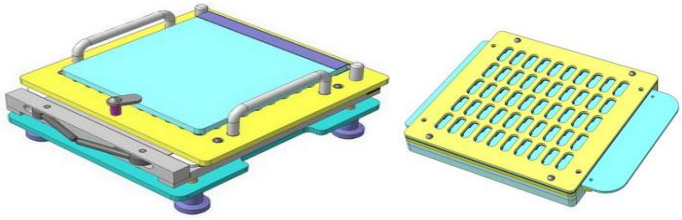


Fig. 31. Manual semi-automatic Capsulator for filling of solid gelatine capsules (model with loading 100 capsules) Performance of the basic set - up to 2,000 capsules per hour.

Laboratory work - 1

«Ferask» capsules

Capsulae «Ferascum»

FSP 42 Uz-1906607-1080-2007

Task

1. Prepare the mass for 30 capsule "Ferask" and fill in solid capsules No. "0".
2. Determine the quality of the capsules.
3. Draw a diagram of the preparation of capsules.

Composition: for 1 capsule

Feramide - 400.0 mg

(PA 42 Uz-0028-2007)

Ascorbic acid - 30.0 mg

(X SP, 4 article; Brit. P., Europ.P., P.of the USA.)

Mass inside of capsule - 430.0 mg

Apparatus and excipients

1. Substance of Feramide and ascorbic acid
2. Parchment paper
3. Scales and weights
4. Capsules with number "0"
5. Grinder or device of "Islamgulov"
6. Sieve with a hole diameter of 0.150 mm

7. Mortar and pestle

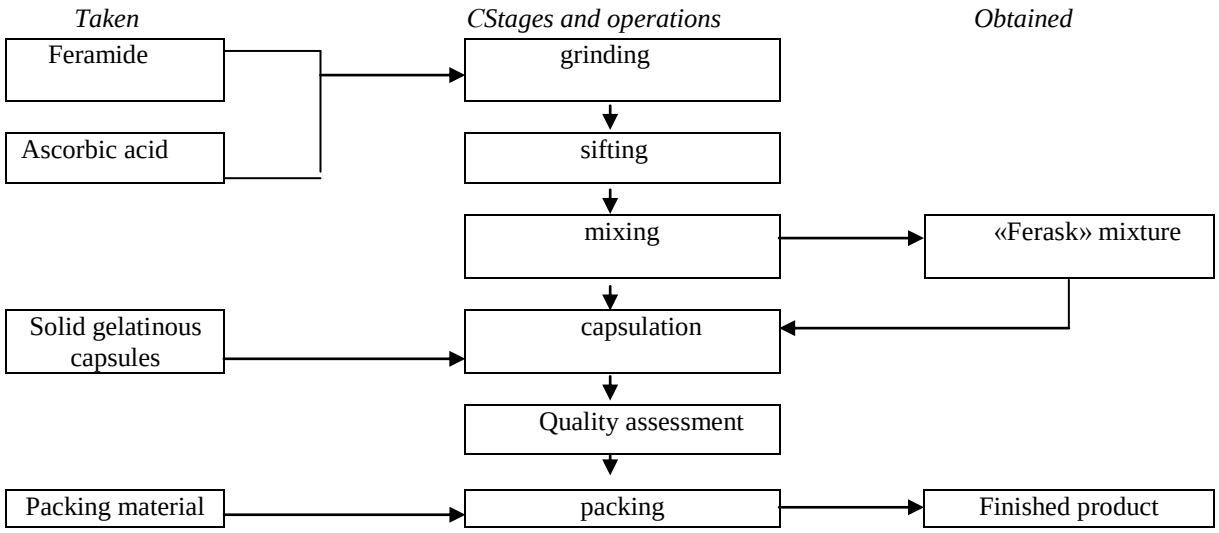
TECHNOLOGICAL PROCESS

Feramide substances and ascorbic acid are taken in the desired quantity and ground in the apparatus of "Islamgulov" for 12 min. After about 40 seconds the lid of apparatus is opened, the milled powder is sifted through a sieve having 0.150 mm diameter of holes and weighed.

From the prepared mass is weighed by 0.43 g and filled in the capsules with number "0".

Finished capsule are assessed for quality and then packaged.

SCHEME OF TECHNOLOGICAL PROCESS



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