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QUALIFICATION WORK

on the topic: **«DEVELOPMENT OF COMPOSITION AND TECHNOLOGY OF CAPSULES FOR THE TREATMENT OF THE BILIARY EXCRETORY SYSTEM DISEASES»**

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ANNOTATION

The qualification work is devoted to the development of the composition of capsules for the treatment of diseases of the bile excretion system. A literature review was conducted regarding the development potential of hard capsules. The nomenclature of drugs for the treatment of diseases of the billiary system was studied. The effect of auxiliary substances on the technological characteristics of encapsulation masses and their quality indicators was studied. The technology for the production of hard capsules containing a mixture of crushed medicinal plant raw materials has been developed.

The work has 51 pages and includes an introduction, three chapters, general conclusions, a list of used sources and appendices. The article contains 30 references to scientific literature and is illustrated with 8 figures and 8 tables.

Key words: a mixture of crushed medicinal plant raw materials, capsules, pharmaceutical technology, treatment of diseases of the bile excretion system.

АНОТАЦІЯ

Кваліфікаційна робота присвячена розробці складу капсул для лікування захворювань жовчовидільної системи. Було проведено дослідження літератури щодо потенціалу розробки твердих капсул. Було вивчено номенклатуру препаратів для лікування захворювань жовчовидільної системи. Досліджено вплив допоміжних речовин на технологічні характеристики мас для капсулювання та їх показники якості. Розроблено технологію виготовлення твердих капсул, що містять суміш подрібненої лікарської рослинної сировини.

Робота має 51 сторінку і включає вступ, три розділи, загальні висновки, список використаних джерел і додатки. Стаття містить 30 посилань на наукову літературу та ілюстрована 8 рисунками та 8 таблицями.

Ключові слова: суміш подрібненої лікарської рослинної сировини, капсули, фармацевтична технологія, лікування захворювань жовчовидільної системи.

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INTRODUCTION

Relevance of the research topic. Diseases of the biliary excretory system occur very often. In the general population on average in 2 and in the female population almost in 10 times higher the number of patients with this disease than patients with ulcer.

Among the many diseases of the biliary tract it is expedient to allocate predominantly functional disorders like (dyskinesia), inflammation (cholecystitis), metabolic (Gallstone disease) parasitic and tumor diseases. It is possible that the first three of these states are separate units or phases of the same pathological process: first appear gallbladder dysmotility, shown hypo or hyper dyskinesia, then develop chronic noncalculous cholecystitis, which eventually transformed into calculary.

Given the similar evolution of the diseases listed above, it is appropriate to consider the most prevalent pathology of the biliary system - biliary dyskinesia.

At the beginning of this century surgeons drew attention to the fact that some patients who complained of attacks of biliary colic during surgery calculus and organic changes in the gallbladder and ducts cannot be found. Even then German clinician G. Bergman for the first time expressed assumption that similar clinical manifestations may be the result of dysfunction of the neuromuscular system of the gallbladder and ducts without serious organic changes.

Today is a view that connects biliary dyskinesia with functional changes remains, remains relevant and modern definition of these states as follows: biliary dyskinesia - it inconsistent, untimely, insufficient or excessive contraction of the gallbladder, ducts and sphincter.

This pathology occurs predominantly in young age (adolescents with biliary tract disease is diagnosed in 58%, and in patients older than 60 years - 27%) and more frequently in females, asthenic constitution and low power.

The purpose the development of science-rationale of technology and composition capsules for the treatment of biliary excretory system.

The object of research a mixture of crushed medicinal plant raw materials.

The following research **methods** were used in the work: complex physico-chemical and technological research and to create the optimal composition of the solid dosage form.

The practical significance of the results. In the course of the work, the rational composition of the capsules was substantiated. The technology of capsules has been developed.

Approbation of research and publication results. The qualification work was tested at the «Current issues of creating new medicines: materials of the XXIX international scientific and practical conference of young scientists and students» (April 19-21, 2023, Kharkiv). - Kharkiv: NUPh, 2023. Published abstracts: Puliaiev D.S., Elmortaji Mohamed-Taha. Development of composition of sedative action capsules. Modern achievements of pharmaceutical business: collection of scientific works, issue 1. – Kharkiv, NUPh publishing house, 2022. P.177.

Structure and scope of qualification work Qualification work is made at 51 pages, consists of the introduction, three chapters, conclusions, list of sources used, which contains 30 items. The work is illustrated at 8 tables and 8 figures.

CHAPTER 1
THE MODERN ASPECTS OF TREATMENT DISEASES OF THE BILIARY EXCRETORY SYSTEM

1.1. The etiology and pathogenesis of the biliary excretory system diseases

The movement of bile in the biliary excretory tract caused by at least two factors: pressure gradient in different parts of the biliary system, and intracavitary pressure difference in blisters and duodenum. There is a complex regulation of the system functions, which carried the certain consistency in the liver, gallbladder, common bile duct, pancreas and duodenum. This ensures the timely accession of bile into the intestines during digestion and its accumulation in the gallbladder when the stomach is empty**.** In the digestive phase bladder pressure phase is rhythmically in intervals between waves duodenal motility, reduction wheal accordance weakening sphincter apparatus [6, 29].

The functioning of this complex system is controlled by a number of neurohormonal factors which bring together all the components of the biliary excretory system, on the one hand, showed his adaptability to the conditions of the digestive system, which is constantly changing, and on the other - makes it possible dysfunction in violation at least one of the many parts of the regulation.

Most sensitive to violations of the regulation is gallbladder, sphincter of the gallbladder region and sphincter of Oddi.

One of the leading places in ensuring the proper functioning of biliary excretory system belongs to the autonomic nervous regulation. It is believed, that moderate irritation of the vagus nerve causes blisters and coordinated activity of the sphincter and excessive irritation - spastic contraction entire system leads to the delays evacuation of bile. Irritation (for various reasons) sympathetic nerve leads to the weakening of the gallbladder.

A great value has humoral factors which selectively influence the various components of the biliary system, such as acetylcholine and various

parasympathomimetics (pilocarpine, proserin) increased motor activity of biliary tract.

Adrenaline, noradrenalin, and hydrocortisone cause contraction of the sphincter of Oddi; adrenoceptor agonists stimulate motility of the extrahepatic bile ducts, and adrenoceptor agonists weaken its, corresponding blockers eliminate these effects. Prostaglandins Group E reduce gallbladder as well enkephalins and angiotensin inhibit his motor activity [16, 18].

Critical role in the regulation of the biliary system played intestinal peptide hormones that commit adultery balanced impact on the tone of predominantly of the gallbladder. On the contrary, neurotensin, hormone and pancreatic peptide - reduce the contractile activity of the gallbladder.

Quite often, these patients detected clear connection between the time of occurrence of pain in the right upper quadrant and various psychogenic factors. So, in the 82% of people who suffer from dyskinesia, especially hyperkinetic forms, at clinical and psychological examination were discovered changes of psychological status with a distinct tendency to the development of anxiety and depressive disorders. There is a view that any form of neurocirculatory dystonia almost always accompanied dysmotility components of biliary system.

Certain role in the development of biliary dyskinesia plays endocrine disorders, thyroid dysfunction, adrenal glands.

To biliary tract dysfunction can leads various infections, particularly infection hepatitis B virus.

Dyskinesia can occur under the influence of pathological impulses emanating from other parts of the gastrointestinal tract and urogenital system (so-called "conflict impulses").

As is evident from pathogenesis of data provided dyskinesias biliary tract is extremely complex and multifaceted, as it involved a violation of innervation of the gallbladder, various humoral factors, intestinal hormones, violation and psychological status of various endocrine disorders.

Classification:

Biliary dyskinesia accepted subdivided:

1. By the etiopathogenetical sign on the:

- primary;
- secondary (symptomatic);

2. By the clinical course distinguished:

- hyperkinetic (increased motility of blister and ducts);
- hypokinetic (reduced motility of blisters and channels);

Also, there is more detailed classification, but in practical terms the most convenient is that shown above.

On the basis of primary dyskinesia is a violation of neurohumoral regulation of motility and tone of the biliary tract on the basis of psychoneurotic, constitutional, endocrine, nutritional, infectious, allergic and intoxications actions.

The main diagnostic triad of primary biliary dyskinesia looks as follows:

- the absence of organic disease of the biliary system and other organs.
- the presence of clinical and laboratory signs of instrumental dysmotility of biliary system.
- availability of psycho-vegetative disorders. Secondary dyskinesia arises at abnormalities of the biliary tract and bladder, hepatitis, cholecystitis, cholelithiasis or reflex at pathological processes in the abdominal cavity.

The clinical picture is due to the nature of the violation of the motor function of the biliary system consists of a set of symptoms associated with dysmotility directly biliary system and common, often neurotic symptoms [7, 11, 28].

The liver is usually not increased during the exacerbation with symptoms of biliary colic may experience slight, often fleeting increase. Stable liver enlargement and change of her palpations properties always testifies against the diagnosis of primary biliary dyskinesia. Sometimes, in some patients, there is a number of local palpation symptoms characteristic of cholecystitis (symptoms Kera, Murphy, Ortner (We discuss in detail of their study when considering the clinic of cholecystitis)).

We cannot ignore them because, they help identify the pathology of the biliary system and encourage doctors to further differential diagnostic search.

Body temperature is often normal. In some cases, when biliary dyskinesia arises with other autonomic disorders, on the background of expressed neurosis may be a monotonous low-grade fever, temperature curve resembles stockade and not exposed to analgesics [15, 30].

Features of clinical picture dyskinesias that occur with different disorders of motor activity of the gallbladder and ducts:

When hyperactivity (hypertension) form of dyskinesia observed more frequently in patients emotionally of labile, thin, with a choleric temperament, localized pain in the right upper quadrant or epigastric region, is cramping in nature (resembling biliary colic).

During the attack she irradiate to the right scapula, clavicle, shoulder, lumbar region or in the left half of the chest and precordium region. The pain is usually short-term, appear unexpectedly few times a day.

Sometimes attacks are accompanied by nausea, belching, patients complain of a sense of bitterness in the mouth, sometimes there is vomiting and bowel dysfunction, often with a penchant for constipation, but there is also diarrhea.

Quite often these patients are accompanied by pain and neuro vasomotion vegetative syndrome, resulting in sweating, tachycardia, hypotension, severe weakness and headache.

Pain is often provoked by eating spicy, fatty and cold meals, but the pain often associated not only with errors in diet, it arises during exercise, psycho-emotional stress, under the influence of shaking in different phases of the menstrual period.

Paroxysmal character of the pain of hyperkinetic biliary dyskinesia is the result of a sudden increase in pressure in the gallbladder, which decreases with acute-onset of sphincter Oddi hypertension [19, 30].

Between attacks, patients feel relatively well, the pain usually do not bother, but may periodically experience a feeling of heaviness in the right upper quadrant.

During duodenal probing, there is labile, sometimes involuntary reflex, rapid evacuation of bile, accompanied by pain and nausea, sensing does not bring relief, often after the procedure, patients feel pain amplification in the right upper quadrant.

Radiologically appears is located high and rapidly such that the gallbladder is emptied, spherical or oval. By size of blisters we can make conclusion about the status of the tone of this body. Normal blood pressure stated when bluster volume equal of 30-50 cm 53, reducing this volume points to hypertonicity. Coefficient emptying of gallbladder exceeds 20% [16, 23].

Hypokinetic form of dyskinesia develops gradually more often in middle-aged women, phlegmatic or melancholic composition, pretty obese, typically given birth. In this form of dyskinesia patients complained of long, almost constant, aching or pressing pain in the right upper quadrant without typical irradiation.

Excessive emotions, and sometimes food increase painful sensations as well feeling of fullness in the right upper quadrant appears 20-30 minutes after meals.

In such patients are frequent complaints of poor appetite, constant belching, nausea, bitter taste in the mouth, bloating, locks, vomiting is more common than the hyperkinetic type.

On palpation is determined moderate pain in area by the gallbladder.

Pain syndrome caused by stretching infundibular part of the gallbladder, it promotes the release of anti-cholecystokinin**,** excessive amount of which leads to a significant reduction formation of cholecystokinin in the duodenum, which further inhibit motor activity of the gallbladder. Hypokinetic dyskinesia occurs much more frequently than hyperactivity.

Duodenal probing brings relief, cystic reflex weakened, emptying of bladder delayed, bile of increased viscosity and dark color stands out with the long intervals, sometimes only after re-entering of the stimulus. of the bile is always sterile, without white blood cells.

Recently, to determine the genesis of dyskinesias and differential diagnosis successfully, used ultrasound inspection after bile excretory breakfast, which in informativeness, simplicity and security far superior cholecystokinin**.**

Speaking about secondary dyskinesia of biliary system it should be emphasized that at stomach ulcers, appear mainly hypokinetic dyskinesia, and when localization of ulcers in the duodenum, at hepatitis and pancreatitis – hyperkinetic [4, 9, 30].

In conclusion, I want to emphasize that now we basically use clinical picture to diagnose dyskinesia. For additional methods used duodenal intubation, ultrasound. From additional methods used duodenal intubation, cholecystography and ultrasound.

Usually, there are no changes in clinical blood tests and others biochemical studies when dyskinesia.

Detection of clinical forms of dyskinesia of gallbladder is important for differential cure.

1.2. Modern aspects of treatment diseases of the biliary excretory system

Treatment of biliary excretory system should start with the removal of neurotic and diencephalic disorders. For this purpose, it is expedient to use different methods and psychological reflexotherapy (in various forms successfully used acoustic, electric and laser puncture). For hyperkinetic forms recommended the appointment of sedative preparations and mixture. In the case of hypokinetic forms, it is recommended tonics.

With explicit communication with dyskinesias menstrual cycle assigned therapy aimed at correcting these violations. That's how in climacteric period prescribed in small doses the testosterone inward or methyltestosterone under the tongue.

The role in the treatment of diseases of the biliary excretory system is paid to a balanced diet. Nutrition should be frequent, fractional and stimulate the flow of bile. The diet should contain enough protein, which increases the coefficient of cholate-cholesterol bile and thereby reduces the risk of stone formation. Animal fat should be limited. For hypokinetic dyskinesia, patient should eat food that has

vegetable oil, which stimulates the production of cholecystokinin. In hyperkinetic type should be excluded from food irritating components. [1, 5, 21]

In food ration must necessarily include foods that contain high amounts of cellular tissue, which improves intestinal emptying and has positive effect of motility on bile ducts. Strong alcoholic drinks and smoking are prohibited because they contribute to the development of spasm of the sphincter of Oddi.

On the mechanism of action they are divided into tools that increase the secretion of bile (choleretics) and stimulate her output.

The classification of these preparations looks as follows [13, 24, 30]:

1. Preparation that stimulate bile formation (choleretics).

1.1. Preparations that increase the secretion of bile and increase the secretion of bile and stimulating for the formation of bile acids (true choleretics).

1.1.1. Preparations containing bile acids.

1.1.2. Synthetic drugs.

1.1.3. Preparation of vegetable origin.

1.2. Drugs that increase the secretion of bile mainly due to water component sodium salicylate, mineral water, drugs valerian.

2. Medications that stimulate bile secretion.

2.1. Drugs that cause increased tone of the gallbladder and reduce tone bile ducts, magnesium sulfate, sorbitol, xylitol, barberry.

2.2. Drugs that cause relaxation of tone of the biliary tract: group of, aminophylline, nitroglycerin.

Basic mechanisms of action of true choleretics are:

- increasing of bile secretion, which carried out in reflexively by irritation of mucosa of the small intestine and directly due to the stimulation of the secretory function the liver parenchyma;

- increasing osmotic gradient between blood and bile, which causes osmotic filtration of the water and electrolytes in bile capillaries;

- increase the outflow of bile to the biliary tract, cautionary convergence of the infection which leads to a decrease in inflammatory processes.

- the increase in bile content, which reduces the risk of stone formation.

After describing the basic mechanisms of action cholagogue, we must stop on tactics of their appointment in various forms of dyskinesias biliary tract.

In the presence of hyperkinetic dyskinesia, that accompanied by sharp attacks of pain, showed destination. Then they added choleretics. Very effective tserukal and tranquilizers, at expressed pain syndrome, resistant hypochondriacal complaints resorted to the appointment of neuroleptics [13, 22]

For the treatment of different types of dyskinesias successfully used herbal medicine. When accelerated emptying of the gallbladder appoint plants mainly with spasmolytic bactericidal and astringent properties.

At hypokinetic dyskinesia appoint herbal medicines which increase the secretion of bile from the gallbladder and ducts into the duodenum and toning their muscles. They include: Lepekha marsh, birch buds, dandelion, corn silk, thyme and yarrow [12, 26].

Of course, indicated actions of plants for different phases of excretory of bile very conditional, because many herbs have both a choleretic action.

1.3. The current state of capsules production technology

1.3.1. Advantages of application capsulated drugs.

In the nomenclature of medicines are important capsules and granules. But recently pay more attention on capsulated drugs.

Gelatin capsules, while still a young dosage form, thanks to a number of advantages and technological progress (emergence of high-performance and high-precision automatic equipment for production and filling capsules) beginning from 50-ies of XX century, become more and more popular for doctors, consumer and manufacturers. Development of modern technological methods that allow encapsulate medicinal substances with different physicochemical characteristics, contributes significantly expand the nomenclature of drugs in this dosage form.

Today, preparations in the form of gelatin capsules designed for peroral and for topical application, make up about 9-12% of nomenclature of drugs in countries with developed pharmaceutical industry [8]. Preparations in the form of gelatin capsules are in the nomenclature of almost all pharmacological groups [3, 27].

Such popularity of this dosage form for producers, consumers and doctors is explained by a number of advantages and positive characteristics, including:

- the accuracy of dosage: modern equipment provides high precision of filling capsules filler (with a tolerance that does not exceed ± 3%) and minimum losses;
- high performance: on the type of equipment used, methods of filling, characteristics of the filler and its dosage, modern automats allow to receive up to 120 thousand capsules per hour;
- high bioavailability: studies conducted by many scientists showed that the capsules break down faster than capsules or pills, and their runny or non-compacted solid content quickly and easily absorbed in the human body [2, 27];
- expansion of indications for use: in some cases, capsules, as dosage form, have helped detect new kind of pharmacological activity, which does not detected at the same dose in other dosage forms (for example, a group of scientists of scientific laboratory of the Italian firm «Pharmagel» found capsules at a dose of 20 mg showed tranquilizing property, while the same dose capsules gives hypnotic effect and can be used as a sleep aid);
- high stability: capsule shell provides a sufficiently high insulation of labile component content from various adverse environmental factors (air oxygen, direct sunlight, humidity variations, etc.), thus you can often avoid the use of antioxidants or stabilizers or reduce their number;
- correcting ability – capsule shell also helps hide the unpleasant taste that have most drugs. This is particularly important in pediatrics because application such a popular in the field of medicine dosage form, such as syrups, not always rational (for example, accuracy dosage, insufficiency stability of some drugs and so on. f.);

- minimizing of the possibility of production errors the possibility of using different dyes and marking allows to reduce danger of mistakes and change of preparations in the production;
- high aesthetics achieved thanks to application of different dyes when receiving shell capsules. Although, the color is not the objective factor of selection of medicines, but it is an important psychological factor in the choice of a drug. On this is based use of additional therapeutic action of color. Today leading pharmaceutical companies are apply to 1000 different colors and shades for coloring membranes capsules [3, 27];
- ability to specify certain properties for medicinal products; most clearly it can be demonstrated by the creation of so-called enteric soluble capsules (resistant to gastric juices, but those that destroyed easily in the environment of the small intestine), and retard capsules (prolonged release of drug) that can be achieved by different technological methods;
- sparing technological modes - technological methods encapsulation allowing avoiding the moisture and pressure exposure for many of labile substances.

A variety of medications in capsule form, difference physicochemical characteristics of encapsulated substances requires sufficiently versatile approaches to creation of drugs in this dosage form. Development of optimal composition and technology capsulated medicinal products is determined by physical and chemical, crystallographic and technological properties of medicinal powders that are included in their composition [27]. These properties are closely related and affect the process of obtaining capsules [3].

Granular medicinal forms by compactness and convenience of application somewhat inferior to capsules, but they should have the priority for development of new dosage forms, which include plant extracts. Latest in tableting stick to the press tool, that can lead to obtaining low-quality products.

1.3.2. Factors that influence on technological and biopharmaceutical indicators of mass for incapsulation.

Choice of the optimal technological scheme of production capsules depends on the physicochemical and technological properties of substances, their number as part of the medicinal product, the fractional composition of the mixture and other factors.

Granulation - the process of converting powdered material into particles (grains) of a certain size. Granules with absolute uniformity may be achieved by varying the ratio of fractions the granulate [27].

Granulation improves fluidity, provides a uniform intake to the capsule strictly certain amount of mass.

To the widely used processes belongs moist granulation, as most medicinal substances have bad fluidity and require insertion of binders and lubricants. In pharmaceutical manufacturing moist granulation is used to produce the finished medicinal form "Granules", intermediate product for medicinal form of "pills" and "capsules". For granules must be observed such technological requirements as fluidity, volume and bulk density, solubility, and others. Traditional method of producing granules consists in mixed components of mass with humidifier and passing a wet mass through a sieve with holes of appropriate size. Size of granules, as the dosage form, is restricted by technical documentation: 0, 2 - 3,0 mm [8, 27].

Changing the properties of granulate may lead to changes in the properties of the drug. Thus, conducting of wet granulation of the mixer, followed by drying in a dryer shelf and the granulators company Glatt, Ball or Zankety with different technologies can provide medications completely different physicochemical properties and affect its bioavailability. For example, by means of multilayer coating particles of active ingredient by appropriate auxiliary substances by appropriate technology is available to get granulate, which will provide slow release of the active ingredient from the dosage form. This will provide prolonged availability of the active substance in the small blood concentrations and relatively weak load on the liver or kidneys, which deduce the drug from the blood. At simple mixing of the same components will be received dosage forms with active ingredients that are released quickly (loading dose of the active substance in the blood, their rapid

withdrawal and high load on the liver or kidneys). Thus, varying the technologies, you can vary the properties of the drug. A similar situation is with the replacement of auxiliary substances. Therefore, approach to the choice of technology of granulation is very complex stage of drug development technologies [27].

Auxiliary substances, that are applied using the method of wet granulation.

Drugs as a complex physical and chemical system, as a whole, not as the active substance, are responsible for the therapeutic effect. All parameters of quality of medicinal product certain extent dependent on the use of auxiliary substances therefore to their optimal selection is paid to more attention. Ingredients of applicable auxiliary substances significantly affects the conditions of the technological process, structural and mechanical properties and consumer properties of the finished product, and therefore - at his value.

Today presented a wide range of auxiliary substances that are used in the manufacture of solid dosage forms. Depending on the physical and chemical properties of the active ingredients, method of getting their recommended dosages and some other factors used auxiliary substances that perform different functions, excipients (solvents), raising agents (disintegrants), antifriction (sliding, lubricating) agents, taste correctors, regulators dynamics of release of active substances, dyes. But, there is no clear separation of auxiliary substances by their function in the dosage form. The same substance, according to the way of application, can be used for different purposes [3, 27].

Most of the medicinal powders require special training before encapsulation. For this purpose, is using the method of wet granulation. The purpose of granulation is the formation of particles of a certain size, shape, structure, with certain physical and chemical properties and pharmaco-technological properties. Granulation allows you to adjust technology properties of powders, provides a more even distribution of the active ingredient, more accurate dose of the active substance reduces the effect of temperature and humidity on the quality of the dosage form.

Nowadays, are used several methods of granulation. Most frequently used method of wet granulation - multi-step process, which is usually has about eight

stages. Use of new binding materials reduces the number of stages. Thus, the use of modified starch as binding agent and filler allows reducing stages of soaking and boiling of starch glue, and consequently - reducing costs. Therefore, this manufacturing process is widely used because most of drugs have a bad turnover and compression, and therefore requires introduction of connecting and plasticizing agents.

If using wet granulation method used fillers, Rippers, binders, lubricate substances.

Fillers provide to mass for filling of capsules required optimum volume. To this end, in the manufacture of medicinal products in the solid form used milk sugar, microcrystalline cellulose (MCC), calcium phosphate dibasic, sodium chloride, polyhydric alcohols (eg, mannitol, sorbitol, xylitol and isomalt, which are formed by oxidation of monosaccharides) and talc, sucrose, lactose, starch, cereals, corn or potato starch and other substances that let you adjust volume and density of fillers to provide the necessary strength, and MCC, in addition, allows to slow down the absorption, which is essential for the prolongation of the drug [3, 27]. It goes well with natural extracts, vitamins supplements and enzymes.

When using fillers, their quantity ranges from 0.02 to 50% relative to the total weight of the mixture.

In order to improve fluidity, improve the accuracy of dosing powdered material, providing the necessary technological properties of granules used binder substances, humidifiers. To achieve the necessary force of adhesion between the particles of complex powders to prevent separation of mixtures with different and complex content of ingredients to content of the granules should is necessary to enter binders' substances. Qualitative and quantitative composition of the binder substances depends on the physicochemical properties of substances subject to wet granulation [26]. As binders' substances used water, ethanol, sugar syrup, 5-10% starch paste, modified starch solutions, gelatin solutions 1-10%, 5-20% solutions of polyvinylpyrrolidone, polyvinyl alcohol, kolidonu, plazdonu 1-2% solutions of methylcellulose, methylcellulose crystal, carboxymethylcellulose, sodium

carboxymethylcellulose, and others. Their composition and quantitative ratio selected individually in each case.

If simple wetting provides normal granulation of powder - use water. Ethanol is used for granulation hygroscopic powders often when the mixture includes a mixture of crushed medicinal plant raw materials. They form a with water sticky, resinous mass, that cannot granulate.

For a mixture of substances, that does not form a granulating mass with ethanol and water, used solutions of macromolecular substances, the effectiveness of which depends on the molecular weight. For example, a preference is given to polyvinylpyrrolidone with trade name Kollidon®, which have a molecular weight from 2,000 to 1,5 x 106, Klucel® EF with a molecular weight of 45,000 to 70000-80000 and others [24, 27].

In evaluating of the effectiveness of binder's substances there are next parameters, which determine the strength of granules: wetting of powders, formation of blinding substance membrane and its deformation. Wetting ability increases in the sequence: PVP - gelatin - hydrolyzed of starch paste - PVS -OPMTS. Binding ability of macromolecular compound also determined by molecular weight of substances. The most efficient and fast binders are cellulose derivatives used for elastic substances less effective - starch derivatives.

Raising agents of substance are introduced into granules to improve their decay in the gastrointestinal tract, which is necessary for the release and subsequent the absorption of the active ingredients. As raising agents used substances of different chemical nature: starch, methylcellulose, sodium carboxymethylcellulose, alginic acid and its sodium salt, amylopectin, Carbopol (improve disintegration due of swelling), Twin (improve wetting of particles).

Antifriction substances increase the fluidity of granulates. They are divided into three groups: 1- moving (starch, talc, kaolin, Aeros, low-fat milk powder, polyethylene 4000); 2- lubricants (stearic acid and its salts, vaseline oil, twin, polyethylene 400); 3 - substances that prevent sticking (talc, starch, stearic acid, its salts).

Lubricants - substances that provide material prevent clutch of its particles, namely magnesium stearate, aluminum and calcium, talc, silicones. When using aids their total share of the total weight of the mixture is 0.1 to 10%, preferably from 0.1 to 1%. Lubricants are also used as hydrophobic agents with a high specific surface, which is very important when using hygroscopic substances. Substances that improve fluidity, such as silica, particularly silicas of high purity produced under the trade name Aerosil®, may be added in an amount of from 0.1 to 5% relative to the total weight of the mixture.

When selecting auxiliary substances great value has their indifference. Many medicinal products under certain auxiliary substances are unstable and they undergo to chemical changes [27].

Thus, for the granulation mixtures which structure includes a mixture of crushed medicinal plant raw materials can be used auxiliary substances, active ingredients that moisturize and do not result in the formation of sticky, resinous mass.

The analysis of the literature concerning pharmacotherapy proved the relevance of new drugs to treat diseases of the biliary excretory system.

CONCLUSIONS TO CHAPTER 1

1. The carried-out analysis of data of literature on pharmacotherapy has proved relevance of creation of new drugs for treatment of diseases of the biliary system.

2. The analysis of current state of production of the encapsulated dosage forms and use of modern excipients at use of method of wet granulation is carried out.

CHAPTER 2
JUSTIFICATION OF THE GENERAL RESEARCH CONCEPT

2.1. General research methodology for the development of capsule composition and technology

The purpose of our work is to substantiate and develop the composition and technology of a new drug in the form of choleretic capsules based on a mixture of medicinal plant raw materials.

Experimental studies to achieve the goal should be started with the selection of active substances, their optimal concentration, which would ensure the necessary pharmacological effectiveness.

The next stage is the optimal selection of auxiliary substances, which allows to ensure the maximum therapeutic effect of the active components of the drug, reduce side effects, and in some cases enhance the effect of the injected substance. Therefore, it is appropriate to study the influence of excipients on technological indicators, bioavailability of active ingredients and stability of the drug during the storage period.

The choice of the optimal form of release of the drug should be carried out, considering the physico-chemical and technological properties of the active substances.

The technology for obtaining the drug should be reproducible and reliable, the number of production stages should be minimal, with the use of a small amount of equipment, and the process itself should be as energy-intensive as possible. Compliance with these requirements will allow to obtain a safe, effective and affordable medicinal form.

Therefore, a research plan was defined to fulfill the tasks:

– study of physico-chemical, technological properties of active substances in order to predict the introduction of auxiliary substances

and justify the choice of a rational technology for the production of an encapsulated medicinal product;

- study of physico-chemical, technological properties of granulate in order to optimize the composition of the drug;
- development of rational technology and creation of technological regulations for the production of capsules;
- establishment of the main indicators of drug quality control and development of a project of analytical regulatory documentation;
- study of the shelf life and stability of the developed dosage form;
- conducting pharmacological studies of the drug.

Compliance with the given plan is a systematic approach to the development of a new medicinal product.

When studying the properties of the developed drug, we used the methods of the state pharmacopoeia of Ukraine 1st ed., generally accepted methods, as well as research methods developed by us, which allow us to objectively assess their quality on the basis of the obtained results.

2.2. Justification of the choice of active components of the dosage form.

The increase in the number of diseases of the hepatobiliary system led us to develop a new drug with choleretic action.

Table 2.1.

The mechanism of action of the substances used.

Medicinal plant raw materials	Mechanism of action
Oman root	Increases bile secretion.
Hypericum herbage	Stimulates the secretion of bile. It has an anti-inflammatory effect.
Calendula flowers	Relieves spasm of biliary tract sphincters.
Mint leaves	Changes the composition of bile.
Bean trefoil herbage	Stimulates the secretion of bile. It has an anti-inflammatory effect.

Studying the literary sources, medicinal plants aroused great interest, namely, oman root, hypericum herbage, calendula flowers, mint leaves, and the bean trefoil herbage. Each of them has a choleretic effect, and a combination of them enhances the pharmacological effect as a whole. In table 2.1. the main mechanisms of the active substances that are included in the composition of the drug are given.

As we can see, each of the medicinal plant raw materials defines a certain function.

2.3. Characterization of active and auxiliary substances as objects of research.

Characteristics of active substances

Oman root (lat. Inula), is a genus of perennial plants of the Asteraceae family (*Asteraceae*). A genus of perennial herbaceous plants of the Compositae family, up to 1.5 m tall, with a dark brown fleshy rhizome and thick, long roots. The flowers of the plant are yellow or orange, single or collected in racemose or shield-shaped common inflorescences.

Preparations made from the roots of Oman root have anti-inflammatory and antiseptic effects, have a diuretic, expectorant, diaphoretic and sedative effect. It is used as an expectorant and choleretic. High divyasyl helps with acute chronic diseases of the respiratory tract, with tuberculosis, gastritis, stomach and duodenal ulcers, diabetes. Burdock root contains essential oil, vitamin E, acetic and benzoic acids.

Calendula officinalis L. Calendula flowers - Flores Calendulae. The aster family is Asteraceae. An annual herbaceous plant 50 cm tall 70 см, the stems are branched. Leaves alternate, sessile or short petiolate, oblong, up to 13 см. Inflorescences in the form of baskets with a diameter of 5- 6 см. The flowers are reeded and tubular, golden-orange. In flower baskets there are carotenoids and flavonoids (carotene, lycopene, violaxanthin, citroxanthin, rubixanthin, flavoxanthin, flavochrome). The pharmacological activity of calendula is due to

these substances. When used internally, calendula drugs show their anti-inflammatory activity, promote the regeneration of mucous membranes of the stomach and intestines, healing of ulcers and erosions, relieve spasm of biliary tract sphincters, increase the secretory activity of the liver and the entry of bile into the duodenum.

Hypericum herbage (lat. Hypericum) is a genus of plants of the Hypericum herbage family (Hypericaceae) of the Malpighiales order. Its medicinal properties are associated with a rather complex chemical composition: flavones, anthocyanin, essential oil, tannins, organic acids, mineral salts, resinous substances.

It has a tonic, anti-inflammatory, hemostatic and astringent effect. Hypericum herbage regulates metabolism, activates digestion, has a choleretic, antispasmodic and sedative effect.

Peppermint - Mentha piperita L. Peppermint leaves - Folia Menthae piperitae. The hyacinth family is Lamiaceae. Perennial herbaceous plant. The leaves are oblong-lanceolate, large, up to 8 см, wide 3 см, with a pointed tip, short-petioled , with an unevenly serrate edge, dark green in color. Peppermint leaves contain up to 3% essential oil (according to GF XI, at least 1% is required), inflorescences - 4-6%. The main component of the essential oil is l-menthol (up to 65%, but not less than 50% in the free state and in the form of ethers). The leaves contain flavonoids, ursolic and oleanolic acids, carotene, hesperidin, betaine, sterols. Azulenes, polyphenols, anthocyanins and leucoanthocyanins, trace elements (copper, manganese, strontium, etc.) are also isolated. Mint preparations have choleretic properties, which are associated with polyphenols. Polyphenolic preparations obtained from peppermint, in the experiment, strengthen not only the exocrine function of the liver, change the composition of bile, increase bile excretion cholates, cholesterol and bilirubin, but also increase the antitoxic function of the liver, normalize metabolism, reduce swelling of hepatocytes in hepatitis.

Bean trefoil herbage, Menyanthes trifoliata - Legume family. A perennial herbaceous plant, 15 cm tall 35 см, with a thick, rather long rhizome. The stem is creeping, jointed, branching. The leaves are alternate, basal, large, more or less

sessile, long-petioled with a three-lobed blade, back-ovate, glabrous. Flavonoids (hyperazide and rutin), bitter glycosides, vitamin C, tannins (3-7%), alkaloid gentianine , ascorbic acid, fatty oil, carotene and other substances were found in the leaves of the watch , in the underground parts - saponins , tannins, traces alkaloids, inulin, betulinic acid and other substances. watch increases the secretion of all glands of the gastrointestinal tract, improves peristalsis of the stomach and small intestine, stimulates the secretion of bile and exhibits anti-inflammatory and laxative effects.

In order to develop the optimal composition and technology of granulated mass for encapsulation, the following excipients approved for medical use were used:

- slippery substances: calcium stearic acid, pretsyrol;
- binders: purified water, potato starch paste, polyvinylpyralidone;
- solvents: purified water.

Characteristics of excipients

Polyvinylpyralidone (PVP) (the state pharmacopoeia of Ukraine 1st ed., p. 436) is a mixture of linear polymers of 1-vinyl-2pyralidone with different chain lengths and different molecular weights. PVP is a white anhydrous, free-flowing and hygroscopic powder without odor or taste. Easily dissolves in water and many organic solvents - alcohols, chloroform, glycols. The viscosity of PVP solutions is stable and does not depend on pH. Aqueous and alcohol solutions are used as adhesives for wet granulation. To prepare the solution, a portion of the drug was poured with water at room temperature and shaken until complete dissolution, after which it was filtered.

Ethyl alcohol (DST 5962-84) is used as an extractant and as an auxiliary substance in the technological process of obtaining various medicinal forms. Ethyl alcohol belongs to surface-active substances. Its action is associated with various mechanisms.

Purified water (the state pharmacopoeia of Ukraine, 1st ed., p. 307) is a colorless, odorless liquid. It is used as an auxiliary substance at various stages of the technological process.

Potato starch (Ph Eur monograph 0355). A white, odorless powder consisting of the smallest particles that crunch when rubbed between the fingers. With iodine, it gives an intense blue color (with the exception of amylopectin starch, which gives a reddish-brown color). Under a microscope in polarized light, the particles show characteristic dark polarization crosses. These particles do not dissolve in cold water, but when heated in water to the temperature of their gelatinization (for most types of starch, 60 ºC), the particles are destroyed and a starch paste is formed.

Calcium stearic acid (Ph Eur monograph 0882) is a white, fine-crystalline, odorless powder that easily forms lumps. Practically insoluble in water, slightly soluble in alcohol and organic solvents, soluble in oils.

Solvents, reagents and solutions used in the work met the requirements of the state pharmacopoeia of Ukraine, 1st edition.

2.4. Characteristics of research methods

Methods of assessment of physico-chemical and technological characteristics of powders and granules.

Medicinal substances were evaluated according to such physico-chemical indicators as the shape and size of particles, dispersion. In addition, the technological properties of powders and granules were investigated: bulk mass (the state pharmacopoeia of Ukraine, 1st ed. item 2.9.15), compaction, angle of natural slope, fluidity (the state pharmacopoeia of Ukraine, 1st ed. item 2.9.16), moisture content, moisture absorption, sieve analysis (the state pharmacopoeia of Ukraine, 1st ed. p. 2.9.12). Capsule parameters were evaluated by disintegration (the state pharmacopoeia of Ukraine, 1st ed. p. 2.9.1), mass uniformity (the state pharmacopoeia of Ukraine, 1st ed. p. 2.9.5), dissolution (the state pharmacopoeia of Ukraine, 1st ed. p. 2.9 .3). The study of technological characteristics was carried out according to the methods of the state pharmacopoeia of Ukraine, 1st edition, which are described below [21, 22, 29].

The fractional composition affects the degree of fluidity, the accuracy of dosage of medicinal substances, as well as the quality characteristics of solid dosage

forms. Sieve analysis was carried out using a set of sieves with a hole size from 0,09 to 3,0 mm. A measure of powder was placed in the upper sieve and the whole set of sieves was shaken on a vibrating device until they were sieved. Each fraction was weighed. The fractional composition was calculated according to the formula:

$$X = m_i/m$$

where: X is the content of the investigated fraction;

m_i – powder weight of the corresponding fraction;

m is the weight of the entire powder.

Powdered medicinal substances consist of particles of various shapes and sizes.

Shape and size of particles of powder significantly affect the quality of the finished product, for example, the strength of solid dosage forms, and depend on the structure of the crystal lattice [15].

Crystallographic studies and determination of linear dimensions were carried out with the help of an electronic bioluminescence microscope. For the powder particles observed in the field of the microscope, the correct geometric shape was selected and its length and width were measured considering the magnification.

To characterize the degree of isodiametricity of the powder particles, the shape factor was calculated using the formula:

$$K = W/D$$

where: W is the average width of the particles, μm;

D is the average length of particles, μm.

Fluidity – the ability of powdered materials to pour out of a funnel with the formation of a discrete flow of material – is one of the most important technological properties. It is fluidity that determines the features of technological processing of materials - transportation, mixing, pressing, packaging and granulation. The choice of equipment for these processes is mainly due to the fluidity. For quantitative

assessment, fluidity is defined as the rate of pouring from the funnel (w), in seconds and tenths of a second, applied to 100 g the sample.

Fluidity was determined according to the state pharmacopoeia of Ukraine method, 1st edition. item 2.9.16 using a watering can (hole size 15 ± 0.01mm) with a VP-12A 0,04 mm vibrator, which provides an amplitude of oscillations from to 0,1 mm with a frequency of 50 Hz.

Five measurements were taken and the average value was determined.

The angle of the natural slope (α) is the angle between the base of the cone of loose material and the horizontal plane. It characterizes the balance of all forces acting on the particles of the powdery material. The angle α is an indicator that determines the potential fluidity of the loose material. For well-flowing materials, it is 20–30º, for less flowable materials – 50–70º.

This value was determined using the VP-12A device. A precise amount of powder (50,0 g) was poured into the funnel, the vibrating device was turned on and the valve was opened. After the powder flowed out, the protractor was brought up and the angle of the natural slope was determined on its scale.

Based on the results of five repeated experiments, their average value was calculated.

Bulk mass is an important technological characteristic. This is a complex indicator that depends on the density of the material, its dispersion, the size and shape of the particles, density, humidity, the forces of interaction between the powder particles and their stacking density, the presence of special impurities in it, as well as external influence. Intensification of processing processes of powdered materials requires an increase in their bulk mass.

The bulk mass during free filling was determined according to the state pharmacopoeia of Ukraine method, 1st edition. clause 2.9.15. The bulk density was calculated according to the formula:

$$R_{vil} = m / V_0$$

where: R_{vil} – bulk density at free filling, g/ml;

m is the mass of the powder occupying the volume V, g;

V_0 – volume before shrinkage, ml.

The amount of bulk mass is used to control some production processes.

Bulk mass at maximum compaction was studied on a shaking device that provides 250±15 cylinder jumps per minute from a height (3±0.2mm) according to the state pharmacopoeia of Ukraine method, 1st edition. 2.9.15. The bulk density at maximum compaction was calculated according to the formula:

$$P_{max} = m/ V_{1250}$$

where: P_{max} – bulk density at maximum compaction (m/V_{1250}, g/ml or t/V_{500}), g/ml;

m is the mass of the powder occupying the volume V, g;

V_{1250} – volume after shrinkage, ml.

Humidity was determined on a VT-12-500 laboratory-type express hygrometer based on torsion scales as the loss of mass during drying. A weight of the drug was placed on the balance scale and weighed, and the device was turned on. Mass measurements were carried out at specified time intervals at a specified temperature until the moment when the change in the readings of the device stopped, that is, until the moment when the change in the weight of the weight completely stopped. The obtained data were substituted into the formula:

$$X = \frac{m_0 - m}{m_0} \cdot 100 \quad ,$$

where: X – sample moisture, %;

m_0 – sample weight before drying;

m is the weight of the sample after drying to a constant mass.

Moisture absorption is one of the parameters that determines the choice of technology, type of dosage form and storage conditions of the drug. The hygroscopicity of the studied substances was evaluated in desiccators with solutions

of substances that have a fixed value of water vapor pressure above their surface (certain relative air humidity, %). The kinetics of moisture absorption was determined by the mass method under conditions of 40% and 100% relative air humidity:

$$X = \frac{m_k - m}{m_k} \cdot 100 \quad ,$$

where: X – moisture absorption of the sample, %;

m_k – weight of the sample after the experiment;

m is the weight of the sample before the experiment.

Specific density ($d_{n)}$ is the ratio of the mass of completely dry crushed raw materials to the volume of plant raw materials. The specific density was determined according to the following method.

Approximately 5,0 g (exact weight) of crushed raw materials was placed in a pycnometer with a capacity of 100 ml, filled with distilled water to 2/3 of the volume and kept in a boiling water bath for 1.5-2 hours, periodically stirring in order to completely remove air from the raw materials. Then the pycnometer was cooled to 20 °C, the volume was brought up to the mark with distilled water. Thus, the weight of the pycnometer with raw materials and water was determined. The weight of the pycnometer with water was previously determined.

$$d_n = \frac{P \cdot d_{ж}}{P - G + F},$$

where P is the weight of completely dry crushed raw materials, g,

d_{is} the specific gravity of water, g/cm3 (a* = 0.9982 g/cm^3)·

G - weight of the pycnometer with water, g;

F - weight of the pycnometer with water and raw materials, g,

The bulk density (d_o) is defined as the ratio of the mass of crushed raw materials at natural or specified humidity to its full volume, which contains pores, cracks and capillaries filled with air. The bulk density was determined according to the following method.

Approximately 5,00 g (exact weight) of crushed raw materials was placed in a pycnometer with a capacity of 100 ml. Distilled water was poured from the burette up to the mark. The contents of the pycnometer were periodically shaken to wet the particles of the crushed raw material. The volume occupied by the raw material was determined by the difference between the volumes of the volumetric flask and the volume used from the burette.

$$V_o = 100 - V_б,$$

where 100 is the volume of the pycnometer, ml;

V_b – the volume used from the burette, ml.

The bulk density was calculated according to the formula:

$$d_o = \frac{P_o}{V_o},$$

where P_o - the weight of crushed raw materials at natural or specified humidity, g;

V_o — the volume occupied by the raw material, cm ^{3}.

The porosity of the raw material determines the number of voids inside the raw material particles and is defined as the ratio of the difference between the specific and bulk density to the specific density.

$$П_c = \frac{d_n - d_o}{d_n},$$

where d_n - specific mass of raw material, g/cm ^{3};

d_o - volumetric weight of raw materials, g/cm ^{3}.

The porosity of the layer characterizes the number of voids between the particles of plant material, defined as the ratio of the difference between bulk and bulk density to bulk density.

$$П_ш = \frac{d_o - d_н}{d_o},$$

where d_o is the volumetric weight of the raw material, g/cm ^{3} ;

d_n - bulk mass of raw materials, g/cm ^{3}.

The free volume of the layer characterizes the relative volume of free space in a unit of the raw material layer (voids inside the particles and between them). It is calculated as the ratio of the difference between the specific and bulk density to the specific density.

$$V = \frac{d_n - d_н}{d_n},$$

where d_n - specific mass of raw material, g/cm $^{3;}$

d_n - bulk mass of raw material, g/cm $^{3.}$

Statistical processing of the results of experimental studies was carried out by generally accepted methods, described in the state pharmacopoeia of Ukraine 1st Supplement, p. 186.

CONCLUSIONS TO CHAPTER 2

1. The general methodology of researches on development of structure and technology of capsules for treatment of biliary system with vegetable raw materials is proved.

2. The characteristic acting and excipients is given.

CHAPTER 3
DEVELOPMENT OF COMPOSITION CAPSULE FOR THE TREATMENT OF THE BILIARY EXCRETORY SYSTEM DISEASES

3.1. Determination of physicochemical and technological characteristics of plant raw materials

The choice of the method of obtaining the drug from a mixture of plant raw materials depends on the main physico-chemical and technological characteristics of individual components, which are determined by their physical properties. First of all, it is the size of the particles that determines the interaction between them. Its hydrophilicity and ability to hold moisture depends on the surface properties of the particles. Therefore, the shape and size of particles, dispersion, moisture are considered as the main indicators. It is these properties of the material that determine their technological characteristics [15,22,29].

The technological and physicochemical characteristics of the studied plant material were studied using the methods given in section 2.

Crystallographic characteristics determine the size and shape of plant material particles. The size of the raw material particles has a great influence on the fluidity. Dispersion is a statistical value of particle sizes. It can express a certain function of particle size distribution or its average size.

The shape and size of the powder were studied using a laboratory microscope equipped with a camera. In fig. 3.1-3.5 show the crystallographic characteristics of medicinal plant raw materials samples.

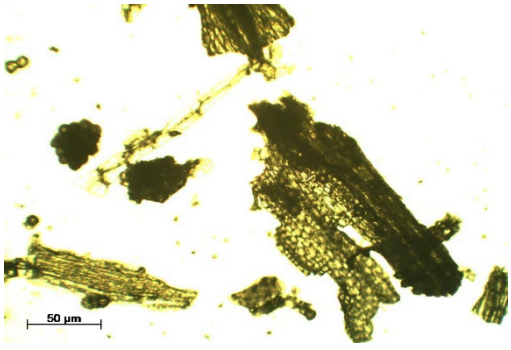

Fig. 3.1. Bean trefoil herbage

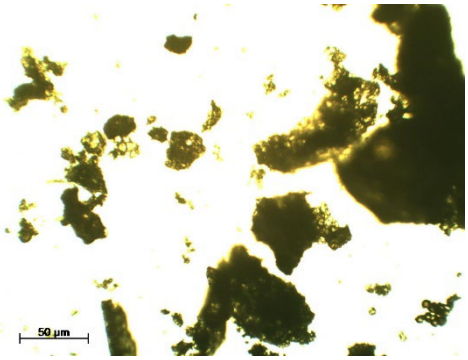

Fig. 3.2. Hypericum herbage

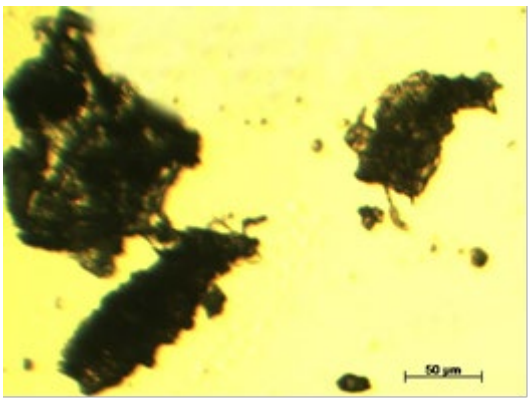

Fig. 3.3. Oman Root

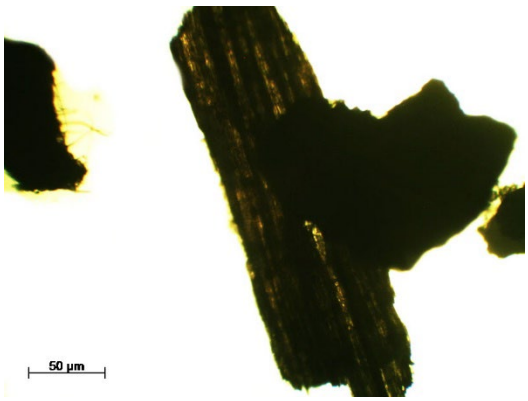

Fig. 3.4. Mint leaves

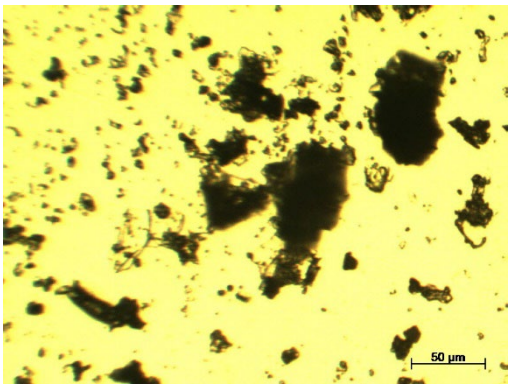

Fig. 3.5. Calendula flowers

As you can see, all raw materials have a polydisperse composition of particles with uneven edges and a rough surface. The particle sizes range from 5 to 400 µm . The obtained data indicate that the mixture may not have sufficient fluidity.

The fractional composition depends on the shape and size of medicinal plant raw materials particles. Therefore, the next stage was the study of the fractional composition, which affects the technological properties, the accuracy of the dosage of the medicinal substance.

A sieve analysis was used to estimate the fractional composition. It was established that the distribution of particles by size obeys the law of normal distribution: the number of the largest and smallest particles is small, and the main mass has approximately the same size, this factor, together with the complex shape and uneven surface, may indicate a high level of particle adhesion to each other, which negatively affects fluidity The size of fractions for all types of raw materials is more 0,5 mm than 62 to 87%, and more than 0.3 from 40 to 23%, fractions less

than 0.3 mm less than 10%. This can be avoided by using a significant amount of sliding substances, which is not always rational, or by increasing the size by using granulation.

The process of manufacturing solid dosage forms is significantly influenced by the technological properties of powders: fluidity, bulk volume, etc.

There are two main methods of fluidity determination in the literature: using a stationary and a vibrating funnel [13,14].

When using the VP - 12A device, the powder particles are affected by the force of the funnel oscillations, which affects the uniform distribution of powder particles throughout the entire working area of the device and exceeds the power of predicting the behavior of powders, in the processes of technological processing, it is necessary to know their speed of pouring from a stationary funnel.

On the basis of the above, we chose the method of determining fluidity using both a stationary funnel and a mobile one, the method of which is given in section 2.

The results of the research are given in table 3.1.

Table 3.2.

Fluidity of the mixture of active plant raw materials

Raw	Fractional composition	Fluidity, g/s	
		Z/V	Used
Calendula flowers	>0.5 >0.3	2.30±0.32 –	– –
Oman Root	>0.5 >0.3	1.04±0.20 1.11±0.15	1.17±0.19 1.49±0.21
Hypericum herbage	>0.5 >0.3	– –	– –
Mint leaves	>0.5 >0.3	3.44±0.32 2.46±0.17	3.08±0.30 2.04±0.20
Bean trefoil herbage	>0.5 >0.3	3.14±0.24 2.76±0.20	3.17±0.24 2.51±0.17

It can be seen from the table that plant raw materials do not have sufficient fluidity. This is explained by the physical and chemical properties of the raw materials that make up our mixture.

The obtained results indicate the need to increase the fluidity of active substances. Adding excipients or increasing particle size using the granulation method can help increase this factor.

One of the necessary indicators for determining the parameters of the technological process is the ability to shrink.

Shrinkage shows the extent to which the raw material can be shaken depending on its volume during free filling. Under statistical conditions, air space is preserved between the particles of bulk raw materials. The technological process is accompanied by dynamic effects that manifest themselves in the form of shaking and vibration, so it was necessary to investigate how substances undergo shrinkage in these conditions.

Bulk density, density after shrinkage, shrinkage were determined according to the methods given in section 2. The obtained results are presented in table 3.3.

Table 3.3.

Technological properties of the studied samples

Raw	Fractional composition	bulk density	Density after shrinkage
Calendula flowers	>0.5 >0.3	0.14±0.01 0.21±0.02	0.18±0.02 0.26±0.02
Oman root	>0.5 >0.3	0.55±0.03 0.51±0.02	0.64±0.02 0.54±0.01
Hypericum herbage	>0.5 >0.3	0.09±0.01	0.13±0.01 0.23±0.02
Mint leaves	>0.5 >0.3	0.26±0.02 0.27±0.01	0.31±0.02 0.32±0.03
Bean trefoil herbage	>0.5 >0.3	0.19±0.01 0.21±0.02	0.21±0.02 0.25±0.02

> 0.3 mm was selected for further research based on bulk density indicators for all types of raw materials.

Study of moisture content of vegetable raw materials.

The moisture content significantly affects the physical and chemical stability, the characteristics of the dispersed structure, the technological behavior of the powder and the final quality of the dosage form, which is especially important in our case, since we have substances of plant origin.

Hygroscopic substances are of great importance in the development of the dosage form. Therefore, determining the moisture content was important for choosing a rational technology.

The initial moisture content of the powder of medicinal plants, with the size of the particles passing through a sieve with the size of the holes 3 mm, was determined by an express hygrometer based on torsion VT-500 scales.

The kinetics of moisture absorption of the mixture is presented in Fig. 3.6.

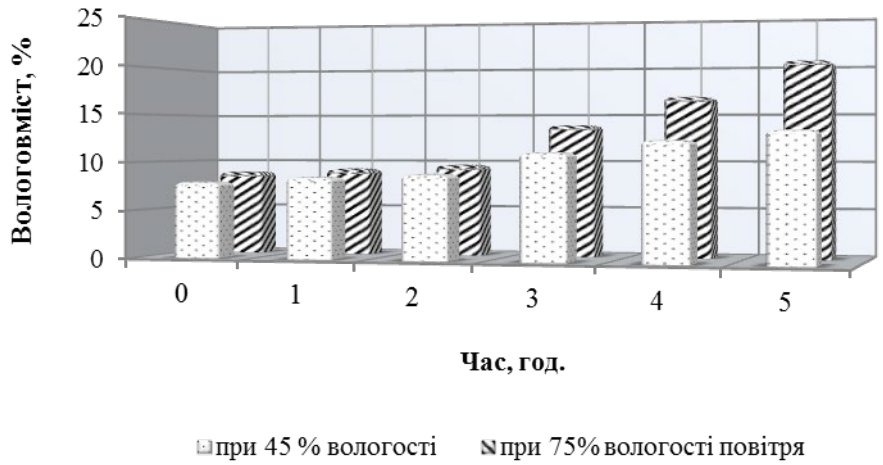

Fig. 3.6 Kinetics of moisture absorption plant mixtures at 45% and 75% relative humidity

The moisture content of the powder increases from 7.92±0.22% and reaches maximum values of 14.05±0.04% and 20.11±0.25% at 45% and 75% relative humidity, respectively. In conditions of 75% humidity, a sharp increase in the mass of the sample is observed during the experiment. There is a visual change in appearance, lumping of raw materials, which will have a negative impact on the technological process. At 45% relative air humidity, an increase in the mass of the

sample is also observed, but more slowly than at 75%, no change in appearance occurs.

Based on the obtained data, it can be concluded that the mixture of medicinal plants is a hygroscopic raw material and is subject to spoilage during long-term storage at high humidity.

Having determined the technological properties of each vegetable raw material separately, we moved on to the study of the mixture as a whole. For this mixture, we determined: bulk density, specific density, bulk density, moisture, fluidity, porosity, porosity, free volume of the layer. The research was conducted according to the methods given in section 2. The data are given in table 3.4.

Table 3.4.

Technological properties of medicinal plant raw materials mixture research

Bulk density		Specific density, g/ml	Bulk density, g/ml	Porosity	Porosity	Humidity, %	Turnover, g/s	Free layer volume
to	after							
0.22	0.32	1.44	1.13	0.22	0.81	6.81	∞	0.85

Determination of moisture content was carried out according to the method given in section 2.

Conducted research on the study of physico-chemical and technological properties of the studied raw materials showed the need to improve them through the use of auxiliary substances from the group of fillers and antifriction, or granulation.

3.2. Determination of the effect of auxiliary substances on the technological properties of the medicinal plant raw materials mixture.

In order to improve fluidity, we decided to add auxiliary substances to our herbal mixture, namely talc and aerosil.

The obtained data are given in table 3.4.

Table 3.4.

Fluidity of plant powder depending on the type of excipients

Substance	Fluidity with vibration, g/s	Fluidity without vibration, g/s
A mixture with talc	1.20±0.03	1.03±0.05
Mixture with aerosol	0.89±0.04	0.99±0.03

According to the table, we can see that the addition of auxiliary substances to the mixture did not give any results. The raw material did not have fluidity, and did not acquire this property when adding both talc and aerosil.

Thus, on the basis of the obtained results, it can be argued that it is rational to improve the technological properties due to granulation.

3.3. Experimental rationale for the choice of mass moisturizer for encapsulation.

The conducted set of studies showed that the technological properties of the active substances do not meet the requirements for powder mixtures that can be encapsulated on continuous capsule filling machines. This led to further research with the use of excipients. In order to improve technological indicators in pharmaceutical production, the granulation method is used. Considering the polydispersity of the active substances, as a result of which powder stratification occurs, the use of dry and structural granulation turned out to be impractical. Therefore, we chose the method of wet granulation. This method includes the

following operations: 1) mixing powder; 2) wetting of powders with a solution of binders and mixing; 3) granulation of wet mass; 4) drying of wet granules; 5) processing of dry granules.

The process of obtaining granules was carried out in laboratory conditions by pressing through perforated plates with a diameter of holes 3,0 mm, as a result of which wet granules were obtained and subjected to drying in a drying cabinet at a temperature of 50-60C ^{0}. After drying, the granules were calibrated.

Definition of moisturizer.

Hydration is a phenomenon that occurs between three phases: solid, liquid and gaseous, or solid and two liquids.

Starch paste of different concentrations of 3%, 5%, 7% and PVP solutions were chosen as a moisturizer. An irrational choice of moisturizer can lead to a shortage: too small a concentration can lead to the scattering of particles, and a large one - the particles will strongly stick together, which will lead to poor dissolution and release of active substances.

Table 3.5

Composition of model samples

No	Composition of samples
1	Vegetable powder and water
2	Plant powder and 5% PVP solution
3	Plant powder and 7% PVP solution
4	Plant powder and 10% PVP solution
5	Vegetable powder and 7% paste of potato starch
6	Vegetable powder and 3% paste of potato starch
7	Vegetable powder and 5% paste of potato starch

For the obtained granules pharmaco-technological studies were conducted (flowability, density before and after shrinkage, shrink ability, moisture content). The obtained results are shown in the table. 3.6.

Table 3.6

Technological indicators of the obtained granulate

No	Fluidity, g/s	Density, g/cm ^{3}	Shrinkage, g/cm ^{3}	Density after shrinkage, g/cm ^{3}	Humidity, %
1	4.00±0.20	0.32±0.02	1.50±0.07	0.37±0.02	7.16±0.35
2	1.55±0.07	0.25±0.01	1.25±0.06	0.42±0.02	4.25±0.21
3	1.03±0.05	0.25±0.01	1.00±0.05	0.39±0.02	4.76±0.23
4	1.46±0.07	0.25±0.01	1.50±0.07	0.31±0.02	6.08±0.31
5	1.83±0.09	0.21±0.01	1.00±0.05	0.26±0.01	6.61±0.33
6	1.96±0.09	0.23±0.01	1.50±0.08	0.36±0.02	6.04±0.30
7	2.84±0.14	0.28±0.01	1.62±0.07	0.35±0.02	4.50±0.02

The use of water gives a high fluidity compared to other samples, but according to organoleptic indicators, which are given in table. 3.6. does not meet technological requirements. The granulate obtained on the basis of PVP solutions has lower fluidity in comparison with the granulate based on starch paste and low compaction ability. Therefore, it is advisable to use potato starch paste for further research. The analysis of experimental data showed that the ability to shrink 1.62 g/cm ^{3} is observed in sample No. 7, which, along with organoleptic indicators and disintegration, allows us to draw a conclusion about the feasibility of using 5% potato paste as a moisturizer.

Table 3.6

Organoleptic indicators of granulate

No	Organoleptic indicators	Decay, min
1	Granules are heterogeneous and fall apart when pressed	to 6 ±0.3
2	Granules are large, heterogeneous, fall apart when pressed	up to 10±0.5
3	Granules are large, heterogeneous, do not disintegrate when pressed	to 13±0.65
4	Granules are large, homogeneous, do not fall apart when pressed	to 11±0.55
5	Granules are large, homogeneous, do not fall apart when pressed	up to 10±0.5
6	Granules are large, homogeneous, fall apart when pressed	to 6±0.4
7	Granules are large, homogeneous, do not fall apart when pressed	to 7±0.35

It can be seen from the given data that the granulate obtained with the help of 5% starch paste has the best technological properties. It provides a moist, dense mixture that does not stick to the hand.

To improve the fluidity of the capsule mass, we introduced an auxiliary substance from the group of antifriction agents - calcium stearate in the amount of 1%.

It is known that substances of plant origin are a favorable environment for the reproduction of microorganisms [3]. In order to ensure the microbial purity of the preparation, we chose the method of drying the wet granulate with simultaneous decontamination by the tendalization method. [66, 75, 89].

Preparations based on vegetable raw materials are highly hygroscopic. Therefore, we conducted studies on the ability of granules to absorb moisture at 45% and 75% relative humidity. The results of the research are presented in fig. 3.7.

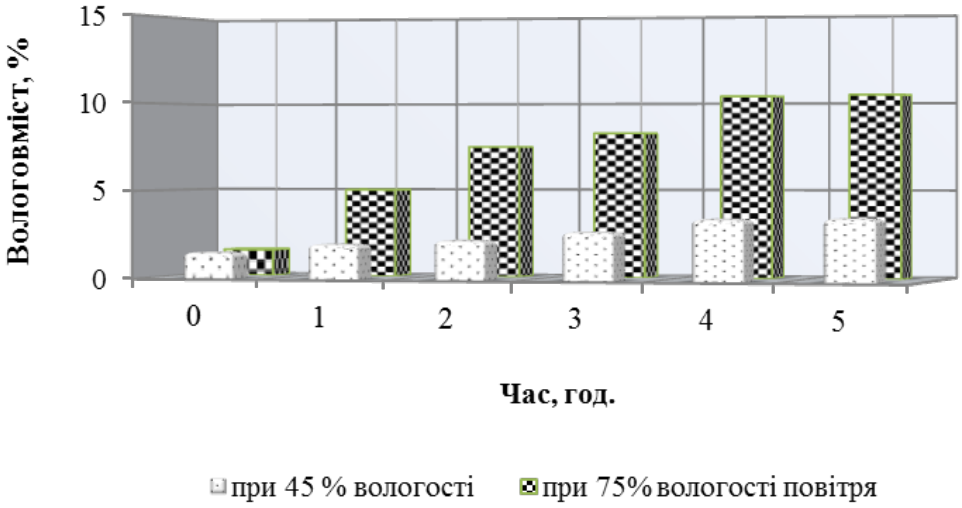

Fig. 3.7. Kinetics of moisture absorption of the obtained granulate

As can be seen from the figure, the obtained granules are very hygroscopic. At 75% relative air humidity, the granules absorb moisture very quickly, while their structure is destroyed. The obtained data allow us to draw a conclusion about the necessity of encapsulating the obtained granules.

Thus, considering the data of pharmaco-technological studies, the optimal composition of the capsules was determined:

Ingredients for one capsule:	Mr
Bean trefoil herbage	0.015
Oman root	0.060
Mint leaves	0.045
Calendula flowers	0.030
Hypericum herbage	0.045
Potato starch	0.003
Calcium stearate	0.002
Weight of capsule contents:	0.200

3.4. Description of the technological process of capsule production

The technological process consists of the following stages. The scheme of the technological process is shown in fig. 3.4.

Stage 1. Sifting. Each batch of raw materials (primary and auxiliary) and packaging material before use in production is subject to control for compliance with regulatory documents. First, the active and auxiliary substances are weighed per batch in a tared and marked collection. The components of the mass for encapsulation (plant components) are weighed on scales and sifted through a sieve with the corresponding hole diameter into tared collections.

Stage 2. Preparation of moisturizer. Water is measured in a measuring cup and fed to the reactor, where sieved and weighed potato starch is loaded. Stir for 20 minutes. The resulting moisturizer is transferred to the granulation stage.

Stage 3. Mixing, moistening and granulation. Mixing and moistening of the mass is carried out in a granulator-mixer with working supply and exhaust ventilation. Sifted and weighed on a scale plant mixture is loaded into the granulator-mixer. Mixing is carried out for (10±1) minutes. Then add a moisturizer to the dry ingredients - 5% paste of potato starch and mix for (10±1) minutes until the moisture is evenly distributed throughout the mass, the latter should be homogeneous, well-moisturized and should clump when squeezed in the hand. Wet granulation is carried out through a granulator with a hole diameter of 1,0 mm. Wet granulate is sent to the collector.

Stage 4. Drying. Wet granulate from the collection is fed into a shelf-type drying cabinet and dried at a temperature of (60±1) ºC for 1.50 hours to a residual moisture content of (2.0±1.5) %. Control and regulation of the drying temperature is carried out by automatic devices. The drying time is set by the time relay. The moisture content of the granulate was determined with a moisture meter. The dry mass is sent to the collector.

Stage 5. Calibration. From the collector (the dry granulate is passed through the calibrator with the diameter of the holes 1,0 mm, collecting the granules in the container.

Stage 6. Powdering. The obtained granules, calcium stearate from the collection are fed into the mixer and powdering is carried out min. The mass is unloaded into the collector.

Stage 7. Encapsulation. Granules from the collection are loaded into the automatic capsule filling machine. Encapsulate with capsules No. 0, average weight 0.5 ± 0.02g.

The required mass of the capsule is determined by the depth of filling the matrix. The matrix filling is regulated using the filling regulator. The weight of the capsules is selectively checked every 30 minutes using electronic scales. During the encapsulation process, a sample is taken for chemical analysis. The receiver with capsules after receiving the positive results of the analysis with the passport, is transported to the packaging stage.

Stage 8. Packaging. Capsules are packed in 10 pieces in blisters made of aluminum film on a machine. Contour packages of 5 pieces together with an insert sheet are placed in cardboard packs. At this stage, the drug is controlled for microbiological purity.

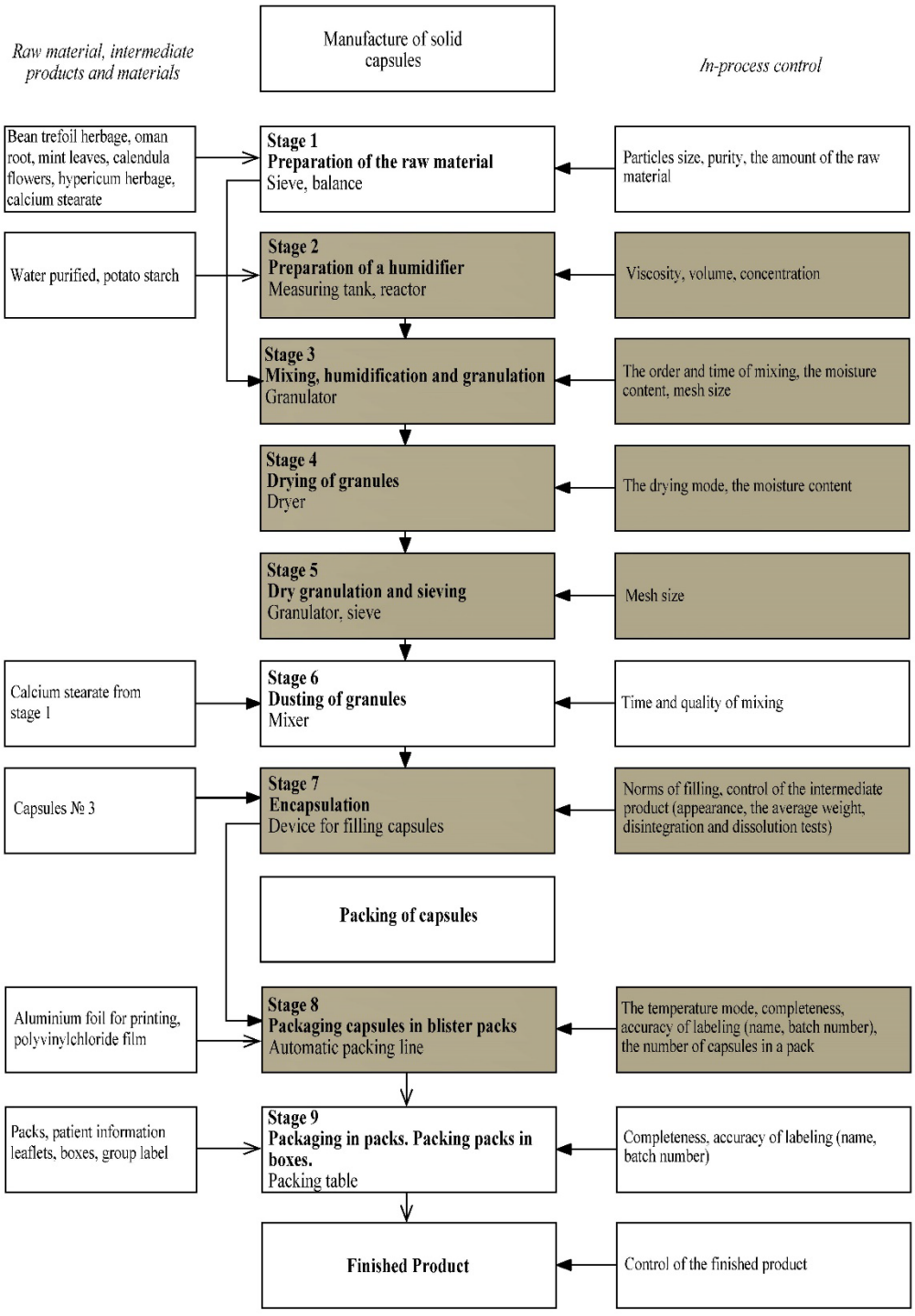

Fig. 3.4. Technological scheme of the capsule manufacturing process

CONCLUSIONS TO CHAPTER 3

1. Physical and chemical, technology indicators of vegetable powder are studied. Results of research have shown that they do not conform to production requirements for medicine creation.

2. Influence of excipients on farmako-technology indicators of the received granulates is studied. It is established that optimum humidifier for the encapsulated mix are 5% paste of potato starch.

3. Researches on moisture absorption have shown high hygroscopicity of the received granulate and have allowed to draw conclusion on expediency of creation of dosage form in the form of capsules.

GENERAL CONCLUSIONS

1. In literature review presented characterization and evaluation of drugs that are used for the treatment of biliary system. The expediency of development of new combination drugs in capsule form based on substances of natural origin. Literature data suggest a scientific and practical importance of the study of medicinal raw material for creating new medicines.

2. The conducted analysis of the current state of production of solid dosage forms in the form of capsules.

3. Were studied physico-chemical and technological parameters of starting substance - plant powder. The results showed that they do not meet the technological requirements for creation of medicinal product.

4. Was studied influence of excipients on farmako-technological figures of obtained granules. It was established that the best moisturizer for mixture, that encapsulated, is 5% potato starch.

5. Moisture research showed high hygroscopic of obtained granulate allows to make a conclusion about advisability of creation of a dosage form as capsules.

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APPLICATIONS

Appendix A

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

АКТУАЛЬНІ ПИТАННЯ СТВОРЕННЯ НОВИХ ЛІКАРСЬКИХ ЗАСОБІВ

МАТЕРІАЛИ
XXIX МІЖНАРОДНОЇ НАУКОВО-ПРАКТИЧНОЇ
КОНФЕРЕНЦІЇ МОЛОДИХ ВЧЕНИХ ТА СТУДЕНТІВ

19-21 квітня 2023 року
м. Харків

Харків
НФаУ
2023

a chronic inflammatory syndrome are the appointment of etiotropic therapy, the treatment of diseases that caused the development of pathology, and the elimination of factors that contributed to its development. Therefore, in the treatment of joint diseases, phlebitis of various origins, complex use of substances with anti-inflammatory, analgesic, venotonic, antithrombotic and antiexudative effects is indicated.

Aim. Development of composition gel for the treatment of arthritis and phlebitis.

Materials and methods. The physicochemical, technological and biopharmaceutical methods have been used in study.

Results and discussion. In literary sources, it has been investigated how drugs used to treat of the musculoskeletal system and phlebitis illnesses are characterized and judged. It has been proven how rapidly new gel-based combination therapies based on the dry extract of Hamamelis and Diclofenac diethylamine may be created. According to the literature, it's crucial to do study on medical raw materials if you want to create new treatments.

As active substances, a Diclofenac diethylamine and dry extract of Hamamelis is proposed, which is characterized by anti-inflammatory, anti-exudative and venotropic actions.

The physicochemical properties of the active substances were investigated in order to justify the method of their introduction into the composition of the dosage form.

The kind of carrier basis and its ideal content were determined through biopharmaceutical and technological studies: carbopol Ultrez 10 – 1.0%, TEA – 1.5%, PG – 10.0%, ethanol (96%) – 8.0%, Nipagin – 0.15%, Nipazol – 0.05%.

On the basis of physicochemical and rheological studies, a rational technology for the production of gel with witch hazel extract and diclofenac diethylamine was developed and justified.

Conclusions. Development of composition of the gel for the treatment of arthritis and phlebitis was conducted.

DEVELOPMENT OF COMPOSITION OF CAPSULES FOR THE TREATMENT OF THE BILIARY EXCRETORY SYSTEM DISEASES

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Introduction. One of the urgent problems of our time is the increase in the growth of diseases of the biliary system. Today, the global pharmaceutical market offers a wide range of drugs for the treatment of these diseases, among which a significant place belongs to solid dosage forms of foreign production. The range of drugs produced by Ukrainian manufacturers is limited, most drugs have a unidirectional effect. Therefore, the development of domestic complex preparations for the treatment of diseases of the biliary system is an urgent task.

Aim. Development of composition capsules for the treatment of biliary excretory system.

Materials and methods. The physicochemical, technological and biopharmaceutical methods have been used in study.

Results and discussion. Literary sources which presented characterization and evaluation of drugs that are used for the treatment of biliary system has been studied. The expediency of development of new combination drugs in capsule form based on substances of natural origin has

been proved. Literature data suggest a scientific and practical importance of the study of medicinal raw material for creating new medicines.

The conducted analysis of the current state of production of solid dosage forms in the form of capsules.

As active substances, a mixture of medicinal herbal raw materials is proposed, which is characterized by stimulation of bile secretion, anti-inflammatory action, relieving spasm of the sphincters of the biliary tract, and changing the composition of bile. The physicochemical and technological parameters of this mixture were studied.

The expediency of use is substantiated and the number of excipients in the composition of the proposed preparation, such as potato starch and calcium stearate, is experimentally confirmed. Was studied influence of excipients on technological figures of obtained granules. It was established that the best moisturizer for mixture, that encapsulated, is 5% potato starch.

Moisture research showed high hygroscopic of obtained granulate allows to make a conclusion about advisability of creation of a dosage form as capsules.

Conclusions. Development of composition of the capsules for the treatment of the biliary excretory system diseases was conducted.

DEVELOPMENT OF THE COMPOSITION OF COMBINATION TABLETS FOR DEMENTIA TREATMENT

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Introduction. According to the World Health Organization (WHO), dementia is a syndrome in which there is a progressive deterioration in cognitive function beyond what might be expected from normal aging. This deterioration can include impaired judgment, memory loss, and difficulty with communication, language, and daily activities. Each type of dementia has its own etiology. Alzheimer's disease is the most common type of dementia and is caused by the accumulation of amyloid plaques and neurofibrillary tangles in most commonly used treatments for dementia include cholinesterase inhibitors (donepezil, rivastigmine, and galantamine), which can improve memory and thinking by increasing levels of a neurotransmitter called acetylcholine in the brain, and memantine, which works by blocking the action of a neurotransmitter called glutamate in the brain and can help to slow down the progression of symptoms in people with moderate to severe dementia.

Aim. Currently, pharmaceutical companies in Ukraine do not produce combination tablets with memantine and donepezil. But such combination has certain advantages. The addition of memantine to donepezil is associated with a favorable risk/benefit ratio in the treatment of patients with moderate to severe Alzheimer's disease and provides additional benefits for patients, caregivers and society at large. The aim of our researches was to study technological characteristics of these active pharmaceutical ingredients, choose excipients for the creation of tablets with memantine hydrochloride and donepezil hydrochloride.

Materials and methods. All excipients in the composition were standard excipients of pharmaceutical quality. We used generally accepted research methods according to the State Pharmacopoeia of Ukraine.

Ф А 2.2.1–32-366

National University of Pharmacy

Faculty for foreign citizens' education
Department of pharmaceutical preparations technologies

Level of higher education master

Specialty 226 Pharmacy, industrial pharmacy
Educational program Pharmacy

APPROVED
The Head of department
of pharmaceutical preparations
technologies
Oleksandr KUKHTENKO
"01" September 2022

ASSIGNMENT
FOR QUALIFICATION WORK
OF AN APPLICANT FOR HIGHER EDUCATION

Elmortaji Mohamed-Taha

1. Topic of qualification work: «Development of composition and technology of capsules for the treatment of the biliary excretory system diseases», supervisor of qualification work: Denys PULIAIEV, PhD, assoc. prof.

approved by order of NUPh from "06 st" of February 2023 №35

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

3. Outgoing data for qualification work: capsules, active ingredients: a mixture of crushed medicinal plant raw materials.

4. Contents of the settlement and explanatory note: literature review on the topic, objects and methods of research, experimental part, conclusions.

5. The work should contain tables, graphs, figures in a volume sufficient to cover the topic.

6. Consultants of chapters of qualification work

Chapters	Name, SURNAME, position of consultant	Signature, date	
		assignment was issued	assignment was received
1	Denys PULIAIEV, associate professor of higher education institution of department of pharmaceutical preparations technologies	17.11.2022	17.11.2022
2	Denys PULIAIEV, associate professor of higher education institution of department of pharmaceutical preparations technologies	09.03.2023	09.03.2023
3	Denys PULIAIEV, associate professor of higher education institution of department of pharmaceutical preparations technologies	21.04.2023	21.04.2023

7. Date of issue of the assignment: «01» September 2022.

CALENDAR PLAN

№	Name of stages of qualification work	Deadline for the stages of qualification work	Notes
1	The study of literary sources in the main directions of the treatment of diseases of the bile excretion system. Writing a literature review.	September 2022	**done**
2	Definition of objects and methods of research. Formation of the second chapter.	October 2022	**done**
3	Study of physico-chemical and pharmaco-technological properties of research objects.	January 2023	**done**
4	Substantiation of the composition and technology of capsules with dry a mixture of crushed medicinal plant raw materials for the treatment of diseases of the bile excretion system. Formation of chapter 3.	April 2023	**done**

An applicant of higher education _____ Elmortaji Mohamed-Taha

Supervisor of qualification work _____ Denys PULIAIEV

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 технологій фармацевтичних препаратів**				
Ельмортажі Мохамед-Таха	Розробка складу капсул для лікування захворювань жовчовидільної системи	Development of composition of capsules for the treatment of the biliary excretory system diseases	доцент Пуляєв Д.С.	доцент Ковалевська І.В.

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

№ 113191 від « 10 » травня 2023 р.

Проаналізувавши випускну кваліфікаційну роботу за магістерським рівнем здобувача вищої освіти денної форми навчання Ельмортажі Мохамед-Таха, 5 курсу, _____ групи, спеціальності 226 Фармація, промислова фармація, на тему: «Розробка складу капсул для лікування захворювань жовчовидільної системи / Development of composition of capsules for the treatment of the biliary excretory system diseases», 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**

1%
28%

Ф А 2.2.1-32-353

REVIEW

of scientific supervisor for the qualification work of the master's level of higher education of the specialty 226 Pharmacy, industrial pharmacy

Elmortaji Mohamed-Taha

on the topic: **«Development of composition and technology of capsules for the treatment of the biliary excretory system diseases»**

Relevance of the topic. The problem of creating solid dosage forms of combined action with the substantiation of the composition, the rational choice of excipients and the optimal technology is quite relevant and opens up new opportunities in the complex therapy of diseases of the bile excretion system.

Practical value of conclusions, recommendations and their validity. The analysis of literature sources on rational pharmacotherapy of diseases of the bile excretion system, considering their etiology and pathogenesis, was carried out, the range of drugs for the treatment of these pathologies available on the pharmaceutical market of Ukraine was studied, and the relevance of developing a new drug in the form of capsules with a mixture of crushed medicinal plant raw materials was proved. A technology for the manufacture of a medicinal product is proposed, according to which a technological scheme for its production is drawn up.

Assessment of work. The results of the experiments were statistically processed and presented in the work in the form of tables and graphs. The conclusions are the logical conclusion of theoretical and experimental studies.

General conclusion and recommendations on admission to defend. The master's work of Elmortaji Mohamed-Taha meets all the requirements for qualification work and can be submitted for defense at the State Examination Commission of the National University of Pharmacy.

Scientific supervisor Denys PULIAIEV

«13» of April 2023

Ф А 2.2.1-32-356

REVIEW

for qualification work of the master's level of higher education, specialty 226 Pharmacy, industrial pharmacy

Elmortaji Mohamed-Taha

on the topic: **«Development of composition and technology of capsules for the treatment of the biliary excretory system diseases»**

Relevance of the topic. One of the urgent problems of our time is the increase in the growth of treatment of diseases of the bile excretion system. The range of medicines for the treatment of these pathologies of Ukrainian production is limited, most of the drugs have a unidirectional effect. Therefore, the development of domestic complex preparations for treatment of the biliary excretory system diseases is an urgent task.

Theoretical level of work. Based on the literature data, the author substantiates the need to create capsules for treatment of diseases of the bile excretion system. Elmortaji Mohamed-Taha conducted a search for the most appropriate active substances and auxiliary components.

Author's suggestions on the research topic. As active ingredients, the author proposed a mixture of crushed medicinal plant raw materials. The expediency of using and experimentally confirmed number of excipients in the composition of the proposed preparation is substantiated.

Practical value of conclusions, recommendations and their validity. In the course of the work, the rational composition of the capsules was substantiated. The technology of capsules has been developed, according to which a technological scheme has been drawn up.

General conclusion and assessment of the work. The conclusions formulated in the work are based on experimental data and follow logically from the results obtained. The qualification work of Elmortaji Mohamed-Taha meets all the requirements for qualification works and can be submitted for defense at the State Examination Commission of the National University of Pharmacy.

Reviewer _____ professor Inna KOVALEVSKA

«18» of April 2023

Ф А2.2.1-91-287

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

Витяг з протоколу
засідання кафедри технологій фармацевтичних препаратів НФаУ
№ 3 від 20 жовтня 2022 року

Голова: завідувач кафедри, доктор фарм. наук, проф. Кухтенко О. С.

Секретар: к. фарм. н., доц. Січкар А. А.

ПРИСУТНІ: зав. каф., проф. Кухтенко О. С., доц. Безрукавий Є. А., доц. Кутова О. В., доц. Ляпунова О. О., доц. Манський О. А., доц. Ніколайчук Н. О., доц. Сайко І. В., доц. Січкар А. А., доц. Солдатов Д. П., доц. Степаненко С. В., доц. Трутаєв С. І., ас. Сердюк Є.В.

ПОРЯДОК ДЕННИЙ:
1. Про представлення до захисту в Екзаменаційну комісію кваліфікаційних робіт здобувачів вищої освіти випускного курсу НФаУ 2022 року випуску

СЛУХАЛИ: про представлення до захисту в Екзаменаційній комісії кваліфікаційної роботи на тему: «Розробка складу капсул для лікування захворювань жовчовидільної системи» здобувача вищої освіти випускного курсу Фм18 (5,0д) англ. – 7 групи НФаУ 2023 року випуску Ельмортажі Мохамед-Таха
Науковий (-ві) керівник (-ки) _к.фарм.н., доц. Денис ПУЛЯЄВ_____
Рецензент_____д.фарм.н., проф. Інна КОВАЛЕВСЬКА_____

УХВАЛИЛИ: Рекомендувати до захисту кваліфікаційну роботу здобувача вищої освіти _5_ курсу Фм18 (5,0д) англ. – 7 групи Ельмортажі Мохамед-Таха
на тему: «Розробка складу капсул для лікування захворювань жовчовидільної системи»

Голова
завідувач кафедри,
доктор фарм. наук, проф. _____ Олександр КУХТЕНКО
(підпис)

Секретар
к. фарм. н., доцент _____ Антоніна СІЧКАР
(підпис)

Ф А2.2.1-32-042

НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ПОДАННЯ
ГОЛОВІ ЕКЗАМЕНАЦІЙНОЇ КОМІСІЇ
ЩОДО ЗАХИСТУ КВАЛІФІКАЦІЙНОЇ РОБОТИ

Направляється здобувач вищої освіти Ельмортажі Мохамед-Таха до захисту кваліфікаційної роботи
за галуззю знань 22 Охорона здоров'я
спеціальністю 226 Фармація, промислова фармація
освітньою програмою Фармація
на тему: «Розробка складу капсул для лікування захворювань жовчовидільної системи»

Кваліфікаційна робота і рецензія додаються.

Декан факультету _____ / Світлана КАЛАЙЧЕВА /

Висновок керівника кваліфікаційної роботи

Здобувач вищої освіти Ельмортажі Мохамед-Таха виконав на кафедрі технологій фармацевтичних препаратів НФаУ кваліфікаційну роботу, яка присвячена створенню складу капсул для лікування захворювань жовчовидільної системи.

В процесі роботи Ельмортажі Мохамед-Таха дослідив загальні напрями етіопатогенезу та терапії захворювань жовчовидільної системи, обґрунтував доцільність створення та застосування капсул із сумішшю подрібненої лікарської рослинної сировини. Автором було обґрунтовано оптимальний склад капсул та розроблено промислову технологію їх отримання.

У цілому подана до захисту кваліфікаційна робота Ельмортажі Мохамед-Таха на тему «Розробка складу капсул для лікування захворювань жовчовидільної системи» відповідає вимогам, що висуваються до кваліфікаційних робіт, оцінюється позитивно і може бути рекомендована для захисту в Екзаменаційну комісію НФаУ.

Керівник кваліфікаційної роботи Денис ПУЛЯЄВ

«13» квітня 2023 р.

Висновок кафедри про кваліфікаційну роботу

Кваліфікаційну роботу розглянуто. Здобувач вищої освіти Ельмортажі Мохамед-Таха допускається до захисту даної кваліфікаційної роботи в Екзаменаційній комісії.

Завідувач кафедри технологій
фармацевтичних препаратів Олександр КУХТЕНКО

«21» квітня 2023 р.

Qualification work was defended

of Examination commission on

« ____ » _____2023

With the grade _____

Head of the State Examination commission,

D.Pharm.Sc., Professor

_____ / Oleh SHPYCHAK /