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QUALIFICATION WORK

on the topic: **«PHARMACOTECHNOLOGICAL STUDIES OF METHYLSULFONYLMETHANE TABLETS WITH CHAMOMILE EXTRACT»**

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ANOTATION

Qualification work is devoted to the substantiation and development of the composition and technology of production of the combined tablet anti-inflammatory drug with methylsulfonylmethane and chamomile extract. The work contains: introduction, literature review, experimental part, general conclusions, list of used sources, appendices, set out on 48 pages, includes 5 tables, 8 figures, 59 sources of literature.

Key words: thick extract, chamomile, tablets, methylsulfonylmethane, medicinal plant raw materials, technology.

АНОТАЦІЯ

Кваліфікаційна робота присвячена обґрунтуванню та розробці складу та технології виробництва комбінованого таблетованого протизапального препарату з метилсульфонілметаном та екстрактом ромашки. Робота містить: вступ, огляд літератури, дослідну частину, загальні висновки, список використаних джерел, додатки, викладені на 48 сторінках, містить 5 таблиць, 8 рисунків, 50 джерел літератури.

Ключові слова: густий екстракт, ромашка, таблетки, метилсульфонілметан, лікарська рослинна сировина, технологія.

CONTENT

LIST OF CONVENTIONAL ABBREVIATIONS

AphI - active pharmaceutical ingredient

BAS - biologically active substance

IS - Interstate standard

SphU - State Pharmacopoeia of Ukraine

CM - computed tomography

MP - medicinal product

MPRM - medicinal plant raw materials

MH- Ministry of Health

MRI - magnetic resonance imaging

RD - regulatory documentation

Nuph - National Pharmaceutical University

CDC - Center for Disease Control

INTRODUCTION

Relevance of topics. Inflammation is a pathological process that is most often blamed on the human body, and the problem of inflammation of vinyl is at the same time with medicine. Inflammation can be blamed as a deterioration of fabrics on the appearance of a sign of the deterioration of the cells of their components. This important and folding process is the result of evolution and formation as a mechanism for defending the body. Headache of inflammation - localization of the pathological pit, removal (elimination) of the pathogenic agent and restoration of the normal function of cells, tissue, organ.

Overheating, as a typical pathological process, is characterized by a natural law, as the presence of a constant and not to fall due to the cause, localization, type of organism and its individual features. This process can be blamed on various organs. A specific type of skin may have its own clinical features, but the pathogenetic scheme of tissue exposure to the body for the ignition agent will be identical to that typical. This uniformity is known in special clinical terminology, as it conveys the introduction of the suffix “it, um” to denote the inflammation process in the same way - appendicitis, peritonitis, cholecystitis, hepatitis, gastritis, enteritis, colitis, cephalocarids, endocarditis, endocarditis, dermatitis, from vasculitis, thrombophlebitis, bronchitis, pleurisy, periodontitis, pulpitis, stomatitis, blepharitis. Irrespective of those that are inflamed by a malignant process, the whole organism also reacts to changes in the fire, which is often manifested by fever, increased erythrocyte sedimentation, leukocytosis. An important role in the formation of the reaction of the body as a whole to the development of the ignition reaction is introduced to the immune, endocrine and nervous systems.

Goals and objectives of research. The purpose of this work is to substantiate and develop the composition and production technology of a combined anti-inflammatory tablet medicine with methylsulfonylmethane and chamomile extract.

In order to achieve the set goal, it was necessary to solve the following tasks:

- to analyze and summarize the current literature data on existing non-steroidal anti-inflammatory drugs, based on which to propose the original composition of the active components of the medicinal product;
- conduct a complex of physico-chemical and technological studies of selected substances of active substances;
- substantiate the composition of excipients and the technology of combined tablets;
- conduct an analysis of the market of non-steroidal anti-inflammatory drugs to substantiate the possible demand for the drug under development.

Object of study. Methylsulfonylmethane, thick chamomile extract, tablet mass and combined tablets.

Subject of study. Development of a scientifically based composition and technology of combined anti-inflammatory tablets with methylsulfonylmethane and chamomile extract.

Research methods. When solving the tasks set in the work, methods were used to evaluate the physical and chemical properties of powders (shape and size of particles, moisture absorption, moisture content); technological properties of powders and tablet masses (flowability, angle of natural slope, bulk volume, compressibility, ejection force); methods of researching the quality indicators of tablets in accordance with the requirements of the state pharmacopoeia of Ukraine (appearance, average mass and uniformity of mass, disintegration, wear ability). The processing of experimental data was carried out using methods of mathematical statistics in accordance with the requirements the state pharmacopoeia of Ukraine.

SECTION 1

PROSPECTS OF THE CREATION AND APPLICATION OF A COMBINED ANTI-INFLAMMATORY DRUG IN THE FORM OF TABLETS (LITERATURE REVIEW)

1.1 General characteristics of anti-inflammatory agents

1.1.1 Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs are a group of drugs that have analgesic, antipyretic, and anti-inflammatory effects, reduce pain, fever, and inflammation. The use of the term "nonsteroidal" in the name emphasizes their difference from glucocorticoids, which have not only an anti-inflammatory effect, but also other, sometimes undesirable, properties of steroids [1-12].

Mechanism of action. Most drugs of this group are non-selective cyclooxygenase enzyme inhibitors, suppressing the action of both its varieties COX-1 and COX-2. Cyclooxygenase is responsible for the production of prostaglandins and thromboxane from arachidonic acid, which in turn is formed from phospholipids of the cell wall due to the enzyme phospholipase A2. Among other functions, prostaglandins are mediators and regulators of the development of inflammation [2, 3, 12].

Classification. Depending on the chemical structure and nature of activity, NSAIDs are classified as follows [12]:

Acids:

– salicylates: acetylsalicylic acid, diflunisal, lysine monoacetylsalicylate;

– pyrazolidines: phenylbutazone;

– derivatives of indoleacetic acid: indomethacin, sulindac, etodolac;

- derivatives of phenylacetic acid: diclofenac, aceclofenac;

- oxicams: piroxicam, tenoxicam, lornoxicam, meloxicam;

- derivatives of propionic acid: ibuprofen, naproxen, flurbiprofen, ketoprofen, tiaprofenic acid.

Non-acid derivatives:

– alkanones: nabumetone:

- sulfonamide derivatives: nimesulide, celecoxib, rofecoxib.

According to the anti-inflammatory effect of medium doses, NSAIDs can be arranged in the following order: indomethacin ↓ flurbiprofen ↓ sodium diclofenac ↓ piroxicam ↓ ketoprofen ↓ naproxen ↓ ibuprofen ↓ amidopyrine ↓ aspirin.

According to the analgesic effect of medium doses, NSAIDs can be arranged in the following order: ketoprofen ↓ diclofenac sodium ↓ indomethacin ↓ flurbiprofen ↓ amidopyrine ↓ piroxicam ↓ naproxen ↓ ibuprofen ↓ aspirin

Indications for use. Drugs of this group are usually used for acute and chronic diseases accompanied by pain and inflammation. Most often, NSAIDs are prescribed for the following conditions:

– rheumatoid arthritis;

– osteoarthritis;

- inflammatory arthropathies (ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome);

– gout;

– dysmenorrhea;

– bone metastases accompanied by pain;

– headache and migraine;

– postoperative pain syndrome;

– pain syndrome of weak or moderate degree of severity in case of inflammatory changes or trauma;

– fever;

– renal colic [1 – 12].

Side effects. The widespread use of NSAIDs has forced attention to the side effects of these relatively safe drugs. The most common effects are related to the digestive tract and kidneys. All effects are dose-dependent and serious enough to limit the use of this group of drugs. In the USA, 43% of all medicinal preparations hospitalizations are due to NSAIDs, most of which could have been avoided [4-12].

Adverse reactions are noted with long-term use of NSAIDs and consist of damage to the mucous membrane of the stomach and duodenum with the formation

of ulcers and bleeding. This lack of NSAIDs of non-selective action led to the development of a new generation of drugs that block only COX-2 (an inflammatory enzyme) and do not affect the work of COX-1 (a protective enzyme). Thus, the drugs of the new generation are practically devoid of the main side effects associated with long-term use of non-selective NSAIDs [2, 3].

1.1.2 Pharmacological characteristics of methylsulfonylmethane

MSM is an organic compound that contains sulfur in a bioavailable form and is necessary for the development and maintenance of the function of connective and other types of body tissues. It is formed in seawater, falls to the Earth's surface with precipitation and is absorbed by plants [13-15].

In nature, MSM is found in many fruits, vegetables, cereals, milk, animal meat, seafood, and eggs. However, most of the MSM in food is lost during cooking. In food supplements, its source is sea water.

In the body, MSM is found mainly in muscle tissue, as well as in heart valves, blood vessels, joint surfaces, spine, hair, skin and bones, nails, etc. The concentration of MSM in the body decreases with age. Unlike other sulfur-containing compounds, MSM is odorless, does not cause gas formation, and does not add any odor to the body [13].

The main functions of MSM [13 – 15]:

• is a component of collagen and promotes its synthesis;

• contributes to the maintenance of healthy eyes, teeth, skin, improvement of brain activity;

• is a source of sulfur for the synthesis of glutathione, which neutralizes free radicals and contributes to the neutralization of toxic substances in the body;

• relieves severe symptoms of allergies and asthma;

• helps to strengthen the connective tissue, supports its integrity;

• necessary for healthy joints, as it effectively increases blood flow and contributes to the proper functioning of muscles and tendons, improving joint mobility. Cells of the surface of the joints - fibroblasts - synthesize glucosamine,

which contains a large amount of sulfur; and if it is not enough, the synthesis of glucosamine, which ensures joint health, is difficult or impossible;

• participates in the processes of healing and restoration of damaged tissues, creates conditions for the normalization of processes of synthesis of new and replacement of aging tissues. MSM has a special effect on the regeneration and restoration of the normal structure of the skin and its appendages: hair, nails, sweat glands;

• has anti-inflammatory and antioxidant activity;

• stimulates the secretion of bile and regulates the processes of excretion of metabolic products;

• necessary for the synthesis of keratin, which ensures the growth of hair and nails;

• necessary for regulating the level of glucose in the blood, as it is part of insulin, hemoglobin and many other proteins, catalysts and enzymes;

• necessary for the flow of oxidizing reactions in cells and maintenance of acid-alkaline balance;

• is part of the chemical structure of such amino acids as methionine, cysteine, taurine and glutathione (the main antioxidant in the body); vitamin B1 and pantothenic acid also contain small amounts of sulfur.

Taking into account the importance of the functions that sulfur carries, it is necessary to constantly enter the body of MSM.

The main indications for taking MSM:

• allergic reactions, in particular those caused by household allergens, hay fever, urticaria, obstructive bronchitis, contact, food and drug allergies;

• diabetes;

• joint and muscle inflammation, pain and muscle spasms, arthritis, arthrosis, osteochondrosis, radiculitis, rheumatoid arthritis, joint pain; MSM was also successfully used by athletes after physical exertion to relieve pain in tense or inflamed muscles;

• gastrointestinal diseases – MSM is effective for various gastrointestinal disorders, diarrhea, chronic constipation, nausea, heartburn, epigastric pain and other gastrointestinal symptoms; the sulfur biocomplex is a natural regulator of the evacuatory activity of the small and, especially, the large intestine, providing a mild laxative and choleretic effect, which is especially important during intestinal cleansing, in weight loss programs, to combat acne;

• inflammatory bowel syndrome;

• rhinitis;

• diseases of hair, skin and nails (when the amount of keratin in them is lower than normal), as well as cosmetic programs for their improvement;

• carpal tendon syndrome;

• scleroderma, fibromyalgia, systemic lupus erythematosus, thermal and sunburns, acne and scar processes;

• a state of chronic fatigue, stress;

• lung diseases;

• prevention of breast and colon cancer;

• multiple blows [13 – 15].

MSM in combination with glucosamine, chondroitin, and hyaluronic acid significantly alleviates the condition of patients with joint pain.

MSM has no side effects. If taken in large quantities, it is excreted naturally without causing harm [13-14].

Thus, MSM is needed to maintain the normal structure of body tissues - from cartilage and bones to hair and skin.

1.1.3 Pharmacognostic and pharmacological characteristics of medicinal chamomile

Chamomile flowers - Flores Chamomillae

Medicinal chamomile - Chamomillae recutita (L.) Rausch.

genus aster - Asteraceae

The plant is an annual herb. The stem is straight, cylindrical, bare, branched, 15-50 cm tall. The leaves are alternate, glabrous, sessile, two- or three-lobed, divided

into thin, narrow, filiform segments. The flowers are small, collected at the ends of the stem in hemispherical or conical baskets; inflorescence elongated-conical, glabrous, hollow; marginal flowers pistillate, ligulate, white, middle - bisexual, tubular, yellow, five-lobed on top; wrapper tile-like, multi-rowed. The fruit is an achene [16 - 17].

Spread. Medicinal chamomile grows in small thickets almost throughout the territory of Ukraine in gardens, wastelands, along roads. Chamomile is cultivated in specialized farms [16-17].

Provision. Flowers are collected during the entire flowering period in dry weather, plucking by hand or with special combs at the very base, so that the remains of flower stalks are no longer than 3 cm. The collected material is dried by spreading in a layer of 2-3 cm in a dry, well-ventilated room or under a cover on free air; artificial drying is possible at a temperature not higher than 40°C [16 – 17].

Chemical composition of raw materials. Chamomile flowers contain blue essential oil (0.8%). Its main components are hamazulene, sesquiterpene hydrocarbons farnesene and cadinene, sesquiterpene alcohol bisabolol, aliphatic terpene myrcene. Flavonoids, coumarins, phytosterol, choline, ascorbic acid, carotene are also found in flower baskets. It was established that hamazulene is formed in flowering baskets from matricin guaianolide (prohamazulene) [12, 16 – 17].

Biological action and application. Medicinal chamomile preparations increase the secretory activity of the digestive glands, stimulate bile secretion and stimulate appetite, eliminate spasms of the abdominal organs, have pain-relieving, anti-inflammatory, anti-allergic, antimicrobial effects. When used externally, chamomile preparations have anti-inflammatory, analgesic, epithelizing, antimicrobial and antifungal effects. An infusion of chamomile flowers is used for rinsing with inflammation of the mucous membranes of the oral cavity, for washing purulent wounds, ulcers, hemorrhoids, douching for colpitis, endocervicitis, etc.

Romazulan, Rotokan, Alorom, Gerbogastrin, Fiton, Kamistad-gel, Gastrolit are made from chamomile flowers, the flowers are part of Arfazetin, Elekasol, anti-hemorrhoid preparations [10 – 12, 16 – 17].

1.2 The current state of technology for the production of medicinal tablets means

In the nomenclature of finished medicines, a significant place belongs to tablets. Tableted preparations occupy about 80% of the total volume of finished medicines [18-21].

The development of the optimal composition and technology of tablets is determined by the physicochemical, crystallographic and technological properties of the components included in their composition. These properties are closely related to each other, they affect the process of pressing and obtaining high-quality tablets [19-21].

1.2.1 The choice of the optimal method of obtaining tablets depending on the physicochemical and technological properties of medicinal substances

The scheme of production of tablets depends on the physico-chemical and technological properties of medicinal substances, on their quantity in the composition of tablets, resistance to the action of environmental factors. These properties are interrelated and in a certain way can affect the process of pressing and obtaining high-quality tablets with the necessary therapeutic effect [19-32].

Volumetric-technological properties of substances to be pressed and physico-mechanical characteristics of the obtained tablets are mainly determined by the crystal structure of the particles, therefore the study of these parameters is mandatory in predicting a rational way of obtaining tablets [33].

Tablets are obtained by pressing powdered or granular medicinal substances. Powdered medicinal substances are characterized by fractional composition, bulk density, fluidity and many other parameters, the consideration of which makes it possible to determine the optimal parameters of the technological process - the nature and amount of humectant, the method of pressing, the volume of the matrix space, etc. Medicinal substances, in addition, must have the ability to press,

necessary for the adhesion of particles in the tablet. The shape, size, and strength of component crystals influence the force of particle adhesion during pressing [19-33].

To assess the suitability of powders for direct pressing (Fig. 1.3), their main characteristics such as fluidity and pressability are determined.

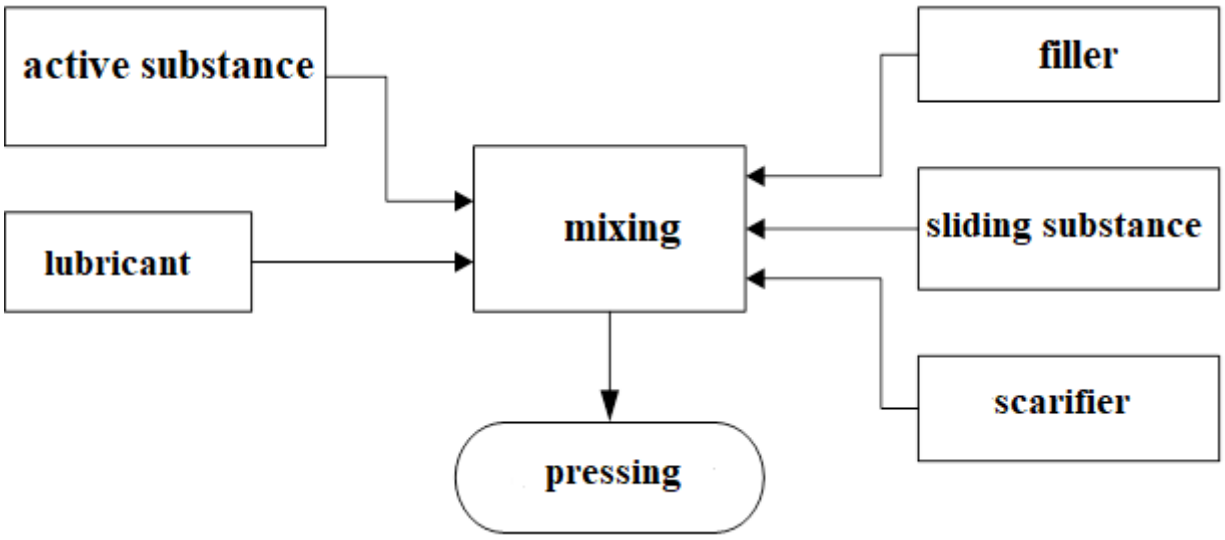


Figure 1.3. The scheme of obtaining tablets by the method of direct pressing

The uniformity of powder flow plays an important role in ensuring a stable mass of tablets. However, when the compression ratio of powders is greater than 20%, significant variations in tablet mass occur regardless of the powder mass flow rate. Devices for tablet presses created in recent years for forced filling of matrices with powder eliminate unevenness of flow. Research is being conducted to study the effect of vibration on the behavior of powders. The effect of the sealing agent on the powder leads to an increase in strength due to an increase in the number of contacts [19 – 33].

The majority of pharmaceutical substances do not have properties that ensure their direct pressing, therefore granulation methods are often used in the technology of solid dosage forms (Fig. 1.4).

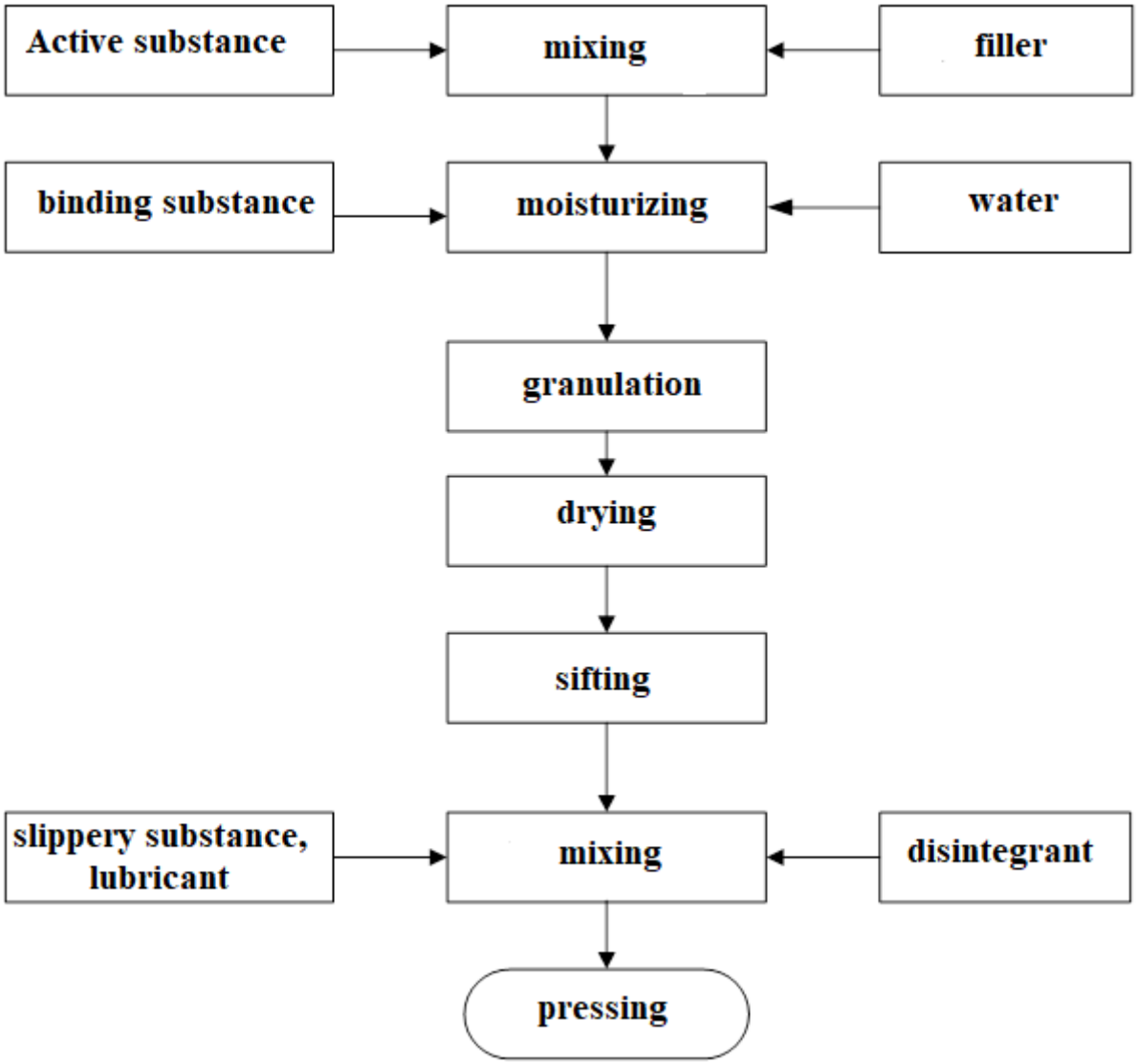


Figure 1.4. The scheme of obtaining tablets by the method of wet granulation

There are three main types of granulation – dry, wet and structural granulation. Wet granulation is most widely used by the pharmaceutical industry, since the bulk of substances require the addition of binding and plasticizing additives during the granulation process [25-33].

1.2.2 Auxiliary substances in the production of tablets by the direct pressing method

The method of direct pressing in the production of tablets allows you to achieve high labor productivity, significantly shorten the technological cycle, reduce production areas, and reduce energy and labor costs. In addition, using the direct pressing method, it is possible to obtain tablets with thermolabile and incompatible components, to increase the shelf life of finished tablets [34-36]. However, as

already mentioned, most medicinal substances do not meet the requirements for direct tableting.

Powdery substances and their mixtures, which are tableted by the direct pressing method, are subject to strict requirements regarding fluidity, cohesion, as well as the ability to push them out of the matrix without reducing the strength of the tablets. The angle of the natural slope is important, which for well-flowing materials is from 25° to 35°. The value of the bevel angle is significantly affected by the roughness of the particles, moisture and dispersion of the powder.

The quality of powder mixtures for direct pressing depends on the size of the particles. The smaller the proportion of the crystalline component in the mixture, the smaller its particles should be - a system containing two fine crystalline powders forms a more homogeneous mixture. With direct pressing, the size of the particles usually does not exceed 50-100 microns, and the mixing process takes place with a high degree of homogeneity.

It is possible to give the medicinal substance the properties necessary for direct pressing by means of directional crystallization, use of forced feeding into the matrix, or selection and introduction of auxiliary substances (Table 1.1). The last method is most often used when obtaining tablets by direct pressing, since auxiliary substances not only improve the fluidity of powders, but also significantly affect the quality indicators of tablets.

The effect of adding auxiliary substances during direct pressing depends on their density, humidity, particle size, etc. The best results are obtained when using excipients whose density value is close to the density value of the medicinal substance, and the particle size and fluidity allow for uniform retention of the particles of this substance.

Different brands of microcrystalline cellulose (MCC) are widely used to obtain tablets by the direct pressing method. This substance significantly increases the fluidity of powders and gives better results than talc and a mixture of talc with magnesium stearate [37].

Table 1.1

The most commonly used fillers
in the production of tablets by the direct pressing method

Filler	Trade Name	Notes
Calcium phosphate	Emcompress®, Di-Tab®	Good flow, high density, insoluble in water
Tribasic calcium phosphate	Tri-Tab®	Insoluble in water
Calcium sulfate	Compactrol®	Insoluble in water i
Microcrystalline cellulose	Avicel®, Emocel®, Vivacel®	High compressibility, low bulk density, acts as a leavening agent
Powdered cellulose	Elcema®	—
Dextrose	Emdex®	—
Lactitol	Finlac® DC	—
Lactose: □ anhydrous alpha- □ anhydrous beta- – □ dried by spraying		
	Pharmatose DCL30®	Good flow
	Pharmatose DCL21®	—
	Fast-Flo®, Zeparox®, Pharmatose DCL11®	—
Mixture of lactose and cellulose	Cellactose®	—
Maltodextrin	Lycatab®, Maltrin®	Soluble in water has a light lubricating effect
Mannitol	Pearlitol®	Freely dissolves in water, cools the solution
Sorbitol	Neosorb®	—
Starch, pregelatinized starch	Starch 1500®, Starx 1500®	Disintegrant
A mixture of sucrose and maltodextrin	Des-Tab®, Dipac®, Nutab®	good flow, sensitive to moisture
Xylitol	Xylitab®	Freely dissolves in water, cools the solution

The properties of powdered mixtures and tablets, which include microcrystalline cellulose, depend on its type, the degree of its grinding and its amount. Due to the low pushing force, it is not a "self-lubricating" substance. Under

the conditions of its use, the tablets may stick to the punches. The introduction of magnesium stearate into the composition of the mixture reduces the value of the coefficient of friction between the pressed substance and the wall of the punch by 90%. The mixture of MCC with starch has the best properties for obtaining tablets by the direct pressing method [37].

Due to the formation of a large number of hydrogen bonds, MCC increases the resistance of tablets to crushing, while exhibiting some loosening effect due to swelling in digestive juices. When increasing the amount of MCC in the composition of tablets, their resistance to crushing increases, but their disintegration time also increases [27, 37]. Therefore, disintegrants are usually added to tablets obtained by direct pressing: croscarmellose sodium, crystalline beta-lactose, alpha-lactose monohydrate, cyclodextrin polymer. So, for example, croscarmellose sodium – a high-molecular compound of a hydrophilic nature, capable of rapid water absorption and swelling with an increase in volume – has a positive effect on the disintegration of solid dosage forms [37].

Milk sugar - lactose, a mixture of lactose with calcium stearate, granulated sulfate, and maltose are often used to improve fluidity. The effectiveness of the action of lactose is determined by the type of its modification and the drying method - there are six known modifications of lactose that have different rheological properties. Granular sulfate, in contrast to non-granular sulfate, has better fluidity and provides tablets of sufficient strength under normal pressing conditions. Maltose has a high flow rate, so its introduction into the composition of the mixture ensures the first stage of pressing. To obtain tablets by direct pressing, it is recommended to use modified starches, carboxymethyl starch, which has the greatest swelling and significant fluidity, sodium starch glycolate, which has the best loosening effect [34-36].

Polyvinyl-pyrrolidone derivatives, as well as their mixtures with MCC, are used to ensure the strength of the tablets [67]. It is illustrated that the best results in terms of mechanical stability are achieved when using a combination of copolyvidone and MCC [38].

Among the lubricants, talc, aerosol, calcium and magnesium salts of stearic acid and their mixtures in various proportions are usually used [34-36].

Some scientists suggest using 2-50% trihalose, as well as sucrose, glucose, fructose for direct pressing [36].

Patented polysaccharides with a density of 0.05 - 0.4 g/ml and a porosity of less than 0.7, which are used for direct pressing as part of tablet dosage forms; they are obtained from starches isolated from corn, potatoes, rice, wheat, sorghum, dextrins. According to their physicochemical parameters and stability, they meet the requirements for the specified dosage form. A composition is known that simultaneously acts as a filler, binder, lubricant and lubricant in dosage forms of vitamin and multivitamin preparations. The specified composition is dry inactivated biomass of single-celled microorganisms, including dry biomass of purified brewer's yeast, dry biomass of single-celled spirulina algae. As a filler during direct pressing, the authors also suggest using chitin obtained from shrimp shells [34-36].

1.2.3 Excipients in the production of tablets by the method of wet granulation

In the process of making tablets by the method of wet granulation, fillers, disintegrants, binders, lubricants and lubricants are used.

Fillers (diluents) are used to obtain a certain weight of tablets, as well as if the amount of medicinal substance in tablets is small and when tableting potent and poisonous substances, in order to regulate some technological indicators [34-36].

Binders are used to improve the compression of tablet masses and increase the strength of granules and tablets. Often, they are used to moisten the mass to be granulated, because of this they are often called granulating agents. Depending on the properties of the substance, purified water, ethyl alcohol, starch paste of various concentrations, sugar syrup, as well as methylcellulose gels, etc. are used as binders [34, 39].

Recently, various types of polyvinylpyrrolidone (PVP), which differ in average molecular weight and, accordingly, physical properties, have been widely used in the pharmaceutical industry [38]. Along with potato, rice, and corn starch,

pregelatinized starch is also used. When in contact with water (temperature 20-25ºC), it has the ability to form a viscous gel, which has binding properties due to hydrogen bonds. These properties allow avoiding the traditional process of preparing starch paste when using corn and potato starch [38]. Hydroxypropyl cellulose is used as a binder [36]. The effectiveness of binders is determined by the concentration, viscosity, and size of macromolecular compounds [36, 40].

In the process of pressing medicinal substances, the porosity decreases and due to this, it becomes difficult for liquid to penetrate inside the tablet. To improve disintegration and dissolution, disintegrants are used, which ensure the mechanical destruction of tablets in a liquid environment, which is necessary for faster release of the active substance. Disintegrants are also used if the medicinal substance is insoluble in water or the tablets are able to cement during storage [34]. The effectiveness of the disintegrants is determined by:

- by determining the speed of absorption and the amount of absorbed water by a mixture of powders;
- disintegration time of tablets containing different concentrations of disintegrants;
- by determining the rate of swelling and the maximum water capacity of leavening agents by means of high-speed photography under a microscope [34].

Antifriction substances are used to reduce the friction that occurs between the particles and the surface of the press tool. According to their purpose, they are divided into sliding, lubricating and non-stick [35].

Lubricants improve the fluidity of granulate or powder, which is necessary for fast, accurate and uniform filling of the matrices of the tablet machine. They are fixed on the surface of particles or granules, eliminate their roughness and thus increase fluidity. Lubricants make it easier to push the tablets out of the matrices. They not only reduce friction at the contact areas, but also significantly facilitate the deformation of particles due to adsorption reduction of their strength. Anti-sticking substances are used to reduce the sticking of the mass to the punches and walls of

the matrixes of the tablet machine, they are also called anti-adhesive (or anti-sticking) [35].

Table 1.2

Most commonly used lubricants

in the production of tablets by the method of wet granulation

Slippery substance	Contents of the tablet (%)	Note
Calcium silicate	0,5 – 2	–
Powdered cellulose	1 – 2	Elcema®, Solka-Floc®
Magnesium carbonate	1 – 3	–
Magnesium oxide	1 – 3	–
Magnesium silicate	0,5 – 2	–
Silicon dioxide colloidal	0,05 – 0,5	Aerosil®, Carb-o-Sil®
Starch	2 – 10	–
Talc	1 – 10	Insoluble in water, but not hydrophobic

Traditionally, magnesium stearate, calcium stearate, and stearic acid are used as lubricants for granules. They are hydrophobic particles of a lamellar structure that surround the granules. As a disadvantage of such lubricants, we can note hydrophobization of the surface of the granules, as a result of which the adhesion of the granules to each other deteriorates during the pressing of the tablet mass, which can cause the need to increase the pressing pressure and lead to an increase in the time of disintegration of the tablets. To reduce the negative properties of the listed antifriction substances, they are recommended to be included in the tablet in an amount of no more than 1% [34-36]. The leading pharmaceutical enterprises of Ukraine are now using new substances from the group of lubricants.

Corrigents are added to tablets in order to improve their taste, color or smell, they also protect drugs from the destructive effect of light, increase their shelf life, with their help, you can mark the therapeutic group or isolate a drug containing a poisonous substance, give it a commercial appearance [34].

The complex of technological properties of auxiliary substances influences the overall properties of the mixture to be tableted and, as a result, the behavior of the granulate during the pressing process [36].

1.2.4 The influence of pressing modes on the quality of tablets

The conditions of tablet pressing affect their quality, as well as the wear and tear and durability of tablet machines. Masses to be tableted are characterized by various properties. The application of the provisions of the physico-chemical mechanics of dispersed systems to the process of tableting and the study of the deformation behavior of masses turned out to be fruitful in solving the problem of using structure formation and in regulating the process of obtaining tablets with specified physico-mechanical properties [19-33].

Pressing is a defining operation in the production of tablets. An important point in regulating the quality of tablets is the choice of pressing pressure. An increase in pressing pressure leads to a decrease in the volume of pores, the formation of bridging bonds between particles, an increase in strength and an increase in the time of tablet disintegration. During tableting, the pressed material receives a certain amount of energy. About 90% of mechanical energy is converted into thermal energy, and about 10% is accumulated by tablets in the form of voltage energy [25-33].

For each drug, the pressing pressure is selected individually and controlled by measuring the strength of the tablets and their disintegration time. Excessive pressing pressure often leads to delamination of tablets or an increase in their disintegration time [33].

Conclusions to section 1

1. A review of literature sources was conducted regarding the pharmacological properties of nonsteroidal anti-inflammatory drugs, methylsulfonylmethane, and chamomile extract.

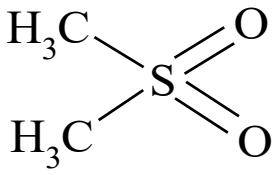
2. The expediency of creating a combined anti-inflammatory drug, which includes methylsulfonylmethane and thick chamomile extract, has been proven.

3. Tablets should be considered the most optimal medicinal form for creating the drug, which ensure the accuracy of dosage of active substances, convenience in using the drug, and stability during storage.

SECTION 2
RESEARCH OBJECTS AND METHODS
EXPERIMENTAL PART

2.1 Objects of research

Methylsulfonylmethane and thick chamomile extract, excipients, tablet masses, as well as developed combined tablets were selected as the research objects.



Methylsulfonylmethane

In order to develop the optimal composition and technology of combined tablets containing methylsulfonylmethane and thick chamomile extract, the following excipients approved for medical use were used:

- fillers: lactose monohydrate;
- substances that increase the strength of the solid dosage form (TSF): MCC;
- binders: purified water, povidone;
- lubricants and non-stick substances: calcium stearate, Aerosil;
- leavening agents: croscarmellose sodium.

Methylsulfonylmethane is colorless prismatic crystals, soluble in benzene, water, and ethanol [13-15].

Chamomile extract is thick - a thick ointment-like mass from light brown to dark brown in color with a green tint; the taste is bitter, the smell is characteristic of the initial raw material; soluble in alcohols and oils, insoluble in water [16-17].

Lactose monohydrate (EF 01/2002:1061) is a white or almost white, odorless, slightly sweet crystalline powder. Easily but slowly soluble in water, practically insoluble in alcohol, chloroform and ether [42].

MCC (EF 0316) is a white or almost white powder or granules, practically insoluble in water, ethanol, toluene [42].

Purified water (DFU I ed., p. 307) is a colorless transparent liquid without odor or taste, pH from 5.0 to 7.0 [41].

Povidone (DFU I ed., add. 1, p. 436) – white or yellowish-white powder or flakes; hygroscopic; easily soluble in water, 96% alcohol and methanol, slightly soluble in acetone [42].

Calcium stearate (EF 01/2002:0882) is a white powder without taste or smell, practically insoluble in water, slightly soluble in alcohol and organic solvents, soluble in oils [42].

Aerosil is a white, amorphous, non-porous, indifferent powder that is sprayed, does not dissolve in water, acids and diluted alkalis [42].

Croscarmellose sodium (EF 01/2002:0985) is a white or grayish-white powder, practically insoluble in water, alcohol, and toluene [42].

The solvents, reagents, and solutions used in the work met the requirements of the State Pharmacopoeia of Ukraine [41].

2.2 Methods of assessment of physico-chemical and technological properties of active substances, tablet masses and tablets

The physico-chemical and technological properties of powdered medicinal substances significantly affect the optimal tableting process and the quality of tablets (strength, disintegration, wearability, etc.) [40].

Substances for the production of tablets were evaluated according to such physicochemical and technological properties as the shape and size of particles, fluidity, and bulk density.

Technological properties such as fluidity and bulk density were studied for the manufactured tablet masses.

Tablets were evaluated according to such parameters as appearance, average mass, uniformity of mass, disintegration, wearability, etc.

2.2.1 Studying the shape and size of particles

Physico-mechanical characteristics of tablets and technological properties of tablet masses to be pressed are primarily determined by the shape and size of powder particles included in their composition, so the study of these indicators allows predicting a rational method of tableting [43].

The crystallographic properties of the powders were determined using optical crystallography and photomicrography using a microscope "Microphot D16B" at a magnification of ×110-250, which made it possible to characterize the shape and surface of the crystals, as well as the average linear size of the dominant particle fractions in accordance with the methodology developed at the State Scientific Center for Medicinal Products means [43].

For this purpose, a small amount of the powder under study was poured onto the surface of the object glass, then by turning the glass 180º, it was shaken by lightly tapping on the glass. The particles that remained on the glass were examined under a microscope and photographed. For a specific crystal, the correct geometric shape was selected from the photographs and its length and width were measured taking into account the magnification. The number of measurements was 150. To characterize the degree of isometricity of powders, the form factor K was calculated according to formula (2.1):

$$K = \frac{Ш}{Д}$$

- Ш – average width of particles, μm;
- D is the average length of particles, μm.

Powdered medicinal substances are divided into two classes according to the linear size and shape of the particles: isometric (K > 0.5), which are in the form of small or large spheres, ellipsoids, globules or plates, and anisometric (K < 0.5), which are in the form of small or large elongated prisms [43, 44].

With the help of a microscope, the size and nature of the surface of the particles was determined - smooth, slightly rough, rough.

In addition, the particle size was estimated by fractional composition by sieving 50.0 g of powder through a set of sieves with different diameters and hole shapes (hole diameters 0.5; 0.315; 0.2; 0.1; 0.09 and 0.071 mm) on vibration unit with the number of oscillations 340 – 360 min–1 for 5 minutes. The content of each sieve was weighed to the nearest 0.01 g, and the content of each fraction in the test sample was calculated as a percentage.

In accordance with the requirements of the State Federal Office of Ukraine, 1st ed., Art. 2.9.12, the granularity of the powder can be expressed by the corresponding sizes of the sieve openings, and it is determined by sieving through sieves with certain numbers and expressed in terms [41].

2.2.2 Determination of moisture content and moisture absorption

Moisture content is the content of moisture in the material, which significantly affects the fluidity and compressibility of powders. Materials subject to pressing and having an increased moisture content are characterized by low fluidity due to the formation of massive adsorption layers on the particles. Drying in this case increases fluidity. In case of insufficient moisture absorption, the force of adhesion of the particles to each other during the pressing process decreases and the strength of the tablets decreases. Therefore, the material to be tableted should have an optimal moisture content [23 – 31].

Optimal moisture is the maximum moisture content bound to the material by adsorption forces during the formation of polymolecular layers. For most materials, the residual moisture is 2-5% [23].

The moisture content is determined by drying the studied powder under certain conditions to a constant mass, then the loss in mass during drying is related to the initial mass and expressed as a percentage [41].

The moisture content of active substances and granules for the production of tablets was determined using an express moisture meter made on the basis of torsion scales of the VT-500 type. Method of determination: first, the balancer of the scales was adjusted to the zero point with the help of the balancer lever, then approximately 0.2 g of the substance under study was weighed in the measuring cup and the electric lamp located under the cup was turned on. During the drying process, as a result of moisture evaporation, the balancer deviated from the zero level, so it was regularly brought to zero with the help of a lever. The end of drying was considered the position at which the balancer remains at the zero point, regardless of the duration of further drying. At the same time, the mass of the dried material was recorded. The moisture content of the material ω was determined by the formula (2.2):

$$\omega = \frac{G_{вол} - G_{сух}}{G_{вол}} \cdot 100\%,$$

 Gvol – mass of material to be dried, g;

 Gcyx – mass of dried material, g.

Moisture absorption is a parameter that determines the choice of technology, as well as the storage conditions of the drug [27].

To study the moisture absorption of powders, granules, and tablets, they were introduced in bags to a desiccator, in which a constant relative humidity of 100% was maintained at a temperature of 20°C. The relative humidity of the air was created with water.

After certain time intervals, samples of the investigated substances were taken from the boxes and their moisture content was determined using an express moisture meter, made on the basis of torsion scales type VT-500.

2.2.3 Determination of turnover

One of the most important parameters that radically affects the properties of the tablet mass and, as a result, the choice of tablet technology, is the fluidity of powders. Fluidity was determined using the funnel method with a vibrating device (DFU I ed., Article 2.9.16, N) [41].

In a dry funnel with a diameter of the outlet opening of 10 cm and an angle of 60°, the outlet opening of which is closed by a valve, a weighing amount of the substance under investigation or granules was placed, the vibrating device was turned on, and after 20 s the outlet opening was opened and the time for the complete outflow of the powder from the funnel was recorded. Fluidity is expressed in seconds and tenths of a second per 100 g of the sample.

2.2.4 Determination of the angle of natural slope

When pouring loose material from a funnel onto a horizontal surface (see item 2.2.3), it crumbles, taking on the appearance of a cone-shaped slide. The angle between the forming cone and the horizontal plane is called the angle of natural slope; it was determined using a protractor. Also, the angle of the natural slope can

be determined by the geometric method by measuring the height of the hill and the diameter of the base of the cone.

Thus, the angle of the natural slope is an additional characteristic of the fluidity of the powdered material or granulate. For well-flowing materials, its value is 25-30º, for low-flowing materials - 60-70º [28].

2.2.5 Determination of bulk volume

The bulk volume was determined by freely pouring 100 g (m is the weight of the test substance, g) of the substance under study into a graduated glass cylinder, which was fixed on the appropriate device. The bulk volume V0 was fixed. 10, 500, 1250 shakings of the cylinder were carried out and volumes V10, V500, V1250 were recorded with accuracy to the nearest mark. If the difference between V500 and V1250 exceeded 2 ml, another 1250 cylinder shakes were performed. The device should provide 250 ± 15 shakings of the cylinder per minute from a height of 3 ± 0.2 mm. Determined:

A) volumes:

 bulk volume – volume before shrinkage V0, ml;

 volume after shrinkage – V1250 or V2500, ml;

B) shrinkage capacity: the difference in volumes of V10, ml and V500, ml;

C) densities:

 bulk density – density before shrinkage m/V0, g/ml;

 density after shrinkage - m/V1250, g/ml or m/V2500, g/ml (DFU I ed., Article 2.9.15) [41, 45].

2.2.6 Definition of compressibility

Compressibility is an indicator of the ability of powder particles to be cohesive under pressure, that is, the ability of particles to

by the action of forces of an electromagnetic nature (molecular, adsorption, electrical) and mechanical engagements to mutual attraction and adhesion with the formation of a stable, strong compressed product [32].

Compressibility was characterized by the strength of the model tablet after the pressure was removed. The better the compressibility of the powder, the higher the

strength of the tablet. If the compressibility is poor, the tablet is formed weakly, and sometimes completely collapses when pushed out of the matrix.

It is established that for substances with the strength of tablets:

 above 70 N/cm2 pure solvents are used for the granulation process; if these are coarse powders with good flowability, they are pressed directly, that is, by direct pressing;

 40 – 70 N/cm2 is enough to use ordinary binders;

 10 – 40 N/cm2, it is necessary to use highly effective binders [30].

Based on the results of determining the compressibility of tablet masses, a conclusion is drawn about the technology of tableting [19-33].

There are no direct methods for determining compressibility.

To determine the compressibility, a weight of powder (granules) weighing 0.3 g was pressed in a matrix using punches with a diameter of 9 mm on a hydraulic press (pressure 120 MPa), after which the strength of the obtained tablet was determined on the TVT model device of the Erveka company (Germany) and expressed in N/cm2.

2.2.7 Determination of the pushing force

The force of pushing the pressed tablet out of the matrix characterizes the force of friction and adhesion between the side surface of the tablet and the wall of the matrix and allows predicting the addition of antifriction substances to the tablet mass [32, 33].

To determine the pushing force, a weight of powder (granules) weighing 0.3 g was pressed in a matrix using punches with a diameter of 9 mm on a hydraulic press (pressure 120 MPa). When the tablet was pushed out with the lower punch, the reading of the manometer was recorded.

2.2.8 Definition of appearance

The appearance of the tablets was determined visually in daylight by viewing them on a white background.

2.2.9 Definition of homogeneity of mass

The tests were carried out in accordance with DFU II ed., Art. 2.9.5 [45].

20 tablets were selected according to a statistically justified scheme, each was weighed separately and the average weight was calculated. Tablets pass the test if no more than two individual weights deviate from the average weight by a value that exceeds □7.5%. At the same time, no individual mass should deviate from the average mass by more than □15%.

2.2.10 Determination of abrasion

The tests were carried out in order to find out the resistance of the tablets to mechanical impact or abrasion. When determining abrasion resistance, a drum-type device with one blade was used as described in DFU II ed., Art. 2.9.7 [45]. 20 tablets were taken for the test. The tablets were dedusted and weighed to the nearest 1 mg before and after the experiment. Abrasion (Ms) is expressed as a loss in mass, calculated as a percentage according to the formula (2.3):

$$M_c = 100 - \frac{P_0 - P}{P} \cdot 100$$

□ P0 – mass of tablets before the start of the experiment, g;

□ P is the mass of tablets after the end of the experiment, g.

Tablets passed the test if there were no chips or cracks on them, and the amount of abrasion did not exceed 1%.

2.2.11 Determination of tablet disintegration

The study of the disintegration of tablets was carried out according to the methodology given in DFU II ed., Art. 2.9.1 [45] on the laboratory identifier of the decay process 545R-AK-1 (MZTU). The temperature was maintained at 35-39°C, the device was turned on for 15 minutes. Tablets passed the test if all six tablets disintegrated after the device was turned off.

Conclusions to section 2

1. This section shows that methylsulfonylmethane and thick chamomile extract, excipients, tablet masses, and developed combined tablets were chosen as research objects.

2. To create the medicinal product, auxiliary substances were used that are quite widely used in the domestic production of pharmaceuticals and meet the requirements of regulatory documents.

3. Reasonably selected methods of studying the properties of substances: crystallographic (shape, size of particles, as well as the nature of their surface), physico-chemical (moisture content and moisture absorption), technological (flowability, angle of natural slope, bulk volume and density, compressibility, strength pushing out), which became the basis for the development of an effective drug.

4. To obtain the dosage form and ensure the necessary quality of the developed tablets, modern research methods and devices were used, which allow determining the quality indicators of the tablets based on their compliance with the requirements of regulatory documents.

SECTION 3
DEVELOPMENT OF COMPOSITION AND PRODUCTION TECHNOLOGY COMBINED TABLETS CONTAINING METHYLSULFONYLMETHANE AND CHAMOMILE EXTRACT THICK

3.1 Justification of the composition of combined tablets with anti-inflammatory effect

The effectiveness and safety of medicines depends on the influence of many factors, which are closely related to each other. Among them, it is possible to highlight the correct selection of active and auxiliary substances, rational technology, and storage conditions. One of the most important criteria is the ability of active substances to have the most targeted effect on the damaged parts of the body, as well as the properties of auxiliary substances that provide such ability [1-15].

The combination of several active substances with different pharmacological properties allows at the same time to positively influence several links of the pathological process, reduce therapeutic doses of active substances, avoid polypharmacy, which makes it possible to significantly reduce the time required for treatment and improve the patient's quality of life [1-15].

Research aimed at substantiating the composition of a combined medicinal product should begin with the selection of active substances and the optimal form of release of the drug, taking into account its specific activity. The next stage of work should be the selection of the optimal concentration of active substances, which would provide the necessary pharmacological properties. After that, auxiliary substances should be selected, which should ensure proper bioavailability of active ingredients, technological properties and stability of the drug during the entire storage period [19 – 32].

We chose to create combined tablets with an anti-inflammatory effect, which included methylsulfonylmethane and thick chamomile extract.

In order to choose the optimal composition, a study of the sources of scientific literature was conducted and the following composition of the indicated medicinal product was proposed:

Methysulfonylmethane 250 mg

thick chamomile extract 70 mg

3.2 Study of physicochemical and technological properties of active substances

The choice of the method of obtaining tablets depends on the main physico-chemical and technological characteristics of powders of active substances, which are determined by their physical properties (shape and size of particles, moisture, etc.).

In order to choose a rational way of carrying out the technological process, we investigated the crystallographic characteristics and fractional composition of methylsulfonylmethane. The research methodology is given in clause 2.2.1.

According to crystallography, methylsulfonylmethane is a coarse crystalline colorless powder with transparent particles of anisodiametric form; particle size from 600x450 microns to 200x100 microns (Fig. 3.1).

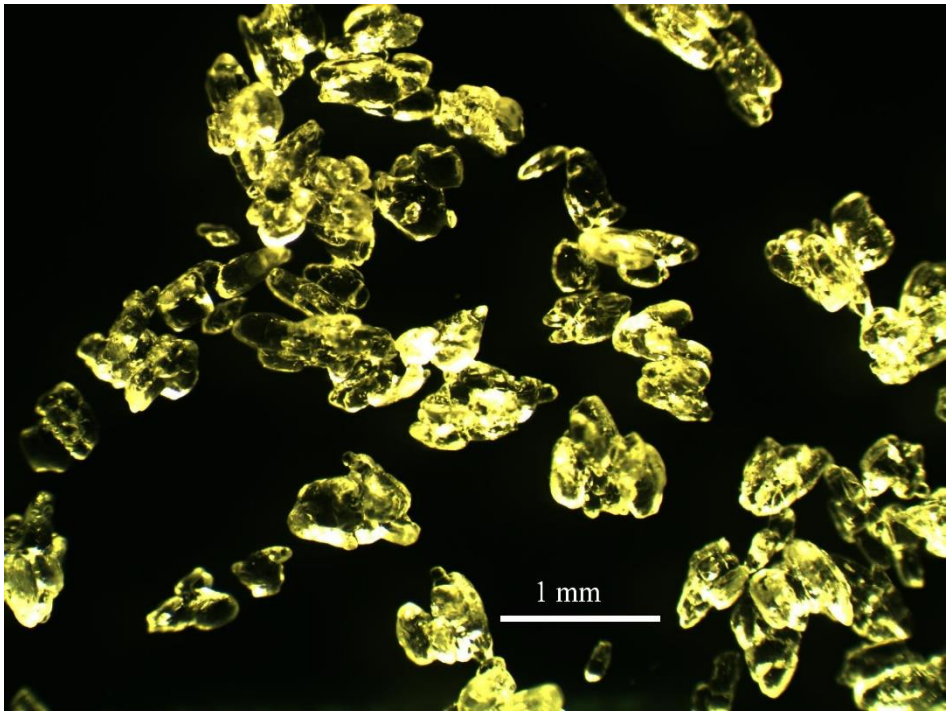


Fig. 3.1. Photomicrograph of methylsulfonylmethane powder

The next stage of research was the study of the fractional composition of methylsulfonylmethane powder. The fractional composition of powders affects their technological properties (flowability, compressibility), as well as the strength and average weight of tablets, the accuracy of dosage of the medicinal substance, and the quality of the tablets obtained. Non-granular powders are characterized by a polyfractional composition. The size distribution of methylsulfonylmethane powder particles is shown in Fig. 3.2 (taking into account the obtained crystallographic characteristics of methylsulfonylmethane powder, sieves with hole diameters of 0.315 and 0.2 mm were used in the experiment).

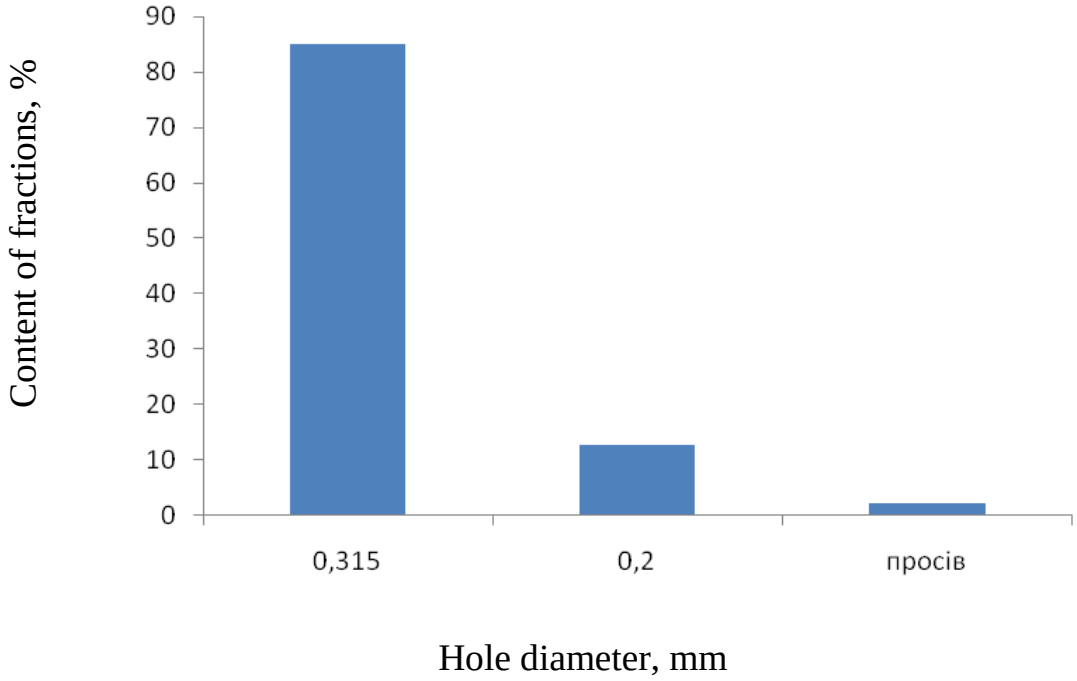


Fig. 3.2. Fractional composition of methylsulfonylmethane powder

Analyzing fig. 3.2, it can be concluded that for methylsulfonylmethane powder, the distribution of particles obeys the exponential law of distribution, that is, the number of the largest particles reaches approximately 90%, and then there is a decrease in both particle sizes and their quantities.

The study of the shape and size of particles, as well as the fractional composition of methylsulfonylmethane allows predicting the introduction of auxiliary substances from the group of antifriction agents into the composition of TLF to improve the fluidity of the tablet mass.

The moisture absorption of the powder of the active substances is of essential importance for the rational choice of auxiliary substances.

In fig. 3.3 shows the graph of the dependence of moisture absorption of the investigated methylsulfonylmethane powder on time at a relative humidity of 100%.

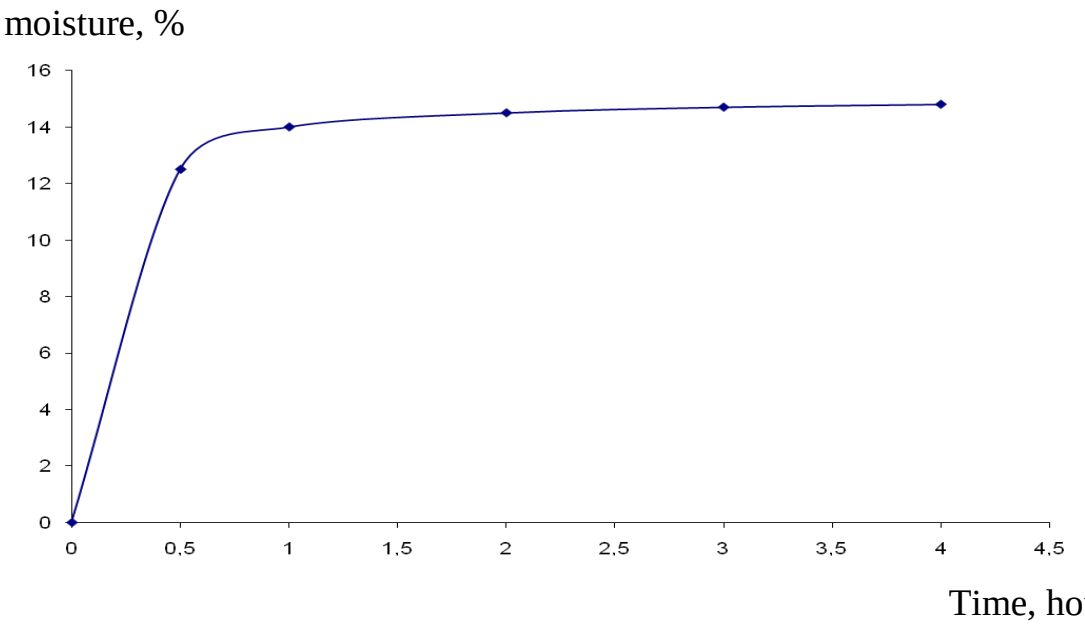


Fig. 3.3. Dependence of moisture absorption of methylsulfonylmethane on time

The data in Fig. 3.3 indicate the possibility of the formation of wet masses during storage and allow predicting the choice of some auxiliary substances. In addition, this indicator affects the fluidity and pressability of powders.

In the table 3.1 shows the technological properties of methylsulfonylmethane powder.

The obtained results indicate that methylsulfonylmethane belongs to the light class in terms of bulk density, the fluidity of methylsulfonylmethane is satisfactory.

In order to eliminate the rapid wear of the press tool of tablet machines, as well as to obtain tablets without mechanical defects, it is necessary to introduce lubricating and anti-sticking substances into their composition [34-36].

Thus, the conducted studies on the study of the physical, chemical and technological properties of powders of active substances showed the need to

introduce fillers, binders, disintegrants and substances that increase the strength of the solid dosage form into the composition of the dosage form.

Table 3.1

Technological properties of methylsulfonylmethane powder

Indicator	The result of the determination
Moisture content, %	1,42±0,01
Fluidity, s / 100 g pouring method with a vibrating device	7,15±0,07
The angle of a natural slope, the method of a watering can with a vibrating device	30,15±2,07
Bulk volume V_0, мл / 100 г	151,52±12,17
Volume after shrinkage V_{1250}, мл / 100 г	128,79±2,47
Ability to shrink, мл / 100 г	10,61±1,24
Bulk density m/V_0, г/мл	0,66±0,05
Density after shrinkage m/V_{1250}, г/мл	0,78±0,02

Note: n = 5, P = 95%

3.3 Development of technology of combined tablets

Biopharmaceutical studies of medicinal products conducted recently show that with the optimal selection of auxiliary substances, it is possible not only to ensure the maximum effectiveness of active substances, but also, in some cases, to enhance the effect of the injected substance or reduce the negative impact on the body as a whole [34-36] . The therapeutic effect of the drug is the result of the influence of a complex of factors, which depend on the completeness and speed of release, pharmacodynamics and pharmacokinetics of active substances. When carrying out a theoretical justification of the composition of a new drug, it is impossible to predict the influence of all factors, therefore research, first of all, should be based on the application of experimental works using various methods. The expediency of introducing each component, its concentration in the composition of the drug must be thoroughly proven and substantiated.

When developing a medicinal product, it is necessary to take into account the following requirements regarding the manufacturability of its production:

 the production technology must be reproducible and reliable with the exclusion of factors that can negatively affect the process;

 it is desirable that the number of production stages be minimal;

 the process of manufacturing the drug should be as energy-intensive as possible, using a small amount of equipment.

Simultaneous compliance with the above requirements is a systematic approach to the development of a new medicinal product.

3.3.1 Selection of excipients and development of the composition of combined tablets

The low flow rate of methylsulfonylmethane (see Table 3.2) and the presence of a thick plant extract in the composition of the tablets determine the choice of appropriate auxiliary substances and the technology of obtaining tablets - the method of wet granulation.

Based on the features and specifics of the wet granulation method and the existing arsenal of auxiliary substances, the following ingredients were introduced into the composition of the tablets: lactose, collidon, microcrystalline cellulose, croscarmellose sodium, aerosil, calcium stearate - the composition and technological properties of the obtained tablet mass are given in the table. 3.2.

Table 3.2

Composition and technological properties of tablet mass and tablets (wet granulation method, 12 mm, flat-cylindrical)

Name	Content in 1 tablet, g	Contents, %	bulk density m/V_0, г/мл	Fluidity, s / 100 g (immovable method watering cans)	Pressing capacity, H	Disintegration, c
Methylsulfonylmethane	0,2500	31,25	0,40±0,02	12,67±1,43	62,67±6,25	245,33±12,5
Chamomile extract is thick	0,0700	8,75				
Lactose	0,3476	43,45				
Kolydon	0,0024	0,30				
MKC	0,0960	12,00				
Sodium croscarmellose	0,0220	2,75				
Aerosil	0,0040	0,50				
Calcium Stearate	0,0080	1,00				

Note: n = 5, P = 95%

The process of obtaining a tablet mass was carried out in the following sequence: the powder of the mixture of active substances was moistened with a binding solution and mixed until homogeneity. The optimal amount of humectant was determined experimentally by adding it to obtain a moist compact mass that is freely granulated. The wet mass was granulated through a sieve with a hole size of 1 mm. Granules were dried in a drying cabinet. The dried granules were subjected to granulation again through the same sieve. Next, the granules were powdered with a mixture of aerosol and calcium stearate and tableted.

From the data given in the table. 3.2, we can see that the method of wet granulation in the production of combined tablets leads to obtaining a tablet mass that meets the requirements for all the investigated indicators.

Thus, we proposed the composition of tablets per tablet:

Methylsulfonylmethane - 250 mg
Thick chamomile extract - 70 mg
Excipients:
Lactose - 347.6 mg
Kolydon - 2.4 mg
Microcrystalline cellulose - 96 mg
Croscarmellose sodium (primrose) - 22 mg
Aerosil - 4 mg
Calcium stearate - 8 mg
The weight of the tablet is 800 mg

3.3.2 Studying the parameters of granulate drying for the production of tablets

When developing the technology of combined tablets, we determined the optimal conditions for granulate drying, namely the temperature and duration of drying.

A graphic representation of the process of drying granules in a fluidized bed dryer is shown in Fig. 3.4.

From Fig. 3.17, we can see that the decrease in the moisture content of the granulate occurs intensively during the first 15 minutes. according to the straight-line law. Then the drying process slows down, the linear law of moisture loss is violated, and after 20 min. from the beginning of the experiment, the moisture

content of the granulate approaches the equilibrium moisture content of 1.5-2.0%, and further removal of moisture from the granulate is observed. Therefore, the drying time of the granulate to the optimal residual moisture content of 1.5-2.0% is 20 minutes.

3.3.3 Study of modes of pressing tablet mass to obtain tablets

The wearability and disintegration time of the tablets are somewhat dependent on the amount of pressing pressure. When determining the optimal pressing pressure, it is necessary to obtain tablets in a certain range of pressures and choose such pressing conditions under which the obtained tablets meet the requirements in terms of rubability and disintegration time, and, therefore, in terms of therapeutic effectiveness. Therefore, to establish the optimal pressing pressure, tablets were pressed from the tablet mass on a hydraulic press in the pressure range of 40-140 MPa. The obtained tablets were studied for their appearance, wearability and disintegration in accordance with those indicated in Sect. 2 methods.

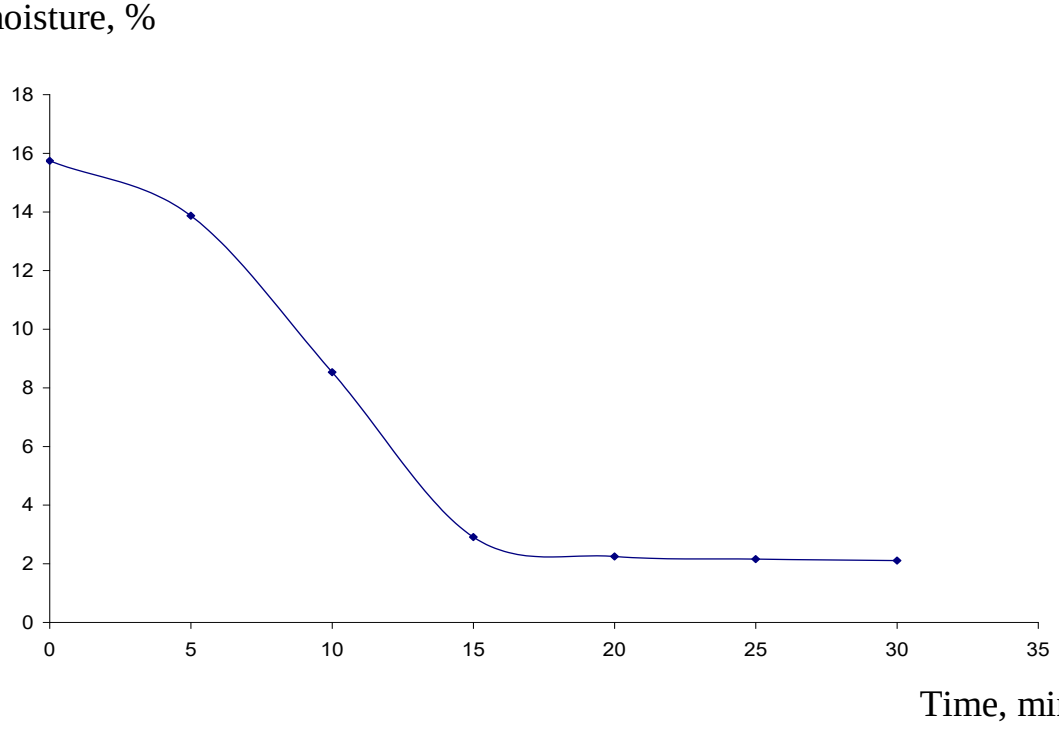


Fig. 3.4. Kinetics of drying granules to obtain tablets in a fluidized bed dryer at a temperature of 75±5ºC

The results of research on establishing the optimal tablet pressing pressure are shown in table. 3.3, from which it can be seen that with an increase in pressing

pressure, abrasion decreases and disintegration time increases. At the same time, it was established that tablets with satisfactory physico-chemical and technological properties can be obtained in the pressure range of 60-100 MPa.

Table 3.3

Dependence of eraseability and disintegration time of the obtained tablets from pressing pressure

№ п/п	Pressing pressure, МПа	Erasure, %	Disintegration, с
1	40	1,2±0,1	150±5
2	60	0,8±0,1	240±5
3	80	0,7±0,1	250±5
4	100	0,7±0,1	360±5
5	120	0,6±0,1	390±5
6	140	0,4±0,1	420±5

Note: n = 5, P = 95%

3.4 Description of the technological process of tablet production

The technological scheme of tablet production is shown in fig. 3.5. It consists of two stages of auxiliary works, five stages of the main technological process (obtaining tablet mass, tableting and dedusting) and three stages of filling and packing tablets.

Stage 1. Preparation of raw materials. Each batch of raw materials (primary and auxiliary) and packaging materials before use in production is subject to control for compliance with regulatory documents. First, the active substances and auxiliary substances are weighed in series in tared and marked collections Z 2.1, Z 2.2, Z 2.3, Z 2.4, Z 2.5, Z 2.6, Z 2.7, Z 2.8 on KP 1 scales, sieved through a sieve GF 3 with the corresponding hole diameter in tared marked collections C 6.1,

C 6.2, C 6.3, C 6.4, C 6.5, C 6.6, C 6.7, C 6.8 and weighed on KP scales 5.

Stage 2. Preparation of moisturizer. In collection Z 7, load KP 5 collidon and thick chamomile extract from collections Z 6.2, Z 6.4 weighed on scales, measure the required amount of purified water into measuring cup M 8, thoroughly mix the mixture for 20 minutes. until complete dissolution. The prepared humidifier is sent to the collection 3 10.

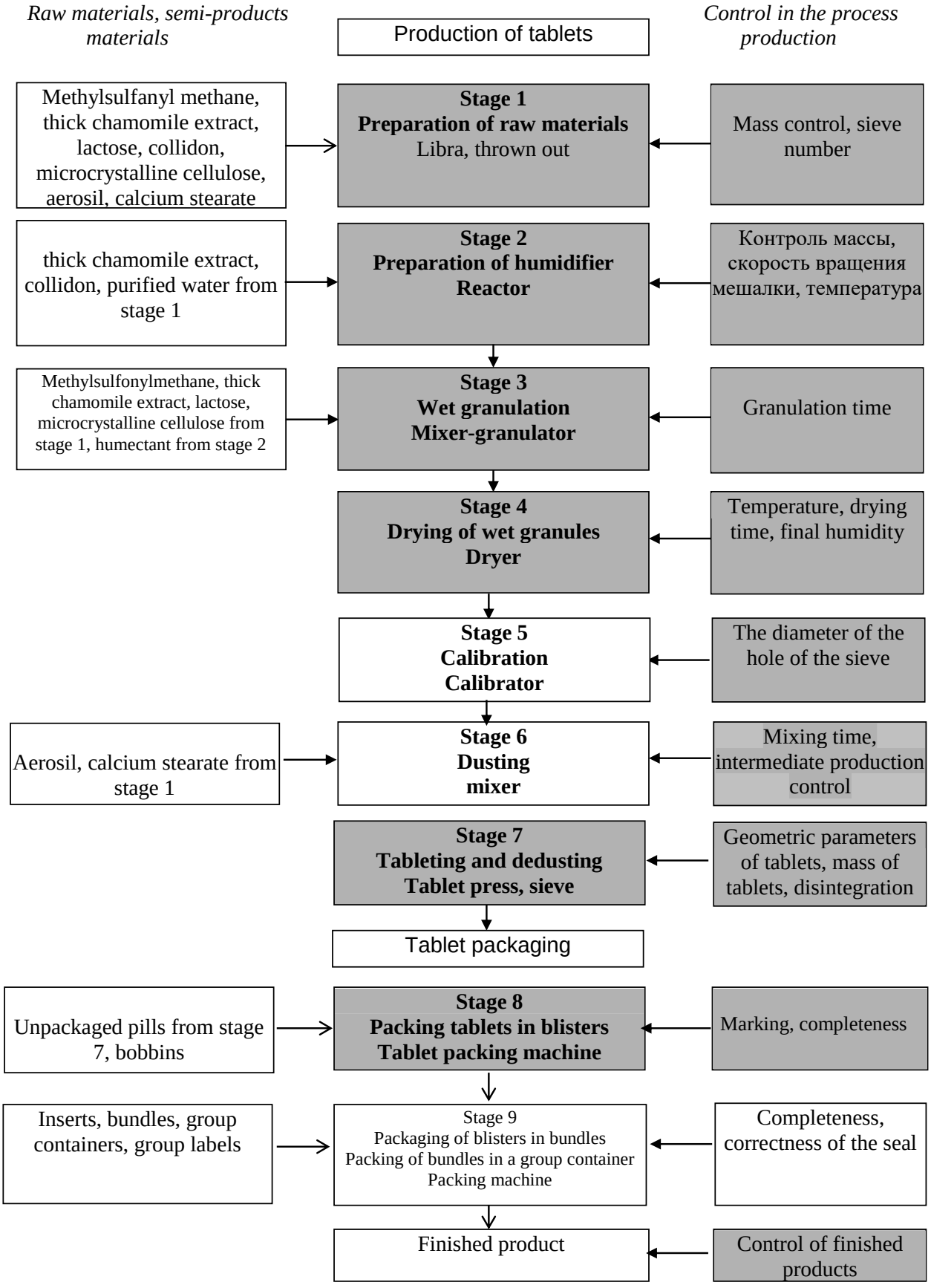


Fig. 3.5. Technological scheme of the production of combined tablets with methylsulfonylmethane and chamomile extract

Stage 3. Wet granulation. Mixing and moistening of the mass is carried out in the granulator-mixer GF 11 with working supply and exhaust ventilation. Methylsulfonylmethane, lactose, microcrystalline cellulose, croscarmellose sodium from collections Z 6.1, Z 6.3, Z 6.5, Z 6.6, sifted and weighed on KP 5 scales, are loaded into the GF 11 mixer. Stirring is carried out for 10±1 min. Add a moisturizer to the dry ingredients and mix for 10±1 min. to uniform distribution of moisture in the entire mass, the latter must be homogeneous, well-moisturized and must clump when squeezed in the hand. Wet granulation is carried out through a granulator with a hole diameter of 1.0 mm. The wet granulate is sent to the collector 3 12.

Stage 4. Drying of wet granules. Wet granulate is dried in a GF 13 fluidized bed dryer at a temperature of 75±5°C for 20 minutes. to residual humidity of 1.5 - 2.0%. 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 is determined with a moisture meter. The dry mass is sent to the collection 3 14.

Stage 5. Calibration of granules. From the collector 3 14, the dry granulate is passed through the GF 15 granulator with a hole diameter of 1.0 mm, collecting the granules in the collector Z 16.

Stage 6. Powdering. The resulting granules from collection 3 16 are introduced into the mixer GF 17, sieved and weighed on KP 5 scales calcium stearate from collection C 6.7 and aerosols from collection C 6.8 are added and dusting is carried out for 5±1 min. The mass is sent to collection point 3 18.

Stage 7. Tableting and dedusting. The powdered granulate is fed to the hopper of the GF 19 tablet machine with the punch diameter of 12 mm of flat-cylindrical shape and tableting is carried out. Tablets with an average weight of 0.8000 g ± 7.5% (from 0.7400 to 0.8600 g), a diameter of 12 ± 0.1 mm and a height of 7.8 ± 0.2 mm are obtained. In the process of work, they periodically check the appearance, mass of tablets, their abrasion, disintegration. Tablets are dedusted using the built-in device of the tablet machine. Ready tablets are collected in collection 3 22. Non-standard tablets are placed separately in collection 3 20 and sent for disposal.

Conditioning tablets are weighed on KP scales 21 and transferred to packaging in tared collections 3 22.

Stage 8. Packing tablets into blisters. Tablets are packaged 10 or 20 pieces in blisters (contour blister packs) according to OST 64-074-91 from polyvinyl chloride film of the "PVC" brand produced by the company "ONGROPACK KFT" (Hungary) or EP-73 polyvinyl chloride film produced by Kleckner Pentaplast Rus LLC. (Russia) and foils of lacquered rolled aluminum with one-sided coating with thermal varnish according to TU U 27.4-30776684-001-2004 of the company "Altrade" (Ukraine) or of the company "Ashu International" (India). The second side of the film is marked with printing ink produced by the company "Fisat sun chemical group S.p.A" (Italy).

Stage 9. Packing blisters into bundles. Two contour blister packs of 10 tablets (№10x2) or one contour blister pack of 20 tablets together with an insert sheet made of label paper according to GOST 7625-86 are placed in a pack made of chrome ersatz "Alaska" cardboard produced by the company "Rarer- Kwindzyn s. a." (Poland). At this stage, the drug is controlled for microbiological purity according to DFU and analyzed according to the main indicators.

Stage 10. Packing of bundles in group containers. The packs are placed in cardboard boxes in accordance with the requirements of GOST 17768-90 and the tablets are transferred to the quarantine warehouse.

3.5 Technological tests of combined tablets

According to DFU [70, 74, 89], the appearance, average mass, mass uniformity, disintegration, and eraseability were determined for the developed tablets [90 – 92].

Description. Flat-cylindrical tablets from light yellow to gray-yellow with a brownish tint. There are specks of different sizes and colors on the surface.

This appearance of the tablets is due to the presence of yarrow extract.

In terms of appearance, the tablets must meet the requirements of the DFU II ed., Art. "Tablets", p. 263 [74].

Average weight. The limits of the average mass should be from 740 mg to 860 mg.

Samples of tablets must meet the requirements of the State Federal Office of the Russian Federation II ed., Art. 2.9.5. The deviation of the average weight of the tablet from the nominal should not exceed □7.5% [74].

Homogeneity of mass. There should be no more than 20 tablets to be tested

2 tablets having a deviation from the average weight of more than □7.5%, there should not be a single tablet having a deviation from the average weight of more than □15%.

Tests are performed for each of 20 tablets according to the DFU method

I.I ed., Art. 2.9.5 [74].

Disintegration Tablet disintegration time when using guide discs should not exceed 15 minutes.

Samples of tablets must meet the requirements of the State Federal Office of the Russian Federation II ed., Art. 2.9.1 and

Art. "Tablets", p. 263 [74].

Erasure. Abrasion should not be more than 1%.

Samples of tablets must comply with the State Federal Office of the Russian Federation II ed., Art. 2.9.7 [74].

Dissolution. This test is according to the requirements of DFU I.I d., Art. 2.9.3 [74] should be used to determine the degree of release of active substances from the tablet; a 0.1 M solution of hydrochloric acid is used as a dissolution medium. The amount of active substances that passed into the dissolution medium after 45 minutes should be at least 75% and not more than 115% of the nominal content specified in the "Composition" section.

Conclusions to section 3

1. The composition of the tablet mass was investigated and the use of the wet granulation method for obtaining the proposed tablets was experimentally substantiated.

2. The crystallographic, physicochemical and technological properties of methylsulfonylmethane powder were studied.

3. The study of the kinetics of drying in a fluidized bed dryer made it possible to set the drying time - 20 min. - at a temperature of 75±5°C to a residual moisture of 1.5-2.0%.

4. Based on the study of physico-chemical and technological properties of tablet masses, a rational composition and technology of tablets were developed.

GENERAL CONCLUSIONS

1. Modern literature data on the pharmacological properties of non-steroidal anti-inflammatory drugs were analyzed and summarized, the feasibility of creating a combined anti-inflammatory drug based on methylsulfonylmethane and thick chamomile extract in the form of a tablet, which ensures the accuracy of dosage of active substances, ease of use of the drug, and stability during storage, was proven.

2. Based on the results of physico-chemical, technological and pharmacological studies of active substance substances, auxiliary substances were selected - it is suggested to use microcrystalline cellulose, croscarmellose sodium, lactose, collidon, aerosil and calcium stearate; the composition of combined tablets is substantiated.

3. The study of the kinetics of drying in a fluidized bed dryer made it possible to set the drying time - 20 min. - at a temperature of 75±5°C to a residual moisture of 1.5-2.0%.

4. Based on the study of physico-chemical and technological properties of tablet masses, a rational technology of combined tablets was developed.

5. Taking into account the unstable financial and economic situation and the presence of a somewhat developed production base for the production of domestic NSAIDs, it is necessary to reduce the dependence of the market on the import of these drugs.

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National University of Pharmacy

Faculty for foreign citizens' education
Department department drug technology

Level of higher education master

Specialty 226 Pharmacy, industrial pharmacy
Educational program Pharmacy

APPROVED
The Head of Department
department drug technology

Liliia VYSHNEVSKAYA
"_28_" _september_ 2022

ASSIGNMENT
FOR QUALIFICATION WORK
OF AN APPLICANT FOR HIGHER EDUCATION

Basma EL MAIDEN

1. Topic of qualification work: «Pharmacotechnological studies of methylsulfonylmethane tablets with chamomile extract», supervisor of qualification work: Mykhailo MARCHENKO, PhD, assoc. prof.,

approved by order of NUPh from "6st" 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: The work is devoted to the development and research of a combined anti-inflammatory tablet medicine with methylsulfonylmethane and chamomile extract.

4. Contents of the settlement and explanatory note (list of questions that need to be developed): analyze and summarize data from modern literary sources related to the treatment of inflammatory processes; conduct an analysis of the pharmaceutical market of Ukraine and establish the feasibility of creating a combined drug for the treatment of the corresponding pathology; on the basis of the conducted complex of physico-chemical and biopharmaceutical studies, theoretically substantiate and experimentally develop a rational composition of anti-inflammatory tablets; to study the stability, conditions and shelf life of the studied tablets.

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

6. Consultants of chapters of qualification work

Chapters	Name, SURNAME, position of consultant	Signature, date	
		assignment was issued	assignment was received
1	Mykhailo MARCHENKO, associate professor of higher education institution of department department drug technology	28.09.2022	28.09.2022
2	Mykhailo MARCHENKO, associate professor of higher education institution of department department drug technology	17.11.2022	17.11.2022
3	Mykhailo MARCHENKO, associate professor of higher education institution of department department drug technology	19.12.2022	19.12.2022

7. Date of issue of the assignment: «28» september 2022

CALENDAR PLAN

№ з/п	Name of stages of qualification work	Deadline for the stages of qualification work	Notes
1	Topic selection	september 2022 p.	**done**
2	Literature data analysis	october 2022 p.	**done**
3	Conducting experimental research	october-desember 2022 p.	**done**
4	Work design	january-march 2023 p.	**done**
5	Submission of finished work to the commission	april 2023 p.	**done**

An applicant of higher education _____ Basma EL MAIDEN

Supervisor of qualification work _____ Mykhailo MARCHENKO

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 аптечної технології ліків**				
Ель Маіден Басма	Фармакотехнологічні дослідження таблеток метилсульфонілметану з екстрактом ромашки	Pharmacotechnological studies of methylsulfonylmethane tablets with chamomile extract.	доц. Марченко М. В.	доц. Азаренко Ю.М.

Підстава: подання декана, візка 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

№ 112414 від «20 » квітня 2023 р.

Проаналізувавши випускну кваліфікаційну роботу за магістерським рівнем здобувача вищої освіти денної форми навчання Ель Маіден Басма, 5 курсу, 8 групи, спеціальності 226 Фармація, промислова фармація, на тему: «Фармакотехнологічні дослідження таблеток метилсульфонілметану з екстрактом ромашки / Pharmacotechnological studies of methylsulfonylmethane tablets with chamomile extract», 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**

5%
29%

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

Basma EL MAIDEN

on the topic: «Pharmacotechnological studies of methylsulfonylmethane tablets with chamomile extract»

Relevance of the topic. The qualification work was made according to the plan of scientific work of the National University of Pharmacy and is dedicated to the study of anti-inflammatory tablets.

Practical value of conclusions, recommendations and their validity. The practical value of the work is based on the study of the physicochemical, pharmaco-technological properties of substances for the treatment of inflammatory processes, in order to organize the industrial production of the drug under appropriate conditions, taking into account the optimal parameters for the technological processing of raw materials, semi-finished products and obtaining products of the required quality.

Assessment of work. The applicant for higher education fulfilled the purpose and objectives of the research in full. The work deserves a positive evaluation.

General conclusion and recommendations on admission to defend. the qualifying paper, completed by the applicant for higher education Basma EL MAIDEN, can be submitted for official defense to the Examination Commission of the National University of Pharmacy.

Scientific supervisor _____ Mykhailo MARCHENKO

«12» 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

Basma EL MAIDEN

on the topic: «Pharmacotechnological studies of methylsulfonylmethane tablets with chamomile extract»

Relevance of the topic. The qualifying work was carried out on the basis of theoretical provisions and experimental studies on the development and study of the composition of anti-inflammatory tablets.

Theoretical level of work. An applicant for higher education conducted a review of modern sources of literature related to the theoretical aspects of the development of drugs for the treatment of inflammatory processes. An analysis of the pharmaceutical market of Ukraine of drugs of the relevant groups was carried out, the expediency of creating tablets for the treatment of pathology was established.

Author's suggestions on the research topic. The composition and technology of the drug in the form of tablets have been developed theoretically and experimentally. Their physico-chemical and biopharmaceutical studies were carried out, stability during storage was studied.

Practical value of conclusions, recommendations and their validity. It consists in the creation of combined anti-inflammatory tablets based on methylsulfonylmethane with chamomile extract.

Disadvantages of work. There are spelling errors and technical errors in the content of the work.

General conclusion and assessment of the work. The qualification work of Basma EL MAIDEN can be submitted for defense to the Examination Commission of the National Pharmaceutical University for the assignment of the master's educational qualification level.

Reviewer _____ assoc. prof. Yulia AZARENKO

«19» of April 2023

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ВИТЯГ З ПРОТОКОЛУ № _9_
«26» квітня 2023 року
м. Харків

засідання кафедри
___ *аптечної технології ліків* _____
(назва кафедри)

Голова: завідувачка кафедри, професор Вишневська Л.І.
Секретар: докт. філ., асистент Коноваленко І. С.

ПРИСУТНІ:

Богуцька О. Є., Зуйкіна С. С., Ковальова Т. М., Крюкова А. І., Марченко М. В., Половко Н. П., Семченко К. В.

ПОРЯДОК ДЕННИЙ:

1. Про представлення до захисту кваліфікаційних робіт здобувачів вищої освіти.

СЛУХАЛИ: проф. Вишневську Л. І. – про представлення до захисту до Екзаменаційної комісії кваліфікаційних робіт здобувачів вищої освіти.

ВИСТУПИЛИ: Здобувач вищої освіти групи Фм18(5,0д)англ-08 спеціальності 226 Фармація, промислова фармація Басма ЕЛЬ МАІДЕН – з доповіддю на тему «Фармакотехнологічні дослідження таблеток метилсульфонілметану з екстрактом ромашки»/ «Pharmacotechnological studies of methylsulfonylmethane tablets with chamomile extract» (науковий керівник, доц. Михайло МАРЧЕНКО).

УХВАЛИЛИ: Рекомендувати до захисту кваліфікаційну роботу.

Голова
Завідувачка кафедри, проф. _____ **Лілія ВИШНЕВСЬКА**
(підпис)

Секретар
асистент _____ **Ілона КОНОВАЛЕНКО**
(підпис)

Ф А2.2.1-32-042

НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ПОДАННЯ
ГОЛОВІ ЕКЗАМЕНАЦІЙНОЇ КОМІСІЇ
ЩОДО ЗАХИСТУ КВАЛІФІКАЦІЙНОЇ РОБОТИ

Направляється здобувач вищої освіти Басма ЕЛЬ МАІДЕН до захисту кваліфікаційної роботи
за галуззю знань 22 Охорона здоров'я
спеціальністю 226 Фармація, промислова фармація
освітньою програмою Фармація
на тему: «Фармакотехнологічні дослідження таблеток метилсульфонілметану з екстрактом ромашки»

Кваліфікаційна робота і рецензія додаються.

Декан факультету _____ / Світлана КАЛАЙЧЕВА /

Висновок керівника кваліфікаційної роботи

Здобувач вищої освіти Басма ЕЛЬ МАІДЕН представила кваліфікаційну роботу, яка за об'ємом теоретичних і практичних досліджень повністю відповідає вимогам до оформлення кваліфікаційних робіт.

Керівник кваліфікаційної роботи

_____ Михайло МАРЧЕНКО

«12» квітня 2023 р.

Висновок кафедри про кваліфікаційну роботу

Кваліфікаційну роботу розглянуто. Здобувач вищої освіти Басма ЕЛЬ МАІДЕН допускається до захисту даної кваліфікаційної роботи в Екзаменаційній комісії.

Завідувачка кафедри
аптечної технології ліків

_____ Лілія ВИШНЕВСЬКА

«26» квітня 2023 року

Qualification work was defended

of Examination commission on

« » June 2023

With the grade _____

Head of the State Examination commission,

DPharmSc, Professor

_____ / Oleh SHPYCHAK /