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NATIONAL UNIVERSITY OF PHARMACY
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QUALIFICATION WORK

on the topic: **«THE CHOICE OF EXCIPIENTS IN THE COMPOSITION OF TABLETS WITH RANITIDINE»**

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ANNOTATION

Qualification work contains 44 pages, 6 tables, 8 figures, bibliography of 30 titles.

The analysis of literary sources on the problem of treatment of antiulcer diseases is given. It has been established that drugs based on Ranitidine remain one of the most common antisecretory drugs and are used in many areas of gastroenterology. A technology for obtaining Ranitidine tablets by direct compression was proposed and a technological block diagram of tablets was developed.

Key words: ranitidine, excipients, tablets, technology.

АНОТАЦІЯ

Кваліфікаційна робота містить 44 сторінки, 6 таблиць, 8 рисунків, список літератури з 30 найменувань.

Наведено аналіз літературних джерел щодо проблеми лікування противиразкових захворювань. Встановлено, що лікарські препарати на основі ранитидину залишаються одними з найпоширеніших атисекреторних препаратів і знаходять застосування в багатьох галузях гастроентерології. Запропоновано технологію отримання таблеток ранитидину методом прямого пресування та розроблено технологічну блок-схему таблеток.

Ключові слова: ранитидин, допоміжні речовини, таблетки, технологія.

THE CONTENT

INTRODUCTION

Actuality of topic. Among the drugs that are used to treat peptic ulcer disease, Ranitidine remains one of the most common antisecretory drugs and is found in many areas of gastroenterology.

H2-blockers are the "gold standard" for the treatment of acid-related diseases, and ranitidine is the best-selling prescription drug.

Ranitidine is an antiulcer drug belonging to the group of H2-histamine receptor blockers. Second generation drug. The action of ranitidine is based on a decrease in the secretion of gastric juice by suppressing the secretion of hydrochloric acid and pepsin. Included in the list of vital and essential drugs.

To improve the technology of production of tablets Ranitidine proposed a method of direct pressing, which has a number of advantages: eliminates the need for heat treatment of the drug substance, enables production of tablets with incompatible substances, also this method allows to achieve high productivity, to reduce production cycle, reduce manufacturing space, reduce material costs and costs in operation.

The purpose and research tasks. The aim of the work is to develop the composition and technology of ranitidine tablets for the treatment of antiulcer diseases. The task of the work is to conduct a review of the literature, a complex of pharmacotechnological studies, the choice of excipients and the development of a rational technology.

Research objects: ranitidine substance, excipients, tableting mass.

The article of research. Development of the composition and technology for obtaining ranitidine tablets by direct compression.

Research methods. When solving the tasks set in the work, the following research methods were used: technological, physical, physicochemical.

Structure of work. The work is presented on 44 pages of printed text, consists of an introduction, a review of the literature, an experimental part, a conclusion and a list of sources used. The work is illustrated with 6 tables and 8 figures. The list of references contains 30 titles.

CHAPTER 1
LITERATURE REVIEW

1.1 State of the market for antiulcer drugs

At present the problem of gastric ulcer and 12 duodenal ulcer, attracts the attention of scientists of many countries of the world and is considered the disease of the XXI century. The pathogenesis of peptic ulcer disease and other diseases of stomach and intestines leads to the development of destructive processes that tend to the progressive development of erosions to deep ulcers. Therefore, great attention is paid to the treatment of diseases of the digestive tract, and the needs of the pharmaceutical market in these drugs are constantly rising, relatedtothefollowingreasons:

– increase in the total number of patients with disorders of the digestion;

– a variety of eating disorders;

– incidence that is growing, allergic diseases, among which widespread food Allergy, Allergy to drugs of different pharmacological groups.

Today in the pharmacy network presents a large number of drugs for the treatment of these diseases. The main remedies are traditional antacids inorganic and antisecretory medicines. The action of modern drugs directed primarily at reducing gastric acidity. Antisecretory drugs reduce the acidity by inhibiting the synthesis of hydrochloric acid. These include representatives of three important groups: proton-pump inhibitors (PPIS), H2-blockers of histamine receptors and M-cholinoblockers(non-selective drugs: atropine, platifillin et al., selective relative to the stomach:M1-cholinoblocker pirenzepine).

It is established that at present the range of anti-ulcer drugs registered in Ukraine, presented labels of two major groups: antagonists of H2-receptors of histamine and proton-pump inhibitors. The first one are trademarks of ranitidine and famotidine, the second group of omeprazole, pantoprazole, lanzoprazola, rabeprazole and esomeprazole. In over-the-counter holidays in Ukraine are the antisecretory drugs of the action, as Ranigast-75, Polpharma (active substance

ranitidine at a dose of 75 milligrams), Kamaelia, Gedeon Richter (the active substance famotidine at a dose of 10 milligrams). All other antisecretory action of drugs dispensed by prescription.

It should be noted that in the pharmaceutical market of Ukraine is currently the main range is formed at the expense of foreign-made drugs: they on the particle accounts for about 80 %, Domestic products occupy the market respectively 20 % of the range, which includes about 210 trade names. Analyzing the registered range of funds under the anti-ulcer sub-groups, it can be noted that among the products of domestic manufacturers mostly blockers of H2-receptors histamine (16 % of the total). The medicines of foreign producers almost equally represented as blockers, and proton-pump inhibitors.

Antiulcer medications put on the Ukrainian pharmaceutical market manufacturers from 13 countries. The analysis of the state register of medicinal products allowed to determine a particle in each of the countries-producers in the product range on the market. The most active positions among countries-importers is a firm of India and Germany that have registered on the Ukrainian market of 46.5, respectively and 7.9% of the total number of titles.

Leading positions in the number of blockers of H2-histamine receptors, which are produced, are pharmaceutical company "Zdorovye", Kharkiv, - 37 % and "Kievmedpreparat" - 24 %.

Expanding the range of domestic pharmaceutical manufacturers in the last few years has been mainly due to the modification of traditional drugs of the item, recreate already existing on the market of medicinal products, the introduction of a bulkdrugsubstance.

The interval of variation for imported products more than domestic drugs. They are represented in all subgroups and blockers of H2-histamine receptors, and proton-pump inhibitors. However, the medicines of these groups have significant differences.

In recent years, increasingly for treatment and prevention of GERD as one of the initial stages of ulcer disease using H2blockers histamine receptors.

Histamine receptors are responsible for the secretion of chlorothalonil acid in the stomach. H2-blockers suppress the production of hydrochloric acid by competitive blocking H2-histamine receptors in the gastric mucosa. HistamineH2-receptorantagonistshave 4 different drugs. Representatives of this class adverse reactions characteristic to a greater extent to cimetidine. H2-blockers subsequent generations (ranitidine, famotidine, nizatidine) is much better tolerated. However, with abrupt cancellation may develop "rebound effect" that is accompanied by secondary hyper hydrochloric acid. H2-blockers have long-term (up to 12 hours) with careful dose separation effect due to the way oppression histamine stimulation of parietal cells of the stomach. The most active and has a long duration of action (up to 24 hours) of famotidine. Ranitidine is valid till 6-8 hours. These drugs differ in pharmacokinetics: ranitidine is to some extent penetrates throughblood-brain barrier and is metabolized in the liver, whereas famotidine almost does not penetrate into the brain and almost not amenable to biotransformation. However, their clinical effect in the relief of heartburn (one of the manifestations of acid-related diseases) deferred. This group of drugs ineffective in long-term use due to development of tachyphylaxis.

The most effective drugs in the management of patients recognized as proton pump inhibitors. They provide long lasting and permanent reduction in intragastric pH, because the molecular mechanism of action are the most effective antisecretory drugs. On antisecretory activity considerably (2-10 times) compared to other H2-blockers. The effect is achieved through a direct action on the final stage of synthesis of hydrochloric acid in the parietal cells of the gastric mucosa. The safety profile during short (up to 3 months) courses of therapy is favorable, and most adverse reactions - light. Not affect the lower portions of the esophagus of gastric emptying and gastric juices. According to some lanzoprazol during the first two weeks of treatment was more effective in lowering the secretion of hydrochloric acid by the gastric mucosa and has helped to reduce symptoms in the shortest possible time. For pantoprazole and rabeprazole virtually unknown interactions with other drugs.

Also, an analysis was conducted of prescribing anti-ulcer drugs in some hospitals of Kharkiv (Fig. 1.1). The greatest number of assignments researched group of drugs accounts for gastroenterologists (62 %) and therapists (18 %). This allowed to identify the main target group of physicians for follow-up study of the use of antiulcer drugs and their promotion on the market.

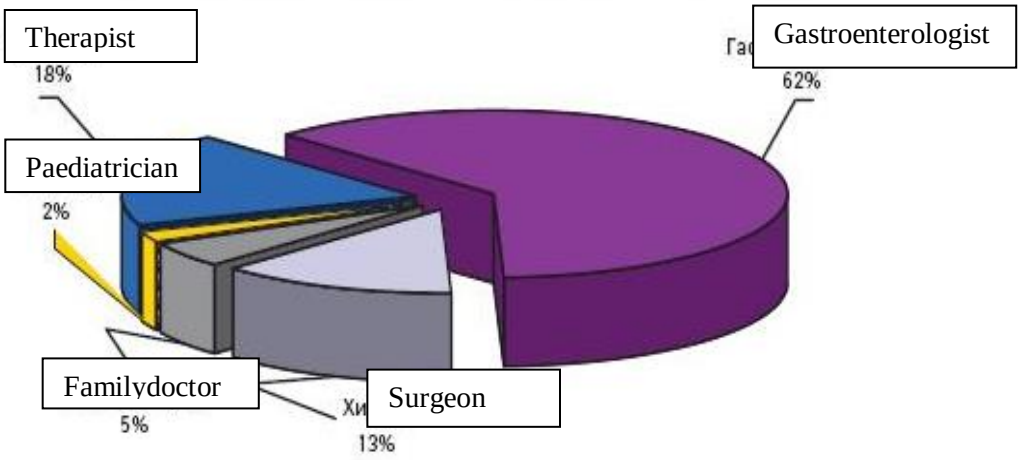


Figure 1.1 Particle specialists, who prescribed anti-ulcer drugs

1.2 Characterization of tablets as dosage forms

Tablets (Tabulettae, from lat. tabula – Board, tabela - Board, tile)– dosage form obtained by compressing the drug or mixture of drug and excipients intended for indoor, outdoor, sublingual, implant or parenteral use.

Tablet as a dosage form, is widespread throughout the world. Currently tablet formulations comprise about 80% of the total volume of finished pharmaceutical products. Positive quality tablets provide:

• should the level of mechanization on the main stages and operations, providing high performance, cleanliness and hygiene of production of these dosage forms;

• accuracy of dosing entered into tablets of drugs;

• portability of tablets providing the convenience of their vacation, storage and transportation;

• long-term safety of drugs in its compressed state;

• for substances not sufficiently stable, the possibility of applying protective coatings;

• masking of unpleasant organoleptic properties (taste, smell, color strength), which is achieved by coating;

• the combination of the medicinal properties associated physico-chemical properties in other medicinal forms;

• localization of action of medicinal substance in a specific Department of the gastrointestinal tract by coating the membranes, soluble in acid or alkaline environment;

• prolongation of action of medicinal substances (by applying certain coatings, the use of special technology and composition of tablets-cores);

• regulation of sequential absorption of several drugs from tablets in a certain period of time (multilayer tablet);

• prevention of errors in the vacation and the medication is by applying on the surface of tablets labels.

CLASSIFICATION OF TABLETS

By way of receiving distinguished two classes of tablets:

1. Pressed, obtained by pressing of pharmaceutical powders on tableting machines with different performance. This method is the basic.

2. Molded or trituration tablets obtained by tableting mass forming. They constitute about 1-2% of the total volume of production of tablets. Triturationtablets contain a small dose of the medication and dilution of substances: their weight can be up to 0.05 g.

Tablets are classified also according to the design feature:

1) Composition: simple (one-component) and complex (multicomponent).

2) According to the structure of the building: frame, single layer and multi-layer (minimum 2 layers), with or without coating.

3) The nature of the coating: sugar-coated, film, and extruded dry coating.

THE MAIN GROUPS OF EXCIPIENTSIN THE PRODUCTION OF TABLETS

Excipients in tablet production is designed to give the tablet mass necessary technological

properties, ensuring dosing accuracy, mechanical strength, disintegration and stability of the tablets during storage.

Auxiliary substances used in manufacture of tablets, are divided into groups depending on the purpose. Major groups and nomenclature of excipients are given in table1.1.

To auxiliary substances the following requirements apply:

• must be chemically indifferent;

• must not have a negative impact on the body of the patient, and on quality tablets at their preparation, transportation and storage.

Table1.1

Excipients used in the production of tablets

Groups	Substances	Quantity, %
1	2	3
Fillers (diluents)	Starch,glucose, sucrose, lactose (milksugar), magnesiumcarbonatebasic, magnesiumoxide, sodiumchloride, sodiumbicarbonate, claywhite (kaolin), gelatin, microcrystallinecellulose (MCC), methylcellulose (MC), sodiumsaltofcarboxymethylcellulose (NaCMC), calciumcarbonate, calciumphosphatedibasic, glycine (aminoaceticacid), dextrin, amylopectin, ultraamylopectin, sorbitol, mannitol, pectin, etc.	Not standardized
Binders	Purified water, ethyl alcohol, starch paste, sugar syrup, solution of carboxymethyl cellulose (CMC), acetylcellulose (CECS),	Not standardized

	oksipropilmetiltselljuloza (OPMC); polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), alginic acid, sodium alginate, gelatin, etc.	
leavening agents: Swelling Gas-forming Improving wettability and permeability	Starch of wheat, potato, corn, rice, pectin, gelatin, amylopectin, agar-agar, alginic acid, potassium, and sodium alginate, etc. A mixture of sodium bicarbonate with citric or tartaric acid, etc. Starch of wheat, potato, corn, rice, sugar, glucose, tween-80, etc.	Not standardized Not standardized Not standardized Tween-80 1%
Anti-friction: Sliding Lubricating Anti-stick	Starch, talc, polyethylene oxide-4000, Aerosil, etc. Stearic acid, calcium and magnesium stearate, etc. Starch, talc, polyethylene oxide-4000, stearic acid, calcium and magnesium stearate, etc.	The talc is less than 3% Aerosil 10 %, stearic acid, calcium and magnesium stearate 1%
Film formers	Acetylphthalylcellulose(AFC), YAC, OPMC, PVP, PVA, ethylcellulose, etc.	Not standardized
Corrigents: Taste Smell color: dyes pigments	Sugar, glucose, fructose, sucrose, xylitol, mannitol, sorbitol, asparkam,glycineetc. Essential oils, fruit juice concentrates, citral, menthol, vanilla, ethylvanillin, fruit essence, etc. The Indigo Carmine, acid red 2C, 00 tropeolin, tartrazine, eosin, tuberosum, ceruleum, Pleurozium, chlorophyll, carotene, etc. Titanium dioxide, calcium carbonate, iron hydroxide, iron oxide, activated carbon, white clay, etc.	Not standardized

Plasticizers	Glycerol, tween-80, mineral oil, oleic acid, polyethylene oxide-400, propylene glycol, etc.	Tween-801 %
The prolongators and substances to create hydrophobic layer	Wax white,sunflower oil, cottonseed oil, monopalmitate, Triowin, paraffin, etc.	Not standardized
Solvents	Purified water, ethyl alcohol, acetone, chloroform, ammonia, hydrochloric acid, etc.	Not standardized

Fillers (diluents) are added to obtain specific tablet weight.

Binders. The particles of most drugs have a small force of adhesion between them, so when they are pelletizing is required to exert high pressure. To achieve the necessary bond strength at relatively low pressures to substances added tablet binders, which, filling the interparticle space, increase the contact surface of the particles and cohesiveness.

Loosening substances. During compaction of pharmaceutical substances is dramatically reduced porosity and thus hindered the penetration of liquid into tablets. To enhance disintegration or dissolution is used loosening substancesthat provide mechanical destruction of the tablets in a liquid medium, which is necessary to accelerate the active substance release

Anti-friction substance. Used for obtaining a good yield of the granulate supply device (funnels, hoppers). Sliding substances adsorbed on the surface of the particles (granules) eliminate or reduce their roughness and thereby increase their fluidity (flowability).Most effective slides have particles with a spherical shape.

Lubricants ease the ejection of tablets from the matrix. They differently are called anti-adhesive or anti-glaucomas substances.

Correcting agents added to tablet formulation to improve the taste, color and smell

The dyes enter into the composition of tablets is first of all to give them a presentation, to identify therapeutic groups of drugs, e.g., hypnotics, poisonous. Additionally, some dyes are stabilizers of photosensitive drugs.

THE TECHNOLOGICAL PROCESS OF PRODUCTION OF TABLETS

In the manufacture of dosage forms from a powder material, in addition to the mixing and pressing operations of milling, granulation and tableting.

The choice of optimum technological scheme of production of tablets depends on the physico-chemical and technological properties of medicinal substances, their quantity in the composition of tablets, stability to influence of factors of external environment, etc.

Currently, there are two main methods of production of tablets by direct compression of substances, and through the granulation.

Direct compression is a combination of various technological techniques to improve the basic technological properties of the tableting material: flowability and moldability, and to obtain from him the tablets, bypassing the stage of granulation.

Granulation of directional coarsening of the particles, i.e., is process of transformation powdered material in grains of certain size.

Granulation is necessary to improve the flowability tablet mass that occurs as a result of a significant reduction in total particle surface area of their adhesion to the granules and, consequently, a corresponding reduction in friction between these particles in the movement.

Method of dry granulation. Is the mixing of powders and the wetting solutions of bonding agents in glass-lined mixers, followed by drying them to a lumpy mass. Then the mass is by means of rollers or mills Excelsior turned into a large powder.

A method of wet granulation. This method of granulation are subjected to the powders that has poor flow properties and poor adhesion between particles.

Granulation or wet mass is made for the purpose of compaction of the powder and obtain uniform granules – granules with good flowability.

In this method, add in the mass of adhesive solutions, which improve the adhesion between the particles.

Stage of wet granulation comprises the following steps:

1. mixing of powders;
2. hydretionpowders with a solution of binders and mixing;
3. the wet granulation mass;
4. drying wet granules;
5. treatment of dry granules.

Mixing of powders. Is made to achieve a homogeneous mass and the uniform distributionof the active substance of tablets. For mixing and wetting the powdery substances are applied to the mixers of various designs: 1) with rotating blades; 2) screw; 3) blended drums.

When mixing powders, you must adhere to the following rules:

• to a large number of add less;

• poisonous and potent substances used in small quantities, pre-sifted through a sieve, add the weights of individual portions in the form of triturate, i.e. in breeding with a filler in a concentration of 1 : 100;

• colored substances and substances with a high specific mass are loaded into the mixer in the last turn;

• volatile essential oils are injected into a dry granular mass before pressing at the stage of dusting, in order to avoid their volatilization.

After mixing of dry powders in the mass of individual portions add a humidifier, which is necessary to prevent it from clumping.

In wet mixing of the powders, the uniformity of their distribution is significantly improved, not observed separation of particles and stratication of the mass, improves its plasticity. Stirring wetted powders is accompanied by some compaction of the mass due to the displacement flow, which allows to obtain more dense solid pellets. Mixing time wet mass: for simple mixtures 7-10 minutes, for compound - 15-20 minutes. The optimal number of the humidifier is determined experimentally (on the basis of physico-chemical properties of powders) and

specified in the regulations.Anincorrectdefinitioncanleadtoanundesirableresult:if the humidifier is to introduce small, then the pellets after drying crumble if a lot of mass will be viscous, sticky and poorly granulated. Weight with optimal humidity is a moist, compact mixture, not sticking to your hand, but crumbling when compressed into separate lumps.

The wet granulation mass. The wet mass is granulated in special machines-granulators, the principle of which is that the material is wiped by the blades, spring rollers or other devices through the perforated cylinder or strainer.

To ensure the process of wiping the machine must work in an optimal fashion without overloading so that the wet mass to pass freely through the holes of the cylinder or the grid. If the mass is moist and moderately plastic, it does not stick hole and the process takes place without difficulty. If the mass is viscous and seals the hole, the machine is overloaded and it is necessary to periodically shut off the engine to wash the blades of the reel.

Currently wet granulation is the main type of granulation in the production of tablets, however it has several disadvantages:

• prolonged exposure to moisture on medicinal and auxiliary substances;

• deterioration of disintegration (solubility) tablets;

• the necessity of using special equipment;

• the duration and complexity of the process.

Drying wet granules. For this purpose there are different types of dryers:

1. shelf dryer with forced air circulation;

2. dryer with silicagel column.

In case you need to regenerate liquid contained in the dried material, used dryers, in which air is

is passed through silica gel. This precious pair are adsorbed, and the warm air is once used for drying material.

Structural granulation. Has a characteristic impact on the material is hydrated, which leads to the formation of rounded and subject to certain conditions and fairly uniform in size of pellets.

Currently there are three ways granulation of this type are used in pharmaceutical manufacturing: granulation in the drageeing boiler, granulation, spray drying granulation and structural.

For granulation in the drageeing boiler load and the mixture of powders while rotating it at a speed of 30 rpm produced a hydration by applying the solution of binding agent through the nozzle. The powders particles stick together among themselves, are dried by warm air, and by friction acquires approximately the same shape. At the end of the process to the dried granulate are added to the sliding substances.

Granulation spray drying, it is advisable to use in cases of unwanted long contacting the granulated product with air, if possible, directly from solution (for example, in the production of antibiotics, enzymes, products from raw materials of animal and vegetable origin).

Prepare a solution or suspension of excipients and of the humidifier and fed through nozzles into the chamber of a spray dryer having a temperature of 150 º C. Sprayed particles have larger surface area, resulting in intensive mass - and heat transfer. They quickly lose moisture and form in just a few seconds spherical porous granules. The resulting granules are mixed with medicinal substances and, if necessary, add auxiliary substances, not previously entered in the suspension. The granules have good flowability and compressibility, so the tablet obtained from such pellets, have high strength and are pressed at low pressures.

Granulating in fluidization conditions (fig. 1.2). Its main distinguishing feature is that the material being processed, and then the resulting granules are continuously in motion. Basic processes – mixing components, moistening the mixture with a solution of an adhesive substance, granulation, drying the granules and makingsubstances – proceed in a single unit. Granulation in the fluidized bed is carried out in two ways:

• spraying of a solution containing drug and an auxiliary substance in a fluid system;

• granulation of powdery substances with the use of fluidization.

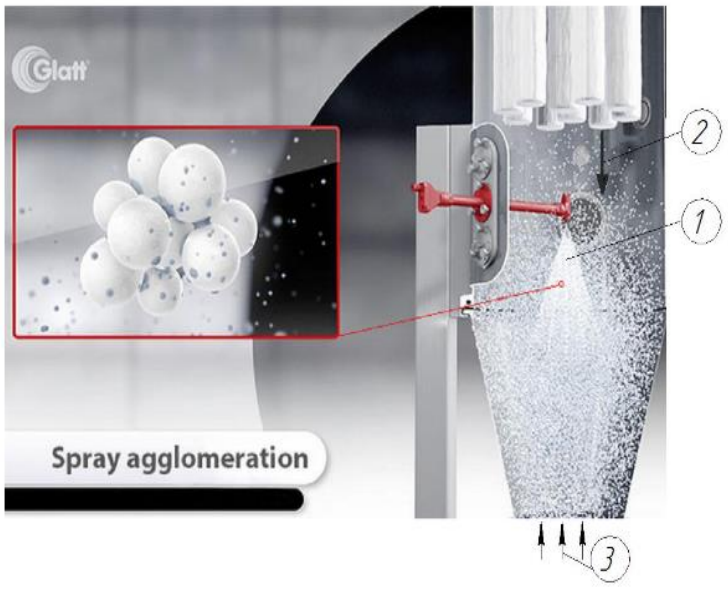


Figure 1.2 Granulation of powdery substances with the use of fluidization

COVERING OF TABLETS SHELLS

Covering of tablets shells masterone has value and has the following objectives:

1. protect tablets from extreme factors of the external environment (impacts, abrasion, etc.);

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

3. masking of unpleasant taste and odor contained in tablets of drugs;

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

5. protection contained in tablets of drugs from the acid reaction of the gastric juice;

6. protection of the oral mucosa, the esophagus and stomach from irritating action of medicinal substances;

7. localization of therapeutic action of medicinal substances in a specific Department of the gastrointestinal tract;

8. prevention of violations of the digestive processes in the stomach, is possible when the neutralization of gastric juice medicinal substances of a basic character;

9. prolongation of the therapeutic action of medicinal substances in tablets;

10. overcoming the incompatibility of different substances in one tablet by introducing them to the shell and the kernel;

11. improving the presentation of the tablets and ease of use

When the covering of tablets shells using various excipients, which can be divided into the following groups: adhesives that provide adhesion of coating materials to the core and to each other (sugar syrup, PVP, CMC, MC, AFC, OPMC, EC, PEG, etc.); structural elements that creates the frames (sugar, magnesium oxide, calcium oxide, talc, basic magnesium carbonate), plasticizers which impart to the coating properties of plasticity (vegetable oil, MC, PVP, CMC, twins, etc.); water repellents coatings giving properties of water resistance (Aerosil, shellac, polyacrylic resin, Zein); colorants used to enhance the appearance or for the designation of therapeutic groups of substances: (tropeolin 00, tartrazine, acid red 2S, Indigo, etc.); corrigenda, giving the coating a pleasant taste (sugar, citric acid, cocoa, vanilla, etc.).

Used more than 50 types of film-forming agents.

Tablet coating depending on their composition and the method of application is divided into the following groups:

1) Pressed (or dry)coatings

Sheathing by molding (dry coating) is carried out using tableting machines type “Drakota” English company Manesty (the machine is a dual unit consisting of two rotors).

2) Film coating

The film coating is called thin (of the order of 0.05-0.2 mm) shell that forms on the tablet after drying on the surface of the solution film-forming substance. They have the following advantages:

1. The selective solubility of tablets in the stomach or the intestine.

2. Regulation of the rate of adsorption of medicinal substances.

3. The possibility of combining in a single dosage form associated drugs.

4. The physical, chemical and mechanical properties of the cores of tablets with the application of film coatings.

5. The original geometrical parameters of the tablets, their shapes, markings, brand marks.

6. Reducing the weight of the volume of the film coating compared to a coating.

7. Possibility of automation of the coating process, the intensification of production and reduction of production areas.

Depending on the solubility of the film coatings may be divided into the following groups:

A) a water-soluble coating;

B) coating soluble in gastric juice;

B) enteric coating;

G) of the insoluble coating.

Water-soluble coverings and coatings, soluble in the stomach. Water-soluble coatings improve the appearance of tablets, correcting the taste and smell, protects from mechanical damage. Cover, soluble in the stomach, protect the tablets from moisture of the air; they are destroyed in the body for 10-30 min.

To obtain coatings of water-soluble polyethylene oxide and polyvinylpyrolidone is applied to tablets in the form of a 20-30% solution in 50% to 90% ethyl or isopropyl alcohol, methylcellulose and sodium salt of carboxymethyl cellulose is in the form of 4-7% aqueous solutions.

The coating soluble in gastric juice, present benzylamino- and diethylaminoethylcellulose, p-aminobenzoate, sucrose, glucose, fructose, mannitol, vinylpyridine, zein and gelatin.

Enteric coatings. Enteric coatings protect the drug-containing tablet from the action of acidic gastric juice, protects the gastric mucosa from irritating action of some medicines, localize the medicinal substance in intestines, prolonging to some extent its action. Enteric coatings are also more pronounced than in the above-mentioned groups of conformal coating effect.

The process of dissolution of enteric membranes in the body due to the influence of the enzyme complex and various solubilizers substances contained in the intestinal juice.

To obtain enteric coatings as film-forming high-molecular compounds are used with the properties of polyelectrolytes with a high number of carboxyl groups. They dissociate in neutral or alkaline medium with the formation of insoluble salts. Apply a natural substance: shellac, Carnauba wax, casein, keratin, paraffin, ceresin, spermaceti, cetyl alcohol, and also synthetic products, stearic acid in combination with fats and bile acids, butylstearate, the phthalates dextrin, cellulose acetate monoacrylate, methylcellulose.

Enteric-coated coating stand (2-4 hours or more) exposure to gastric juice that allows these pills unchanged through the stomach; the intestinal juice, they disintegrate within 1 hour, providing a release of drug substance in the intestine.

Insoluble coverings. The main purpose of coatings of this type protect the tablet from mechanical damage and from exposure to atmospheric moisture, elimination of unpleasant odor and taste of the drug, prolonging its action. These include ethylcellulose, monolaurate polyethylene sorbitol, surfactants, etc. The mechanism of release of medicinal substance from the tablets with an insoluble membranes is as follows. After receipt of the tablets in the gastro-intestinal tract of the digestive juices penetrate into it through the micropores of the membranes and cause the dissolution or content of tablets, or swelling. In the first case the dissolved substance diffuse through the film in the opposite direction – in the direction of the gastro-intestinal tract under the influence of the concentration difference, in the second case there is a rupture of the shell due to the increase in volume pills, after which the medicinal substance is liberated by usual way.

Sugar-coated coverage. (from the French. dragee – coating sugar shell) – this is the oldest type of tablet casings used from the beginning of the twentieth century. The main purpose of these membranes is to protect tablets from external influences, masking of unpleasant taste and odour of drug substances, improving the

appearance of tablets. Sometimes in the composition of shells add nutrients to protect your tablet from the effects of gastric juice.

Sugar-coated tablet consists of a tablet core containing a drug substance and a coating containing a complex of auxiliary substances.

CONCLUSION TO CHAPTER 1

1. Among the drugs that are used to treat anti-ulcer diseases, ranitidine remains one of the most common antisecretory drugs and is found in many areas of gastroenterology.

2. A study of the market of antiulcer drugs was carried out.

3. The characteristics of antiulcer drugs in different dosage forms are presented.

4. The technological aspects of obtaining tablets are described.

CHAPTER 2
OBJECTS AND METHODS OF RESEARCH

This chapter presents the objects and methods of research, which together reflects the nature and character of the work to meet the challenges of this problem.

2.1 The objects of study

Ranitidine hcl is a white crystalline powder or almost white, very hygroscopic, easily soluble in water, slightly soluble in methanol, very slightly soluble in 96% alcohol, practically insoluble in chloroform.

Calcium stearate (TU 6-04-4233-76) is a white crystalline powder, odorless, insoluble in water.

Plasdone 90 D (European Pharmacopoeia) – the binder.

Cellactose 80 (European Pharmacopoeia) – for the preparation of tablet mass.

Eudragit-substances of a polymeric nature, which are copolymers of esters of acrylic and methacrylic acids (F. USP 23; NF-18, S, the company "Rohm Pharma Gmd", Germany).

2.2 Methods for determination of physico-chemical and technological properties

The shape and size of the particles. Powdered medicinal substances are particulate systems and have particles of various shapes and sizes. Most of them is crystalline systems; amorphous state is less common.

Many drugs particles anisodiametric (unbalanced, raznosnye). They can be elongated when the length greatly exceeds the lateral dimensions (sticks, needles, etc.), or plate, when the length and width significantly greater than the thickness (plates, scales, signs, leaflets, etc.). A smaller part of the powdered substance has a

particle sociomatrices (symmetric, equiaxed) is a globular masses, lumps, polyhedra, etc.

The shape and size of powder particles depend: crystalline substances (chemical and pharmaceuticals) – from the structure of the crystal lattice and the conditions of particle growth during crystallization, the powdered plant materials – from the anatomical and morphological features of ground plant organs and the type of grinding machine.

The particle size of powders is determined by their length and width, which is measured with a microscope equipped with a micrometer grid, at magnification of 400 or 600 times.

The shape of the particles set by the ratio of the average particle length to the average width. In this method, particles are divided into three main types: elongated – ratio of length to width of more than 3:1; the plate – length exceeds width and thickness but not more than 3 times; equiaxed – a spherical, polyhedral shape close to sociometrically.

Only substances belonging to the cubic system, are compressed into tablets directly, i.e. by direct compression, without granulation and excipients (sodium chloride, potassium bromide).

Powders with equiaxed shape of the particles – coarse, low compaction, low porosity (lactose, hexamine, salol).

The harder the surface of powder particles, the greater the adhesion and the less the flowability and vice versa.

Bulk (volume) density is the mass per unit volume freely poured a pulverous material.

Bulk density depends on the shape, size, density of powder particles (granules), moisture content.

The value of bulk density it is possible to predict the volume of the channel matrix.

Determination of the bulk density of the powder is carried out on the device «PharmaTest», Germany(Fig. 2.1).

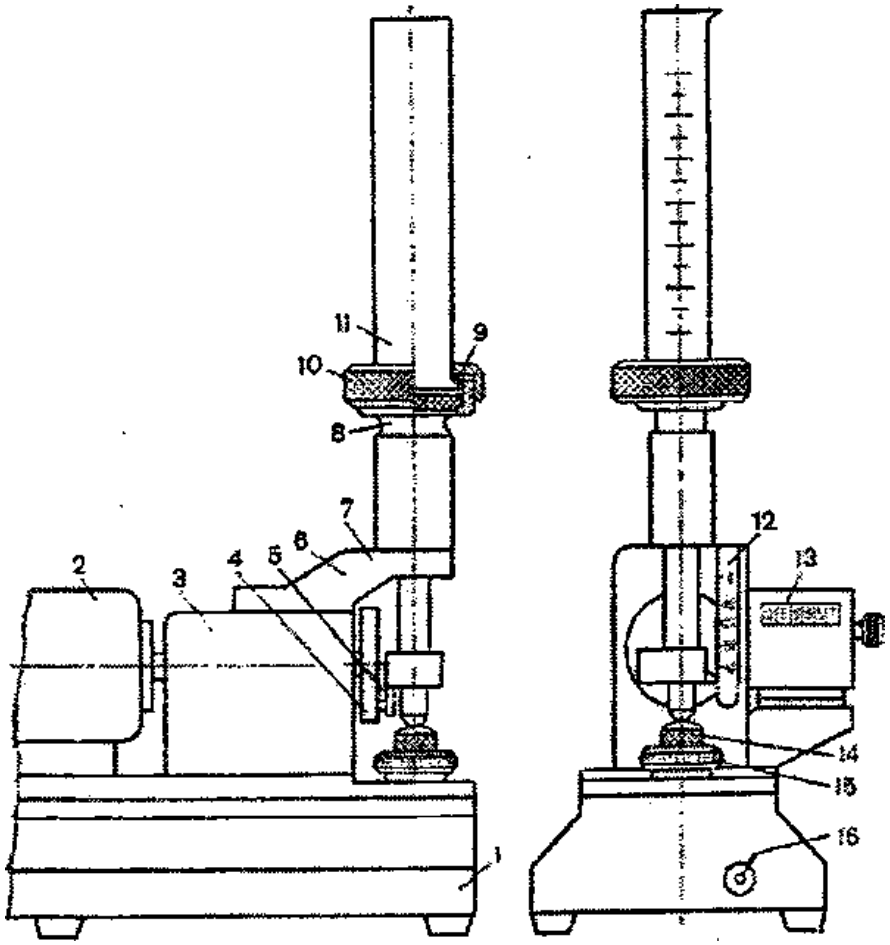


Figure 2.1 Density meter

Bulk density is calculated by the formula:

$$\rho_н = \frac{m}{v}$$

where ρ_n – bulk density, kg/m^3;

m is the mass of granular material, kg;

v – volume of powder in the cylinder after compaction, m^3.

Depending on the bulk density powders are distinguished as follows:

ρ n > 2000 kg/m3 – very heavy;

2000 >ρ n > 1100 kg/m3 – heavy;

1100 >ρ n > 600 kg/m3 – average;

ρ n < 600 kg/m3 light.

The fluidity (flowability) the ability of pulverous system to sleep from the container or funnel flow under gravity and to ensure a uniform filling of the channel matrix. A material with poor flowability in the funnel, adheres to its walls, which disturbs the rhythm of its receipt in the matrix. This leads to the fact that the specified weight and density of tablets will vary.

The flowability is determined on a vibratory device for characterizing bulk materials VP-12A (Fig. 2.2).

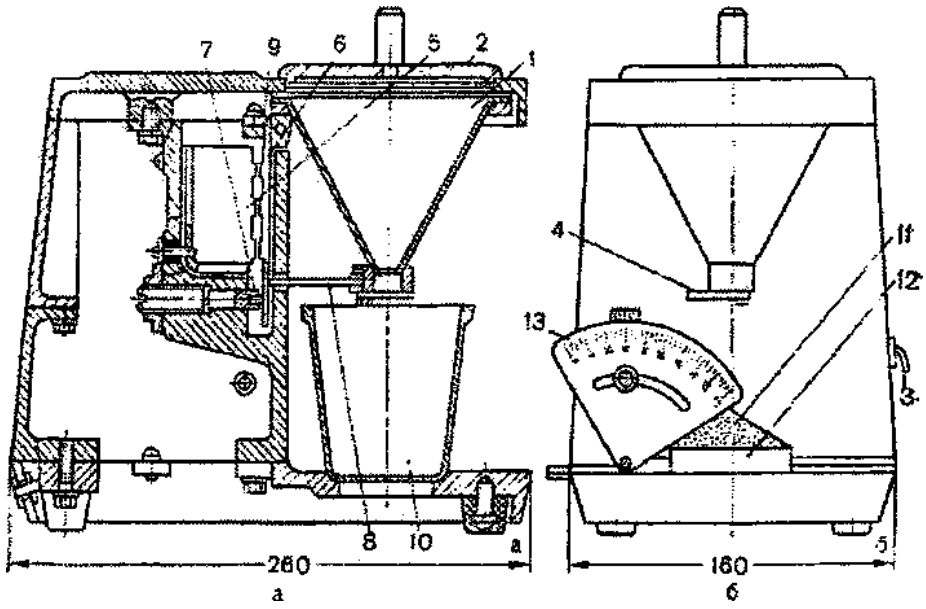


Figure 2.2 Flowability tester

Compressibility – the ability of a powder to cohesion under pressure, i.e. the ability of particles under the influence of forces of an electromagnetic nature (molecular, adsorptive, electrical) and mechanical links for mutual attraction and bonding to form a stable strong pressing.

The compressibility is characterized by the strength model of the tablet after removal of the pressure. The better the moldability of the powder, the higher

strength tablets. If the moldability is poor, the obtained tablet are fragile, and sometimes completely destroyed during ejection from the die.

The nature of the relationship of particles in tablets. Tableting is based on the properties of powdered medicinal substances to be condensed and procnotice under pressure. Thus substructural material becomes bonded dispersed system with a certain degree of porosity. This system is largely similar to the compact body, which has certain cohesive forces.

2.3 Methods of evaluation of the quality of tablets

1. Evaluation of appearance of tablets. Looking at 20 pills and make a conclusion of surface defects or the absence of them. Determine with calipers the size of the tablets (diameter, height), type of pills according OST-072-89, as well as the color and separation risk. The pills should be of the following defects size, color, cover, font, dividing the risks:

• a protrusion (the surface protrusions sticking of powder particles);
• the deepening (holes, spalled parts of tablets);
• dirt or dust on tablets;
• mottled (uneven color, local, local color change);
• chipping (peeling or chipped tablets, thickness reduction);
• adhesion (the sticking together of the two pills together, or their connecting surfaces destroyed);
• crushing;
• deformation (violation of oblong form);
• the scratches (applying a risks – scratches on the surface of tablets);
• defect in the coating (the coating surface is uneven, different thickness, offset from the nucleus).

The pills must be of a circular or other form with a flat or lenticular surfaces, solid edges, the surface should be smooth and uniform, color is uniform, if in private the articles States otherwise.

2. Determination of tablet disintegration. The most appropriate method for determining the disintegration of tablets would be the observation of their behavior in the human stomach by obtaining renthenznimky. However, for mass production of tablets is difficult, resulting in globally accepted conventional methods for determination of tablet disintegration that takes place outside the body chelovecheski.

The device consists of a swinging basket , the vessel with the liquid medium (water, artificial gastric or intestinal juice), the immersed basket thermostatic device to maintain a constant temperature environment within 37± 2° With and electric motor that tells the basket back and forth motion. Swinging the basket consists of 2 bakelite discs with a diameter of 90 mm with concentrically spaced 6 holes. In the holes of the discs is inserted a glass tube with a length of 77.5 mm and an outer diameter of 25.5 mm. the Lower disk is provided with a grid of stainless steel wire with a hole diameter of 2 mm. the Basket through the steel rod attached to the lever of the electric motor.

The advantage of this method is the standardization of test conditions, the constant amplitude of the oscillations, the frequency of 28-32 cycles / min., the removal of particles of broken tablets, the constancy of temperature, regulation of the particle size, the ability to test simultaneously 5-6 tablets, mechanization definition.

The disadvantage is the need for visual observation for the purpose of establishing the date of final raspadenie tablets.

A better method is the determination of tablet disintegration in the instrument company “Erveka” (Germany). Different this device the device is producing automatic termination of the oscillation of the basket in a moment of raspadenie pills. At the same time automatically, the clock stops and time is fixed raspadne.

The rate of tablet disintegration:

1. conventional tablet – 15 minutes;

2. tablets, coated membranes, soluble in stomach – no more than 30 minutes (unless otherwise instructed in a separate pharmacopoeial articles). Tablets, coated enteric-soluble shell, should not disintegrate within 1 hour in hydrochloric acid

solution 0.1 mol/l, and after washing with water should decompose in no more than 1 hour in an alkaline solution of sodium bicarbonate;

3. sublingual tablets – water, 30 minutes;

4. tablets for the preparation of solutions – water, 5 minutes;

5. tablets prolonged action – by the methods given in Pharmacopoeia articles;

6. vaginal tablets – lactic-acid medium, no more than 10 min.

3. Determination of mechanical strength of tablets. Determination of mechanical strength of tablets is carried out on the devices, some of which allow to determine the compressive strength (split), others resistance.

The compression strength. The mechanical strength of tablets the compression can be identified on different devices.They All work on the principle of a spring dynamometer.

The strength value should be 0.45 to 1.2 MPa.

Abrasion resistance. Mechanical strength is also characterized by the degree of abrasion of the tablets. Abrasion occurs during packaging, packing and transport, being especially strong in packaging machines. A symptom of resistance to abrasion is the formation of powdery dust on the pills and packaging. Abrasion instrument determine on the drum – friabilator 545-R-AK-8 or by “ERWEKA”.

The tablets should not be changed in the process of wear. Abrasion resistance shall be not less than 99%. For tablets, coated tablets, microtablets and the tablets resistance to abrasion is determined.

4. Dissolution. Determination of tablet disintegration provides no information about the release of medicinal substances from the disintegrated dosage form and does not allow to make a conclusion about their availability.

A more reliable monitoring method is “test solution”. When analyzed number of medicinal substances (in time intervals), diffusing from whole or broken tablets in a solvent liquid (water, 0.1 n hydrochloric acid solution, 0.1 n solution of sodium hydroxide, buffer solutions, artificial digestive juice, etc.)

The average weight and variation in weight of individual tablets. 20 tablets are weighed to the nearest 0.001 g and the result divided by 20. The weights of

individual tablets is determined by weighing 20 tablets individually to the nearest 0.001 g deviation in the weights of individual tablets (excluding tablets, coated tablets method of building) is permitted within the following limits:

• for tablets weighing 0.1 g and less than ±10%;

• weighing more than 0.1 g and less than 0.3 g ±7,5%;

• a weight of 0.3 and ±5%;

• weight of individual coated tablets obtained by the method of building, should not differ from the average weight by more than ±15%.

Two tablets can have deviations from average weights in excess of those limits, but not more than twice.

CONCLUSION TO CHAPTER 2

1. The objects and methods of research are given.The main properties of ranitidine substance and excipients are presented.

2. The methods of physicochemical, pharmacotechnological, analytical studies that were used in the work are given.

CHAPTER 3
DEVELOPMENT OF THE COMPOSITION AND TECHNOLOGY OF RANITIDINE TABLETS

3.1 Study of the properties of the ranitidine substance

The production of tablets begins with learning the properties of medicinal substances, which largely determine the rational method of tableting; range of choice and amount of excipients. As a starting material use of granular matter in the form of a powdery (particle size up to 0.2 mm) or granular (particle size from 0.1 to 3 mm) forms, which have the following properties:

– physical - density, shape, size and nature of the surface of the particles, the adhesive force (adhesion on the surface) and cohesion (adhesion of particles inside the body), surface activity, melting point etc.;

– chemical - solubility, reactivity;

– technology - bulk density, degree of compaction, flowability, moisture content, size distribution, dispersibility, moldability and Jn.;

– structural-mechanical - ductility, toughness, elasticity, viscosity of the crystal lattice, etc.

The research object of our work was the Ranitidine in the form of tablets. In the process, have been studied physico-chemical and technological properties of Ranitidine. This substance belongs to the group of substances, is susceptible to humidity and light. The improvement of the production technology of the drug Ranitidine is to use the method of direct pressing, which helps to eliminate the negative effects of humidity and temperature these factors on the medicinal substance, in comparison with the method of dry granulation, which was used before.

Direct pressing allows to eliminate 3 to 4 technological operationsand, thus has advantage over the dry granulation of powders. To protect Ranitidine from the

influence of the light efficiently to provide for the application of the shell on the tablet core.

The aim of our work is to improve the technology of tablets Ranitidine by switching to direct pressing with the use of auxiliary substances and application technology of film-forming membranes from an aqueous suspension of film-forming substances. Thanks to the introduction of the quality and efficacy of the drug will grow significantly.

At the beginning of experimental studies, the crystallographic (Fig. 3.1) and pharmacotechnological properties of the substance were studied (Table 3.1).

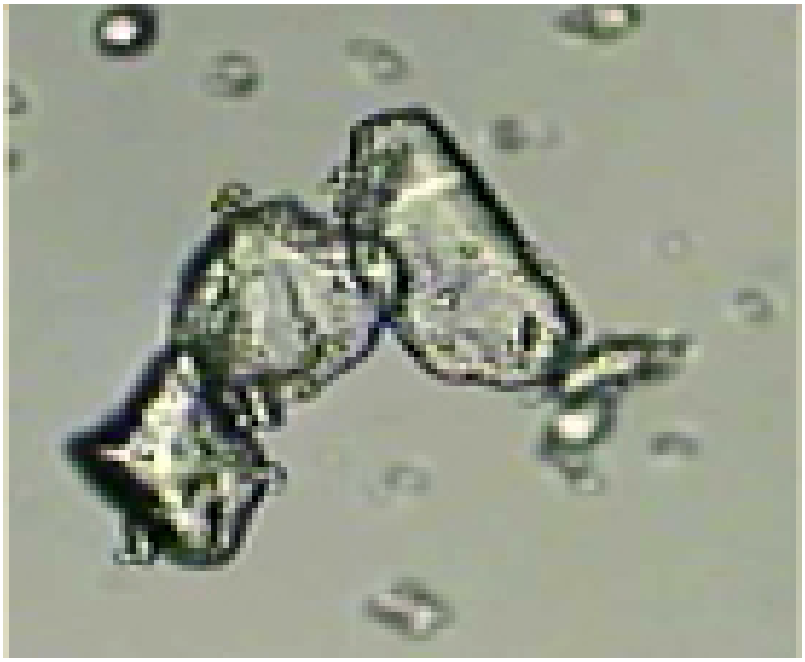


Figure 3.1 Micrograph of ranitidine substance

On the basis of crystallographic data, it can be assumed that the ranitidine substance, due to the complex surface of the powder particles, has a high adhesion value, which will affect the fluidity value, reducing it.

According to the method described in section 2 were studied technological properties of the drug substance Ranitidine.

The results of studies of the pharmaco-technological properties of the Ranitidine substance are shown in table 3.1.

Table 3.1

Pharmaco-technological properties of Ranitidine substance powder

Parameters	Units of measurement	Meaning
Bulk density	g/ml	0,48±0,05
Density after shrinkage	g/ml	0,67±0,03
Flowability	Seconds per 100 g of sample	57,1±1,5
The angle of repose	degrees	62±3
Moisture content	%	0,5±0,10
The compressibility	H	15,1±0,1

Note:n=5, P=95%.

Analysis of the technological properties showed that the flowability of these powder has a low value, which is confirmed by the high value of the angle of cut.

The difference in the values of the bulk mass and density indicates the ability of the powder to caking with formation of a sufficiently resistant to fracture systems.

In addition, the choice of the optimal size of the tablet is determined by its average capacity and the density of its content.

The compressibility is characterized by the strength model of the tablet after removal of the pressure. The irregular shape of the powder particles promotes the tablets. Substance of ranitidine has unsatisfactory value of compressibility.

The better the compressibility of the powder, the higher resistance to crushing tablets. This is important because in the manufacture of a medicinal product in an industrial environment on the tablet core is influenced by the

following factors: the total mass of the tablets, their free fall, kinetic energy and destructioneffect.

Unsatisfactory values of technological properties, namely flowability and compressibility, led to the choice of auxiliary substances to obtain mass for tabletting by direct compression.

3.2 Choice of auxiliary substances

For the formulation of tablets used excipients:fillers, binders, lubricants,film-forming. As formative substances are used auxiliary substances: sorbitol, MCC 102, sucrose, tablettose 80 and cellactose80 (table 3.2).

Table 3.2

Pharmacotechnological properties of fillers

Substance	Solubility	Bulk density, g/ml	Density after shrinkage, g/ml	Flowability,seconds per 100 g of sample	Carra Index, %
Sorbitol, «Meggle Excipients» Germany	Soluble in water	0,65±0,02	0,73±0,02	15,3±0,5	19±0,5
MCC 102, «JRSPHARMA» Germany	Practically insoluble in water	0,33±0,01	0,45±0,01	30±0,8	26±0,8
Tablettose 80 «Мерск», Germany	Dissolves slowly in water	0,45±0,01	0,71±0,02	9,3±0,2	21±0,5
Cellactose 80 «Мерск», Germany	Soluble in water	0,43±0,01	0,57±0,01	27±0,7	24±0,6
SucrosebrandB «Südzucker», Germany	Soluble in water	0,65±0,02	0,72±0,02	2,8±0,07	9,7±0,2

Note: n=5, P=95%.

Subsequent studies were aimed to study the flowability of the tablet mass of ranitidine with the aforementioned auxiliary substances. The results are shown in Fig. 3.2.

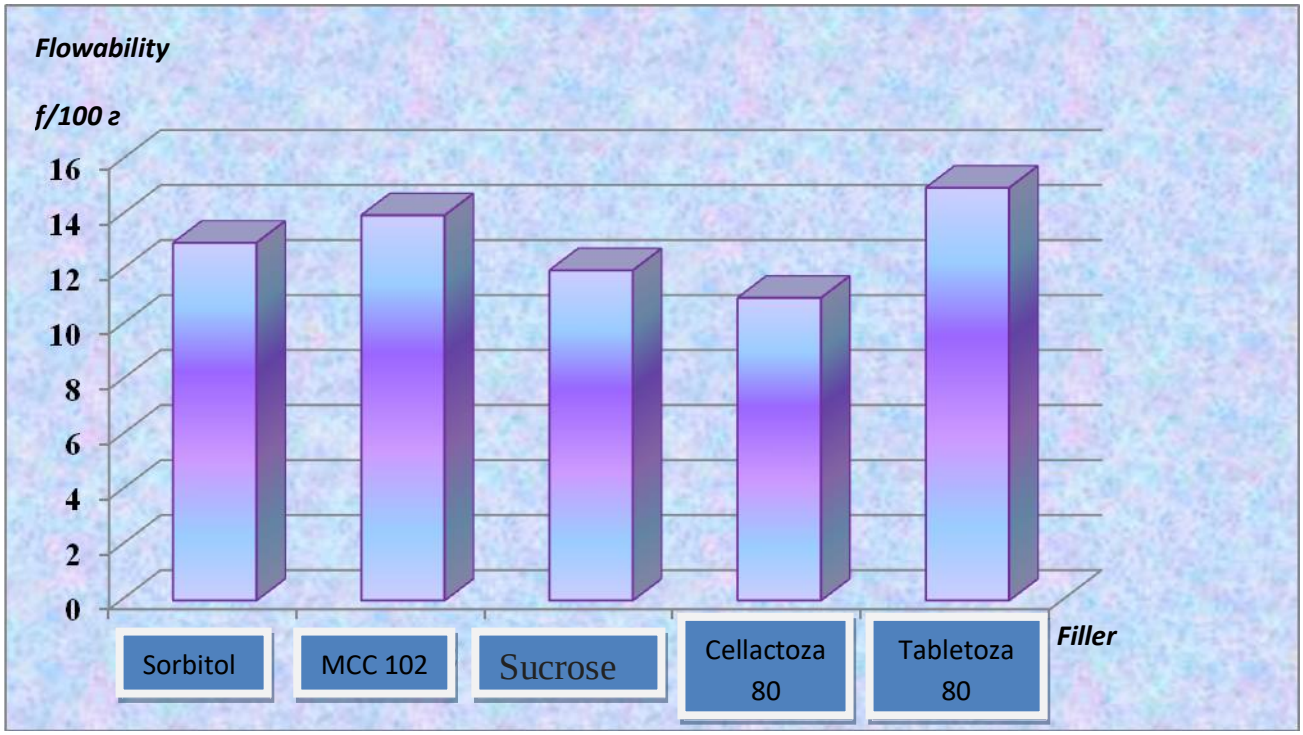


Figure 3.2 Comparative diagram of flowability with different fillers

From these figure, we see that forming substances improve the value of flowability. Tablet weight ranitidine and sorbitol has a value of flowability 12, 102-13,8 with MCC, with sucrose 11,8 , tablettose 80 -14,7.The most satisfactory value has a mixture of ranitidine with cellactose 80.

For prevention of adhesion, improvement of flowability used sliding substances.

Marked another function, which carry out sliding substances. It is the removal of an electrostatic charge of the powder particles or granules that also improves their flowability.

Therefore, for dusting applied to calcium stearate in an amount of 1 %.

Tablets were obtained by direct compression, the average mass of 0.25 g and a diameter of 9 mm compositions of the mixtures and the quality of tablets - cores are given in the table 3.3.

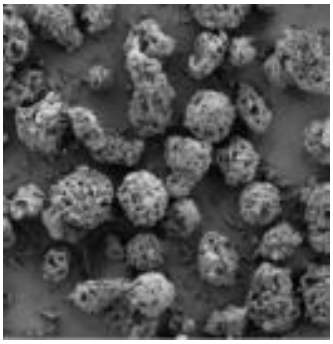
Table 3.3

Compositions of the mixtures and the quality of tablets - cores

The composition of the mixture	Quality indicators of tablets - cores		
	Disintegration, min.	Resistance tocrushing, H	Abrasion, %
Ranitidine 66,8% Sorbitol 32,2% Calciumstearate 1 %	11,2±2	22,5±1,4	3,5±0,1
Ranitidine66,8 % MCC 102 32,2 % Calciumstearate 1 %	9,1±1	19,8±1,1	3,2±0,2
Ranitidine 66,8% Sucrose 32,2 % Calciumstearate 1%	12,2±2	20,8±1,5	3,7±0,3
Ranitidine 66,8% Tablettose 80 32,2% Calciumstearate 1 %	8,1±2	23,0±1,5	3,1±0,1
Ranitidine 66,8% Cellactose 80 32,2% Calciumstearate 1%	5,3±2	25,3±1,0	2,3±0,1

Note: n=5, P=95%.

Tablets obtained from these mixtures meet the requirements of pharmacopoeiasat the time of disintegration (15 minutes), except in mixture with sucrose. The resistance of tablets to crushing was also satisfactory, but the tablet core will be coated, therefore, the value of resistance it is desirable to have more. All the formulations did not pass the test on wearability. The most satisfactory performance is the last part of cellactose 80.



Cellactose® 80

Lactose and cellulose are substances of natural origin and are widely used in the production of solid dosage forms.

The peculiarity of the technology of obtaining celactose due to the synergism effect allows to increase the pressing, adhesive ability of the tablet mass.To obtain celactose, a spray dryer is used to integrate alpha-lactose monohydrate and powdered cellulose into a single mixture.

As a result, a combined auxiliary substance for direct pressing Cellactose® 80 containing 75% alpha-lactose monohydrate and 25% powdered cellulose was obtained.

Advantages: high homogeneity of mixtures due to low segregation of the active ingredient;ideal core surface for light and economical coating;tableting of "complex" APIs due to excellent pressing;low fluctuation of tablet hardness due to the rational ratio of lactose / cellulose;high uniformity of tablet mass at high pressing speeds.

Field of application: Cellactose® 80 has been developed for direct pressing.Compared to the corresponding mechanical mixture, Cellactose® 80 is characterized by less segregation, better fluidity and adsorption, a higher degree of pressing;Cellacto¬se® 80 is used when pressing coated microparticles or, if necessary, to prevent incompatibility with MCC;due to its properties, Cellactose® 80 is ideal for low-dose medicinal products.In addition, due to the high pressing of Cellactose® 80, it is possible to directly press formulations with a high concentration of the active ingredient.

And our subsidiary substance - cellactose 80, a complex substance that consists of 75% lactose monohydrate and 25% cellulose powder, characterized by high strength, good flowability, uniformity, adhesins ability. These properties allow the use of cellactose during tableting by direct compression.

For the purpose of improved friability in the tablet mass was added to the binder – plasdone 90 D.

The dependence of abrasion on the concentration plasdone 90 D shown in Fig. 3.3.

Abrasion, %

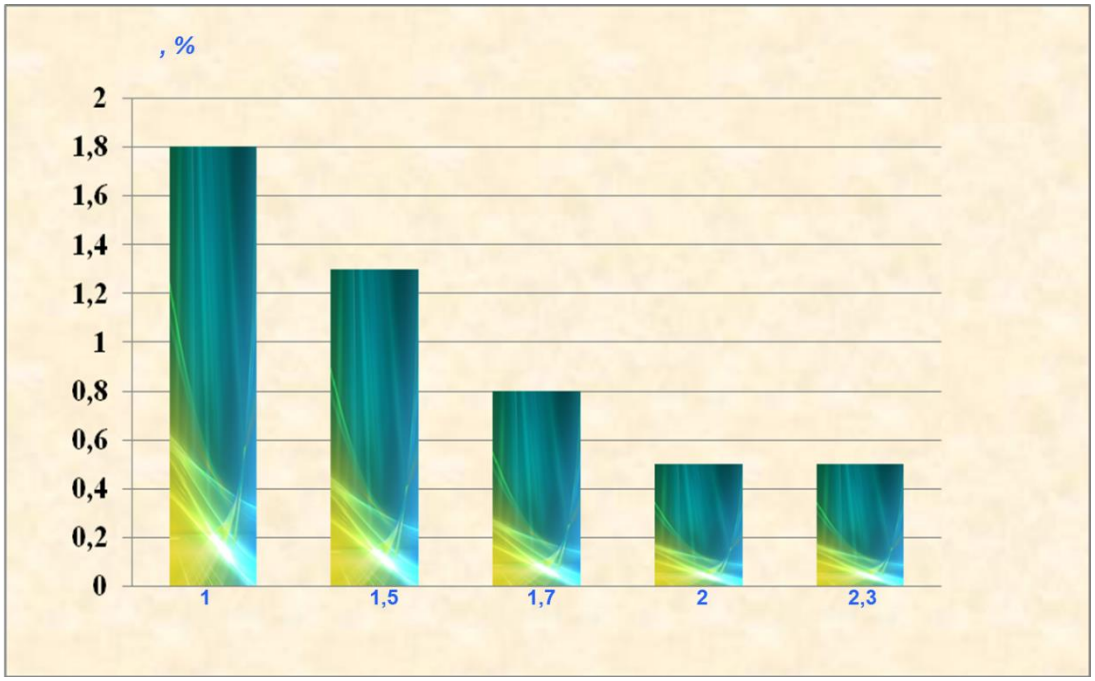


Figure 3.3 Dependence of abrasion on the concentration of plasdon 90 D

Thus we see that plasmon 90 D improves the value of abrasion.

When the concentration plasdone 90 D 1 % of the tablet mixture in the abrasion value is equal to 1,8%, and at concentrations of 2 and 2.3 % value of abrasion does not change and has a constant value at 0.5%.

Therefore, we chose a concentration of 2%.

3.3 Development of the composition, technology and standardization of ranitidine tablets

Thus, on the basis of the conducted research, we have developed the composition of the tablet-core (table 3.4):

Table 3.4

Composition of the tablet-core

Component	g	%
Ranitidine hydrochloride	0,15000 g	60%
Cellactose	0,0925	37%
Plasdone 90 D	0.005	2%
Calcium stearate	0.0025	1%
Only	0.25	100%

In recent years, the technology of obtaining tablets with polymer film coatings, which are soluble in water, has gained significant development.The practice of using water-soluble coatings in industrial conditions is due to their safety, harmlessness and availability.

For coating uses a powder mixture of Opadry, by Colorcon, USA.

Requirements for film-forming substances:

1. Complete harmlessness for the organism.
2. Good solubility in commonly available solvents.
3. Good film-forming properties.
4. Chemical indifference.
5. Stability during prolonged storage (durability, elasticity and solubility).
6. Accessibility.

The most widely used method of applying film coatings in the drageeing boiler. This method is inexpensive, is applicable to solutions of practically any viscosity, it has high performance. For applying a covering biconvex tablets are placed in the drageeing boiler, which during the work rotates at a speed of 20-25 turns/minutes. Before starting the coating process with surface tablets a strong air jet removes the dust. The covering solution is injected into the boiler by periodic

sprinkling installed at the openings on the boiler nozzles. For drying of shells tablet in the boiler are blown by air stream.

Film coating increases the weight of the tablets.

Film coating can be applied not only on tablets, but for pellets or particles of powdered material.

Tablets cover must be flat to prevent sticking. Pelleting is proposed for type of tablet oval with an average surface, the depth of curvature of approximately 15% of the diameter , the height of the centre of 25-30% of diameter.

For this purpose, prepared suspension of powdery mass concentration of 12%, which ensures a quick application process and high coating quality. This high-efficient film coating provides protection substances from moisture, light, guarantee the stability during storage.

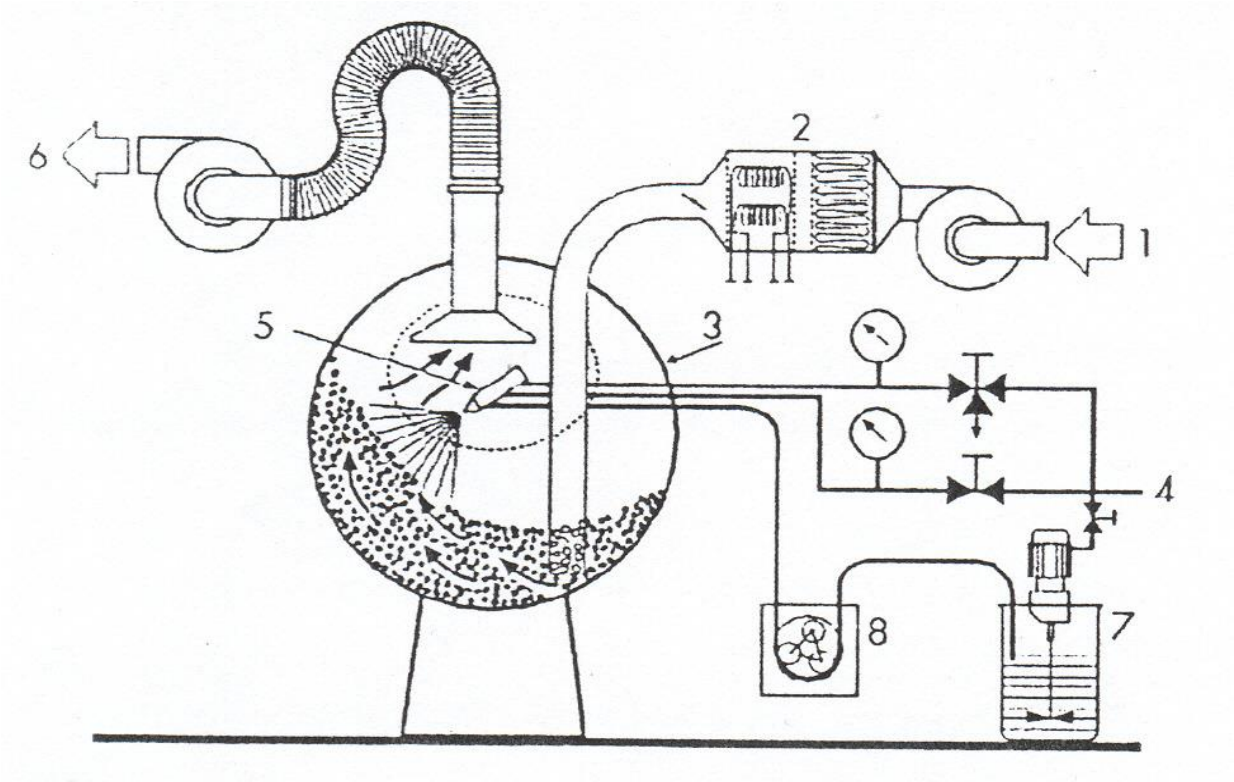


Figure 3.4 Film coater

1 - inlet air

2 - the input filter and air heater

3 - reel apparatus for coating

4 - compressed air

5 is a pneumatic spraying

6 - output air

7 - collection with pneumatic stirrer

8 - peristaltiki pump

Coating in an amount of 5% by weight of the tablet-core was sufficient to protect the tablet-cores from external conditions (light, atmospheric oxygen, humid environment).

The technological process of production of tablets

1. Preparation of production
2. Preparation of raw materials. Screening materials
3. Obtain mass for tabletting. Mixing
4. Tableting
5. Coating of tablet cores with a film coating
6. Packaging of tablets in blisters
7. Packing of blisters in packs
8. Packing packs in group containers.

One of the main conditions of industrial production of tablets is the finished product to the requirements of the current normative-technical documentation. The quality of the tablets is determined by various indicators, which are divided into the following groups:

1. Organoleptic
2. Physical
3. Chemical

4. Bacteriological

5. Biological

Determining the quality of tablets begins with an assessment of their appearance (organoleptic properties) that are affected by the following factors:

• conditions of compression;

• adhesive and cohesive properties to be tableted mass, moisture content;

• granulometric composition;

• the surface and the accuracy of the press tool;

• method coating, etc.

Physical indicators of quality are geometric (the shape of the tablet, the geometric appearance of the surface, the ratio of the thickness of the tablet to its diameter, etc.) and physical parameters (mass of tablets, deviation from the target value of the weight, strength, porosity, bulk density, and indices appearance – colour, blotch, integrity, signs or inscriptions, no metal contamination, etc.).

Chemical indicators include: disintegration, solubility and persistence chemical structure, the activity of the drug substance, shelf life of tablets, their stability during storage, etc.

For bacteriological indicators of quality include contamination of the tablets microorganisms, spores and bacteria non-pathogenic nature containing not more than the set number.

Quality control of the finished tablets is carried out according to the requirements of the Pharmacopoeia monograph “Tablets”, as well as private pharmacopoeial articles according to the following criteria:

• organoleptic properties

• mechanical strength

• disintegration

• dissolution

• the average weight of the tablets and the deviation in weight of individual tablets

• the content of drugs in tablet dosage uniformity determination of talc, Aerosil.

Some additional requirements on the quality of the tablets described in Pharmacopeia of private articles.

Standardization of tablets of Ranitidineobtained by the method of direct pressing (table 3.5).

Table 3.5

Standardization of tablets of Ranitidine

Parameters	Control method	Indicator characteristic
1. Description	Organoleptic	The tablets are pale yellow, interspersed with a characteristic odor. For appearance shall meet the requirements of pharmacopeia
2. Identification	Chemical	UV absorption spectrum of the tested solution should have the highs
3.Average tablet weight, g	Gravimetric	0,25±0,01875
4. The tablet height, mm	Physical	3,0±0,4
5. Thetablet diameter, mm	Physical	9,0±0,3
6. Disintegration time of the tablet core, min	Chronometric	Not more than 15 min.
7. Disintegration time of tablet in the shell, min	Chronometric	Notmorethan30 min.
8. Dissolution	Chemical	Content of ranitidine, which has passed into solution after 45 min., must be at least 85 %
9. Quantification	Chemical	Content of ranitidineper 1 tablet 0,1425-0,1575 g in terms of the average mass of the tablets
10.Microbiological purity	Microbiological	The drug conditions tested possesses antimicrobial activity. 1 g of the drug allowed no more than 1000 bacteria and 100 fungi and yeast (total).

Note: n=5, P=95%.

Indicators of quality control of tablets of Ranitidine meet the requirements of the Pharmacopoeia.

CONCLUSION TO CHAPTER 3

1. The physicochemical and technological properties of ranitidine substance were studied.

2. Proposed technology for producing Ranitidine tablets by direct compression

3. For production of tablets of ranitidine by the method of direct compression was used auxiliary substances: sorbitol, MCC 102, sucrose, tablettose 80 and cellactose80.To improve the rate of abrasion to the tablet mass added binding agent - plasdone 90 D.

GENERAL CONCLUSIONS

1. The analysis of literary sources on the problem of treatment for peptic ulcer disease.

2. Found that drugs based on Ranitidine remain one of the most common antisecretory drugs and find use in many areas of gastroentrology.

3. The physicochemical and technological properties of ranitidine substance were studied.

4. For production of tablets of ranitidine by the method of direct compression was used auxiliary substances: sorbitol, MCC 102, sucrose, tablettose 80 and cellactose80.To improve the rate of abrasion to the tablet mass added binding agent - plasdone 90 D.

5. With the aim of improving the quality of a drug proposed the application of a film coating the powdery mixture Opadry light yellow color.This high-efficient film coating protects the nutrients from the action of moisture and ensures stability while keeping.

6. Proposed technology for producing Ranitidine tablets by direct compression.7.The analysis of the standardization of Ranitidine tablets with the following parameters: description, identification, average mass of tablets, the tablet strength, the height, the diameter of the tablet, the disintegration time of the tablet core, the disintegration time of the tablets in the shell, dissolution, quantification, and microbiological purity.

REFERENCES

1. Physiology of the Gastrointestinal tract. New York, Raven Press, 2016. P. 1556-1865.
2. Gastrointestinal Physiology / ed L. R. Johnson. 5th ed. New York : Plenum Press, 2013. 720 p.
3. Hydrolytic and Reductive Transformations of Nifuroxazide / L. A. Trukhacheva et al. *Pharm. Chem. J*. 2015. Vol. 39, № 7. P. 43–46.
4. Слабкий Г. О., Теряєва О. Г. Виховання здорової людини як засіб первинної профілактики захворювань. *Медичні перспективи*. 2011. Т. 4, № 1. С. 118-120.
5. Drogovoz S. M., Shtrygol S. Y, Shchekina E. G. Pharmacology to help the student, pharmacist and doctor: Textbook-directory. Kharkov, 2013. P. 444-452.
6. WHO Model Lists of Essential Medicines. URL: http://www.who.int/medicines/publications/essentialmedicines/en/index.html.
7. WHO Collaborating Centre for Drug Statistics Methodology. URL: http://www.whocc.no/atc_dc.
8. Jensen D.M. New developments in the diagnosis and treatment of severe upper gastrointestinal bleeding Current topics in gastroenterology and hepatology. Stuttgart. NewYork: 2011. 422 p.
9. Levine JS, Klor H.-U., Oehler G. Gastroenterologisc Differential diagnostik. Stuttgart, NewYork: 2012.
10. Swain CP. Upper gastrointestinal haemorrhage Recent advances in gastroenterology (Ed. R.E.Pounder). Edinbugh London Madrid Melbourne New York, Tokyo: 2015. 9. 13550.
11. Wagner PK. Gastroduodenal bleeding. Symptoms and signs, diagnosis, therapy. Hoechst Meducation Update. Frankfurt am Main. 2012.
12. Walt RP. Upper gastrointestinal bleeding Recent advances in gastroenterology (Ed.R.E.Pounder). Edinburgh London Melbourne New York: 2017. 8. 10116.

13. Захарочкина Е.Р. Противоязвенные лекарственные препараты. URL: file:///d:/Downloads%20Mozilla/protivoyazvennye-lekarstvennye-preparaty.pdf
14. Perederiy V. G., Tkach S. M. Principles of Internal Medicine: Textbook 1. Kiev, 2009. P. 359-371.
15. European Pharmacopoeia. 8th ed. Strasbourg : EDQM, 2013.
16. Інфекції – реальна загроза населенню України / Ж. І. Возіанова та ін. *Інфекційні хвороби*. 2017. № 1. С. 347.
17. Diaplant: development of technology and pharmacoeconomic evidence of therapy : monograph / T. Germanyuk, L. Bobrytska, T. Ivko, R. Fares ; Edited by Germanyuk T. ; Lambert Academic Publishing of International Book Market Service Ltd., 2019. – P. 60 ISBN 978-620-0-47182-6
18. Diaplant: Manufacturing technology and rationalization of costs of acute intestinal infection pharmacotherapy / R. Fares et al. *International Journal of Green Pharmacy*. 2017. № 11 (3). P. 584–589.
19. Development of the composition and manufacturing technology of the new combined drug Lavaflam / M. A. Aslanian et al. *Turkish Journal of Pharmaceutical Sciences.* 2018. № 15 (3). P. 263-270.
20. Фарес Р., Бобрицкая Л. А. Разработка состава и технологии комбинированного лекарственного препарата для лечения кишечных инфекций. *Фармацевтический журнал.* 2016. № 1. С. 72-78.
21. Допоміжні речовини в технології ліків: вплив на технологічні, споживчі, економічні характеристики і терапевтичну ефективність / І. М. Перцев та ін. ; за ред. І. М. Перцева. Х.: Золоті сторінки, 2010. 600 с.
22. Современные направления в технологии твердых лекарственных средств: учеб. пособ. для студентов высш. фармац. учеб. учрежд. / Е. А. Рубан и др. Х.: НФаУ, 2016. 88 с.
23. Технология лекарств промышленного производства: учебник для студ. высш. учеб. завед. / В. И. Чуешов и др. ; НФаУ. Винница: Нова Книга, 2014. 696 с.
24. Technological aspects of development of a new drug in tablets called

«Lavaflam» and its pharmacoeconomic evaluation / M. Aslanyan et al. *Research Journal of Pharmaceutical, Biological and Chemical Sciences.* 2017. № 4 (8). P. 808-814.

25. Злагода В.С., Бобрицька Л.О. Багатофункціональність prosolv® smcc в технології прямого капсулювання. *Актуальні питання медико-біологічних і фармацевтичних наук:* матеріали III Всеукраїнської студ. наук.-практ. конференції, м. Житомир, 30 березня 2023 р. С. 61-62.
26. Iqubal MK, Singh PK, Shuaib M, Iqubal A, Singh M. Recent advances in direct compression technique for pharmaceutical tablet formulation. IJPRD, 2014 March; Vol 6(01):49-57.
27. Демчук М. Б., Грошовий Т. А., Леськів О. М., Маланчук Н. В. Порівняльні дослідження деяких марок лактози як наповнювачів для прямого пресування таблеток. *Фармацевтичний часопис*. 2021. № 2. С. 5-13.
28. Van Snick B, Holman J, Cunningham C, Kumar A, Vercruysse J, De Beer T, et al. Continuous direct compression as manufacturing platform for sustained release tablets. International Journal of Pharmaceutics. 2017 Mar 15; 519 (1-2): 390-407.
29. Almaya A, De Belder L, Meyer R, Nagapudi K, Lin HH, Leavesley I, et al. Control Strategies for Drug Product Continuous Direct Compressiond State of Control, Product Collection Strategies, and Startup/Shutdown Operations for the Production of Clinical Trial Materials and Commercial Products. J Pharm Sci. 2017 Apr; 106(4): 930-43.
30. Maltais M, Vargas R, DiPaolo T. Development of a new formulation for direct compression of a natural product. Journal of Pharmaceutical Technology & Drug Research. 2015;4(2):1-6.

APPENDIXES

Ф А 2.2.1-32-366

National University of Pharmacy

Faculty for foreign citizens' education
Department of Industrial Technology of Drugs
Level of higher education master
Specialty 226 Pharmacy, industrial pharmacy
Educational program Pharmacy

APPROVED
The Head of Department
of Industrial Technology
of Drugs

_____
Olena RUBAN
"_15_" __of May__ 2022

ASSIGNMENT
FOR QUALIFICATION WORK
OF AN APPLICANT FOR HIGHER EDUCATION

El Maziri Wyssal

1. Topic of qualification work: « The choice of excipients in the composition of tablets with ranitidine», supervisor of qualification work: Larysa BOBRYTSKA, PhD, prof.
approved by order of NUPh from "6th" of February_2023 № 35

2. Deadline for submission of qualification work by the applicant for higher education: april 2023.

3. Out going data for qualification work: ranitidine substance and excipients, tableting mass

4. Contents of the settlement and explanatory note (list of questions that need to be developed): literature review, objects and methods, experimental part, references

5. List of graphic material (with exact indication of the required drawings):
tables– 6, pictures – 8

6. Consultants of chapters of qualification work

Chapters	Name, SURNAME, position of consultant	Signature, date	
		assignment was issued	assignment was received
1	Larysa BOBRYTSKA, professor of higher education institution of department Industrial Technology of Drugs	20.05.2022	20.05.2022
2	Larysa BOBRYTSKA, professor of higher education institution of department Industrial Technology of Drugs	15.12.22 - 21.01.2023	15.12.22 - 21.01.2023
3	Larysa BOBRYTSKA, professor of higher education institution of department Industrial Technology of Drugs	18.02.2023	18.02.2023

7. Date of issue of the assignment: «15» May 2022.

CALENDAR PLAN

№ з/п	Name of stages of qualification work	Deadline for the stages of qualification work	Notes
1.	Literature review	September	**Done**
2.	Experiment planning	October	**Done**
3.	Experiment execution	November-February	**Done**
4.	Processing of results	March- April	**Done**
5.	Submission to EC	April	**Done**

An applicant of higher education _____ Wyssal EL MAZIRI

Supervisor of qualification work _____ Larysa BOBRYTSKA

ВИТЯГ З НАКАЗУ № 35
По Національному фармацевтичному університету
від 06 лютого 2023 року

нижченаведеним студентам 5-го курсу 2022-2023 навчального року, навчання за освітнім ступенем «магістр», галузь знань 22 охорона здоров`я, спеціальності 226 – фармація, промислова фармація, освітня програма – фармація, денна форма здобуття освіти (термін навчання 4 роки 10 місяців та 3 роки 10 місяців), які навчаються за контрактом, затвердити теми кваліфікаційних робіт:

Прізвище студента	Тема кваліфікаційної роботи		Посада, прізвище та ініціали керівника	Рецензент кваліфікаційної роботи
• **по кафедрі заводської технології ліків**				
Ель Мазірі Віссал	Вибір допоміжних речовин у складі таблеток із ранитидином	The choice of excipients in the composition of tablets with ranitidine	проф. Бобрицька Л.О.	доц. Січкар А.А.

Підстава: подання декана, згода ректора

Ректор

Вірно. Секретар

Ф А2.8-47-110

ВИСНОВОК

Комісії з академічної доброчесності про проведену експертизу

щодо академічного плагіату у кваліфікаційній роботі

здобувача вищої освіти

№ 112307 від « 13 » квітня 2023 р.

Проаналізувавши випускну кваліфікаційну роботу за магістерським рівнем здобувача вищої освіти денної форми навчання Ель Мазірі Віссал, 5 курсу, _____ групи, спеціальності 226 Фармація, промислова фармація, на тему: «Вибір допоміжних речовин у складі таблеток із ранитидином / The choice of excipients in the composition of tabletswith ranitidine», Комісія з академічної доброчесності дійшла висновку, що робота, представлена до Екзаменаційної комісії для захисту, виконана самостійно і не містить елементів академічного плагіату (компіляції).

Голова комісії,
професор **Інна ВЛАДИМИРОВА**

0%

30%

Ф А 2.2.1-32-353

REVIEW

for qualification work of the master`s level of higher educftion, specialty 226 Pharmacy, industrialpharmacy

Wyssal EL MAZIRI

on the topic: «The choice of excipients in the composition of tablets with ranitidine».

Relevance of the topic. Among the drugs that are used to treat peptic ulcer disease, Ranitidine remains one of the most common antisecretory drugs and is found in many areas of gastroenterology.

H2-blockers are the "gold standard" for the treatment of acid-related diseases, and ranitidine is the best-selling prescription drug.

Ranitidine is an antiulcer drug belonging to the group of H2-histamine receptor blockers. Second generation drug.

To improve the technology of production of tablets Ranitidine proposed a method of direct pressing, which has a number of advantages: eliminates the need for heat treatment of the drug substance, enables production of tablets with incompatible substances, also this method allows to achieve high productivity, to reduce production cycle, reduce manufacturing space, reduce material costs and costs in operation.

Practical value of conclusions, recommendations and their validity.

Based on the analysis of literature data, the author selected a substance of synthetic origin and its concentration. By conducting technological research, excipients and their amounts in the composition of the tablets were selected. A rational technology for obtaining a solid dosage form of tablets has been developed.

Assessment of work. The successful solution of tasks enabled the author of the qualification work to achieve the goal and obtain practical and theoretical results. The work was done at a sufficient scientific level, which indicates the author's

ability to work with literary sources, analyze, systematize and generalize the experimental data obtained.

General conclusion and recommendations on admission to defend. The qualification work of Wyssal EL MAZIRI meets all the requirements for qualification works and can be presented for defense at the Examination Commission of the National University of Pharmacy.

Scientific supervisor _____ Larysa BOBRYTSKA

«05» April 2023.

Ф А 2.2.1-32-356

REVIEW

for qualification work of the master`s level of higher educftion, specialty 226 Pharmacy, industrial pharmacy

Wyssal EL MAZIRI

on the topic: «The choice of excipients in the composition of tablets with ranitidine».

Relevance of the topic. At present the problem of gastric ulcer and 12 duodenal ulcer, attracts the attention of scientists of many countries of the world and is considered the disease of the XXI century. The pathogenesis of peptic ulcer disease and other diseases of stomach and intestines leads to the development of destructive processes that tend to the progressive development of erosions to deep ulcers.

H2-blockers are the "gold standard" for the treatment of acid-related diseases, and ranitidine is the best-selling prescription drug.

Ranitidine is an antiulcer drug belonging to the group of H2-histamine receptor blockers. Second generation drug. The action of ranitidine is based on a decrease in the secretion of gastric juice by suppressing the secretion of hydrochloric acid and pepsin. Included in the list of vital and essential drugs.

Theoretical level of work. The author studied and worked out the methods of conducting pharmacotechnological studies, showing the appropriate level of knowledge of theoretical provisions and the topic of the work. The composition of the necessary excipients for the creation of tablets has been selected. The material is presented logically and consistently.

The author's suggestions on the topic of research. As a result of the research, the author of the work proposed the qualitative and quantitative composition of excipients, developed the technology of tablets and described the stages of the technological process.

Practical value of conclusions, recommendations and their validity. Based on the results of pharmaco-technological studies, the author of the work substantiated the composition and developed the technology for producing the tablet; a technological scheme is drawn up. The material of experimental studies is presented logically, consistently, and the results are structured. The reliability of the results is confirmed by a significant volume of conducted studies and statistical methods of their processing.

Disadvantages of work. There are incorrect expressions and grammatical errors in the work.

General conclusion and evaluation of the work. The qualification work of Wyssal EL MAZIRI based on the results of research and the volume of the experiment performed can be presented for defense at the Examination Commission of the National University of Pharmacy.

Reviewer _____ assoc. prof. Antonina SICHKAR

«10» April 2023.

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'ЯУКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ВИТЯГ З ПРОТОКОЛУ № 9

« 21 » квітня 2023 року

м. Харків

засідання кафедри

заводської технології ліків

ПРИСУТНІ: проф. Рубан О.А., проф. Бобрицька Л.О., проф. Гриценко В.І., доц. Хохлова Л.М., доц. Сліпченко Г.Д., доц. Ковалевська І.В., доц. Криклива І.О, ас. Пономаренко Т.О., лаборанти та аспіранти.

ПОРЯДОК ДЕННИЙ:

1. Обговорення кваліфікаційних робіт щодо їх представлення до захисту в Екзаменаційній комісії НФаУ.

СЛУХАЛИ: здобувачку вищої освіти 5 курсу групи Фм18(4,10) англ-1 Віссал Ель Мазірі про представлення до захисту в Екзаменаційній комісії НФаУ кваліфікаційної роботи на тему: «Вибір допоміжних речовин у складі таблеток із ранитидином». (Керівник: д.фарм.н., проф. Лариса БОБРИЦЬКА).

В обговоренні кваліфікаційної роботи брали участь проф. Бобрицька Л.О., доц. Хохлова Л.М., доц. СліпченкоГ.Д.

УХВАЛИЛИ: рекомендувати до захисту в Екзаменаційній комісії НФаУ кваліфікаційну роботу здобувачки вищої освіти факультету з підготовки іноземних громадян групи Фм18(4,10д) англ-1 Віссал Ель Мазірі на тему: «Вибір допоміжних речовин у складі таблеток із ранитидином».

Голова

Завідувачка кафедри ЗТЛ
доктор фарм. наук, проф. **Олена РУБАН**

Секретар
кандидат фарм. наук, асист **Тетяна ПОНОМАРЕНКО**

Ф А2.2.1-32-042

НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ПОДАННЯ

ГОЛОВІ ЕКЗАМЕНАЦІЙНОЇ КОМІСІЇ ЩОДО ЗАХИСТУ КВАЛІФІКАЦІЙНОЇ РОБОТИ

Направляється здобувач вищої освіти Віссал Ель Мазірі до захисту кваліфікаційної роботи за галуззю знань 22 Охорона здоров'я

спеціальністю226 Фармація, промислова фармація

освітньою програмою Фармація

на тему: «Вибір допоміжних речовин у складі таблеток із ранитидином».

Кваліфікаційна робота і рецензія додаються.

Декан факультету _____ /Світлана КАЛАЙЧЕВА /

Висновок керівника кваліфікаційної роботи

Здобувачка вищої освіти Віссал Ель Мазірі у процесі роботи розглянула сучасні підходи до лікування противиразкових захворювань, провела аналіз асортименту засобів для терапії даного захворювання та обґрунтувала доцільність створення нового вітчизняного лікарського засобу у формі таблеток. Автором обґрунтовано оптимальний склад і розроблено технологію одержання таблеток. Віссал Ель Мазірі допускається до захисту даної кваліфікаційної роботи у Екзаменаційній комісії Національного фармацевтичного університету.

Керівник кваліфікаційної роботи

_____ Лариса БОБРИЦЬКА

«05» квітня 2023 року

Висновок кафедри про кваліфікаційну роботу

Кваліфікаційну роботу розглянуто. Здобувачка вищої освіти Віссал Ель Мазірі допускається до захисту даної кваліфікаційної роботи в Екзаменаційній комісії.

Завідувачка кафедри

заводської технології ліків

_____ Олена РУБАН

« 21» квітня 2023 року

Qualification work was defended

of Examination commission on

« ____ » _____2023 г.

With the grade_____

Head of the State Examination commission,

DPharm Sc. Professor

_____ / Oleg SHPYCHAK /