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MINISTRY OF HEALTH OF UKRAINE
NATIONAL UNIVERSITY OF PHARMACY
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Department of Industrial Technology of Drugs

QUALIFICATION WORK

on the topic: **"DEVELOPMENT OF THE COMPOSITION AND TECHNOLOGY OF TABLETS WITH RHODIOLA ROSEA EXTRACT"**

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ANOTATION

Qualification work contains of 48 pages, 5 tables, 5 figures, a list of references from 59 names.

To dissolve a warehouse of tablets for the treatment of nervous disorders, it is advisable to use pharmaceutical additives - extract of Rhodolia erysipelas and quercetin. On the basis of the complex, additional words were added. A technology for storing chewable tablets has been developed.

Key words: tablets, rhodiola, quercetin, technology.

АНОТАЦІЯ

Кваліфікаційна робота містить 48 сторінки, 5 таблиць, 5 рисунків, список літератури з 59 найменувань.

Для розробки складу таблеток для терапії нервових розладів обрані активні фармацевтичні інгредієнти природного походження – екстракт родіоли рожевої та кверцетин. На підставі комплексу досліджень підібрані допоміжні речовини. Розроблено технологію одержання жувальних таблеток.

Ключові слова: таблетки, родіола, кверцетин, технологія.

CONTENTS

LIST OF CONDITIONAL ABBREVIATIONS

MP – medicinal product

API – active pharmaceutical ingredient

CG – cinnamyl glycosides

SIRS – state of nonspecific increased resistance

USP – United States Pharmacopeia

SPU – State Pharmacopoeia of Ukraine

HPLC – high-performance liquid chromatography

INTRODUCTION

Relevance of the research topic. According to the WHO, a person is in a state of psycho-emotional stress on average every 25 minutes. The modern pharmaceutical market offers a number of medicinal products (MPs) with pharmacological effects aimed at preventing and eliminating psychoemotional stress. The vast majority of such drugs contain active pharmaceutical ingredients (APIs) of chemical origin. However, the global pharmaceutical market is growing in demand for medicines of natural origin. For example, the Ukrainian pharmaceutical market offers Rhodiola rosea extract, which is a tonic and adaptogenic drug. At the same time, in some cases, the use of liquid rhodiola extract is limited due to the content of ethyl alcohol.

Given the antioxidant effect of quercetin, it is considered appropriate to develop a drug that combines the general tonic effect of dry Rhodiola extract and the capillary stabilizing activity of quercetin in the form of chewable tablets. The advantages of this dosage form are that it can be used by almost all age groups, since it does not contain alcohol. [1-4].

Current pharmaceutical market does not have such a drug, a number of issues need to be resolved regarding pharmaceutical development, including: determining the composition, technological scheme of production, methods of technological control, pharmacological effect, etc.

In connection with the above, the development of a medicinal product containing dry extract of Rhodiola rosea and quercetin in the form of chewable tablets is an actual task today.

Objective of the study. Rationale for the development of a technology for a medicinal product in the form of chewable tablets based on a dry extract of Rhodiola rosea and quercetin.

Achieving this goal required solving the following research tasks:

1. To analyze the literature data on the current state of use of adaptogens and general tonic drugs.

2. To study the assortiment of the Ukrainian pharmaceutical market for the presence of drugs with adaptogenic and tonic activity based on natural rhodiola and quercetin dry extract.

3. Justify the methodology for creating a medicinal product in the form of chewable tablets.

4. To develop the composition and technology of chewable tablets with rhodiola extract and quercetin based on a set of pharmacological, technological, physicochemical studies.

Objects of study: dry extract of Rhodiola rosea, quercetin, mass for granulation, granulate, chewable tablets with adaptogenic and tonic activity.

Subject of the study: composition and technology of chewable tablets with adaptogenic and tonic activity.

Research methods: bibliosemantic (to summarize the results of the literature analysis); organoleptic, physicochemical and pharmacotechnological (to substantiate the composition and technology of chewable tablets with rhodiola extract and quercetin); statistical (to study the optimal tableting parameters).

Approval of research results and publications. Fragments of the master's thesis are covered in the publication:

Asaad M., Ruban O. A. Studies of the pharmacotechnological properties of the Rhodiola rosea and Quercetin extract powder. *Problems and Achievements of Modern Biotechnology: Materials of the III International Scientific and Practical Internet Conference*, Kharkiv, 24 March 2023. Kharkiv: NUPh, 2023. P. 47–48.

Structure of the work. The master's thesis is presented on 48 pages of printed text and consists of the following structural elements: introduction, literature review (Chapter 1), experimental part (Chapters 2-3), general conclusions, references, which includes 59 sources. The paper is illustrated with 5 tables and 5 figures.

SECTION 1
MAIN DIRECTIONS OF DEVELOPMENT OF A NATURAL-BASED DOSAGE FORM WITH ADAPTOGENIC AND TONIC ACTIVITY (LITERATURE REVIEW)

1.1. The use of herbal remedies in modern therapy

One of the leading problems of modern medicine is the development of means and methods to prevent the development of pathological changes in the body caused by stress reactions of various nature [5].

Psychosomatic diseases are one of the most characteristic manifestations of the so-called diseases of civilization. This problem is especially relevant in terms of preventing disorders of the central mechanisms of adaptation of the body to damaging factors of various nature. Psycho-emotional and cerebrovascular disorders arise as a result of age-related changes in the structure and function of the brain, chronic stress, and the pathological factor itself.

Nowadays, the problem of both treatment and prevention of a wide range of diseases caused by chronic stress - various forms of psychosomatic pathology and neuroses - is very relevant. It is at the stage when the pathology has not yet developed that adequate pharmacological correction can prevent the negative dynamics of pathological changes, normalize the manifestations of the conflict between the human body and the environment, which is typical today.

The general state of human health is a complex concept that includes the state of the immune system, the presence of diseases, mental state, endurance, and performance. In the modern century, unfortunately, there are more irritating factors of general human health than those that have a positive impact, so the body's ability to recover from stressful conditions is significantly reduced. The decline in the population of healthy people, reduced efficiency and quality of life are serious problems of modern medicine that require immediate measures to address these

problems. Unfortunately, improving the ecological state of our planet is a difficult problem to solve (although it depends entirely on people), and the stressful living conditions associated with progress are almost impossible to change. Therefore, humanity is left with few ways to solve problems related to the overall health status, namely, strengthening the immune system, increasing the body's adaptive capacity and, thus, improving the overall tone of the body.

One of the ways to solve these problems may be the use of drugs with adaptogenic and general tonic activity, the arsenal of which is nowadays quite wide and includes synthetic and natural drugs. Phytotherapy can rightfully take one of the first places in their ranks.

Medicinal and aromatic plants, as well as other natural medicinal raw materials, have long played a significant role in all spheres of human life.

Herbal remedies have always occupied a fairly large share of the global pharmaceutical market (up to 40% or more) and continue to grow. At the same time, no more than 5 % of the hundreds of thousands of species of the plant kingdom are used for medicinal purposes by humanity today [1].

About 23,000 plant species are used as medicinal plants worldwide, which is approximately 7% of the world's flora. The breadth of use of medicinal species and the degree of their study vary. The active ingredients in most plants used in folk and traditional medicine are unknown, their pharmacodynamic properties have not been studied, and their use is based on empirical experience. The number of medicinal plants introduced into scientific medicine is much smaller. In total, including medicinal plants that are processed at factories to produce individual substances or purified drugs and are not supplied to pharmacies as raw materials, more than 200 medicinal plants are officially used.

Active substances refer to components that have high pharmacological activity, which determines the therapeutic effect of a plant or its preparations. The accompanying substances are also pharmacologically active to a greater or lesser extent, but their action does not determine the main therapeutic effect. However,

concomitant substances can significantly affect the activity of active substances, potentiating or suppressing their pharmacological effect. Ballast substances are generally inactive, but their presence should be taken into account when preparing, storing and using herbal dosage forms. It is possible that a certain therapeutic effect of herbal preparations is associated with ballast substances [6-7].

Herbal remedies have a milder effect and are less likely to cause unwanted complications. Natural biologically active substances often have a synergistic effect and have a comprehensive therapeutic effect on all biochemical systems of the body [6,8]. Today, almost 5% of pharmaceutical products in the world are made from medicinal plants. Herbal remedies are widely used in both developed and developing countries [9].

In Ukraine, in recent years, there has been a steady increase in demand for products of natural origin. Despite significant advances in the chemistry of synthetic drugs, substances of natural origin more fully meet the requirements of modern medicine in terms of efficacy and safety. In terms of the above, a plant such as Rhodiola rosea is of particular interest.

1.2. The use of medicinal products based on Rhodiola rosea as potent adaptogens

The problem of finding modern medicines that help maintain the vitality of the human body continues to be quite relevant.

Rhizomes and roots of Rhodiola rosea L. (Crassulaceae L., Fatty) are widely used in folk and traditional medicine (Tibetan, Chinese, Korean, etc.), as well as in official medical practice.

The plant is widely known as the "golden root". The name is due to both the color of the rhizome and its high price, and it has been around for a long time.

Rhodiola rosea grows in the mountains of northern Europe, in the Tien Shan Mountains and the Far East. Most of the Rhodiola rosea thickets are concentrated

at an altitude of 1700-2200 m above sea level. Under conditions of rational exploitation, Rhodiola rosea thickets recover very slowly, so it is obvious that the problem of the raw material base can only be solved by industrial cultivation of this plant. According to the available literature, rhizomes and roots of Rhodiola rosea contain organic acids (oxalic, citric, malic, succinic), sugars (glucose, fructose, sucrose), essential oil, phenolic compounds, monoterpenes, sterols, cinnamaldehyde and its glycosides, as well as a large amount of manganese [10].

The underground part of the Rhodiola rosea plant has long been used in folk medicine to eliminate fatigue and increase efficiency: in the form of an infusion (10 g of dry rhizome per 500 ml of water) orally, 1 tablespoon 2-3 times a day, or tincture (50 g of dry rhizome) 500 ml of 40% ethyl alcohol) 20-25 drops 30 minutes before meals 2-3 times a day for 10-20 days [10].

The underground parts of the plant are used for bone fractures to accelerate the growth and formation of bone callus as an antipyretic agent for the treatment of pulmonary tuberculosis, skin diseases, tumors and wounds. In the latter case, an aqueous infusion of roots and rhizomes in the form of a thick mass is used to apply to open wounds.

In official medicine, a liquid extract of Rhodiola rosea rhizomes and roots is prescribed for oral administration as a general tonic and adaptogen.

Currently, more than 20 types of rhodiols have been tested for biological activity. Many of them have pronounced antioxidant, stimulating and adaptogenic properties. In the study of alcohol extracts of rhizomes and roots of different types of rhodiolae, their hepatoprotective, nootropic, antiarrhythmic and cardioprotective properties were clearly demonstrated. Cinnamaldehyde glycosides, cinnamyl glycosides (CG), and salidroside are the main carriers of biological activity of rhodiola preparations, which determines their numerous pharmacological effects. A number of authors associate the increased biological activity of Rhodiola rosea extracts with the presence of rosavin, rosin and rosarin, compared to preparations from other Rhodiola species. Many studies have shown the stimulating effect of

Rhodiola rosea preparations on the central nervous system. Of great interest is the ability of Rhodiola rosea to increase the body's resistance to various stress factors. The liquid extract of Rhodiola rosea has immunostimulating, antimicrobial, hepatoprotective and hypoglycemic effects [11-13].

The physiological activity of rosavin, which coincides with the activity of Rhodiola rosea extracts, has been described in a number of studies. The antihypnotic, stimulating and immunomodulatory activity of this glycoside has been shown [14].

A long-term comparative study of rhodiola and Eleutherococcus preparations has shown that golden root has a stronger stimulating and adaptogenic effect. It has also been noted that in some cases it is superior to ginseng in terms of its stimulating properties, especially during prolonged physical activity [15-16].

It has been established that the adaptogenic effect of Rhodiola rosea medicinal substances is due to the development of a state of nonspecific increased resistance (SIRS) in the body [12, 13].

The mechanism of the adaptogenic effect of Rhodiola rosea preparations is manifested in the antitoxic effect, which is active against methemoglobin formers (sodium nitrite, aniline) and strychnine [17]. Another manifestation of adaptogenic properties is associated with the inhibition of the onset and development of an acute leukocyte reaction caused by subcutaneous injection of milk or turpentine. It is assumed that the inhibition of the leukocyte reaction by the golden root extract is realized through the central nervous system [10].

The extract has an activating effect on thyroid function, antihypnotic and antioxidant effects [18].

There is evidence of the use of golden root extract in the treatment of occupational hearing loss, as well as in the activation of regenerative processes in the liver and normalization of biliary function. The anticancer properties of Rhodiola rosea extract are also described. In the study of antimicrobial properties

of substances from Rhodiola rosea, the tuberculostatic activity of rosiridin was revealed [19-21].

Detailed studies of the effect of rhodosin on the development of the infectious process and the immunobiological reactivity of experimental animals have been conducted. The results showed that the course of infection in animals under the influence of rhodosin is significantly facilitated and the percentage of animal death is halved [10, 21].

In dental practice, Rhodiola rosea extract is used to lubricate the gums in case of pyorrhea [22].

The study of the phytochemical composition of the underground organs of this medicinal plant allowed us to establish the structure of most biologically active compounds and to determine some of their main pharmacological effects.

In Sweden, in 2009, an article [23] was published on the isolation of rosavin from rhizomes and roots of Rhodiola rosea using supercritical carbon dioxide extraction. The authors selected different extractants and found that the highest yield of the product occurs when using supercritical carbon dioxide extraction and water as a modifier.

In 2011, an article [24] was published in China on the supercritical carbon dioxide extraction of Rhodiola rosea rhizomes and roots. The authors extracted salidroside from rhizomes and roots using alcohol as a modifier. By selecting the extraction conditions, they found that the yield using supercritical carbon dioxide extraction is much higher than the yield obtained by using the classical extraction using the Soxhlet apparatus.

In Latvia, work has been done and patented to obtain a dry extract from the rhizomes and roots of Rhodiola rosea and to create a tablet preparation based on it [10].

However, despite these studies, the number of galenic preparations of Rhodiola rosea rhizomes and roots used in Ukrainian medical practice has remained unchanged. The liquid extract and tincture of Rhodiola rosea currently

used are not optimal in terms of technology and stability. The disadvantage of these dosage forms is the inconvenience of their use by the patient, as well as transportation and storage. In addition, obtaining only a liquid extract using 40% ethyl alcohol as an extractant excludes the possibility of extracting a wider range of active substances from Rhodiola rosea rhizomes and roots.

In this regard, it seems relevant to research on the development of technology for the production of dry extraction drugs from rhizomes and roots of Rhodiola rosea, containing a complex of biologically active substances of this plant, and the development of modern drugs based on them, presented primarily in the form of solid dosage forms: tablets, granules, capsules.

1.3. Properties of the bioflavonoid quercetin and its use in a wide range of pathologies

Quercetin is a rutin aglycone with a powerful antioxidant effect, reactivating sulfhydryl compounds and vitamin C, as well as glutathione and tocopherols, and preventing the conversion of adrenaline to toxic adrenochrome. Quercetin prevents the damaging effects of free radicals, inhibits the processes of lipid peroxidation of cell membranes and serum lipoproteins, and improves intratissue respiration. In addition, this flavonoid is a natural inhibitor of hyaluronidase, an enzyme that increases vascular wall permeability; has a capillary-protective effect (reduces capillary permeability and fragility); improves microcirculation.

Quercetin flavonols (primarily glycosides) are the most common representatives of flavonoids, they are present in a fairly large number of foods (berries, apples, grapes, onions, tea, tomatoes), as well as in seeds, nuts, certain cereals, flowers and leaves of garden and medicinal plants. A significant portion of quercetin consumed with food is its glycosides; quercetin aglycones are present in the diet in a much smaller amount.

A diet with minimal fat or lecithin also improves quercetin absorption, and its excretion from the body is slowed down when a significant amount of fat is included in the diet [25].

Quercetin has many positive properties, some of which have been confirmed by serious clinical studies. Animal studies have shown that the antioxidant properties of quercetin protect the brain, heart, and other tissues from damage caused by ischemia and reperfusion, toxins, and other factors that lead to oxidative stress [26]. However, most researchers focus exclusively on the antioxidant potential of this flavonoid, while little attention is paid to other perspectives of the drug's use. In addition to its well-known antioxidant properties, quercetin is a powerful medicinal agent in many areas according to certain clinical indications. Quercetin has demonstrated its effectiveness in a number of medical fields, namely allergology and immunology, endocrinology, gastroenterology, urology, and has prospects for use in psychiatry and oncology. Given the almost complete absence of side effects (doses of up to 1 g per day have no significant effect on hepatic and renal function, electrolyte levels, and hemostasis), good tolerability and efficacy, quercetin has prospects in the treatment of many diseases in which it has demonstrated significant efficacy in studies [26].

1.4. Characteristics and use of chewable tablets

When creating a new drug, an important step is to choose a dosage form that meets all the requirements set by both technologists and consumers. Among the known dosage forms, the most common are solid dosage forms, which are considered convenient for use. However, many patients have difficulty swallowing tablets and capsules, mainly due to their size [27]. To improve compliance and ease of use, several types of tablets have been developed, including chewable tablets [28-30].

According to the US Pharmacopoeia, there are two types of chewable tablets: the first can be chewed to facilitate swallowing, and the second must be chewed or crushed before swallowing to prevent obstruction and better release of the API [31-32].

Chewable tablets have a number of advantages over other solid oral dosage forms: better stability, higher bioavailability due to avoidance of breakdown (and increased solubility), patient compliance due to the possibility of using them without water, they can replace liquid dosage forms and provide a rapid onset of action, improved consumer characteristics, which is especially important in pediatrics and geriatrics, due to improved taste and, accordingly, the ability of the product to occupy a promising market [33-35]. Chewable tablets are an alternative dosage form for vitamin, analgesic, and cough medications for colds [36-37].

However, there are certain limitations to the use of chewable tablets. This is the case when the drug product contains a large amount of APIs with an unpleasant taste that is difficult to correct and/or hide [37-38]. The peculiarities of using this type of tablets are that the substances are in long-term contact with the human taste and olfactory receptors. Therefore, in addition to such traditional organoleptic properties as taste and smell, it is necessary to study the aftertaste, aroma, "aftertaste," and "sensations in the mouth" [39]. This is especially relevant when developing a drug product based on APIs with a bitter taste, especially at a high dose [40-41].

For the pharmaceutical development of high quality chewable tablet formulations and technologies, the first step is to establish a complete profile of the API. Information on physical properties (color, odor, taste, aftertaste, and oral sensation), physical form (crystal, amorphous powder, solid, oily liquid, etc.etc.), melting and pouring point, polymorphism, solubility, moisture content, stability, cohesion, chemical properties (chemical composition and chemical class, major reactions of this chemical class, major incompatibilities), API dose in the formulation, and any limitations on the final tablet size [32].

The following technologies are used to produce chewable tablets: wet granulation, microencapsulation, solid dispersions, ion exchange, spray curing and spray coating, adsorption formulation using dissolution or melting, as well as molecular complex technology and lyophilization [42].

Wet granulation can be used to coat API particles to mask flavor [43-44]. In this case, the APIs are wet granulated with an anhydrous polymer solution, dried, sized, and mixed with a flavoring agent and other ingredients to produce a material suitable for pressing. In general, this is the simplest approach to flavor masking. In wet granulation, fillers can be added [37, 45-46]. The requirements for this process in the production of chewable tablets are: the formation of a plastic rather than brittle film, the absence of an unpleasant taste or odor, and the coated particles should not dissolve in saliva. [34, 46-47].

There are three important aspects of chewable tablet development: ensuring the required particle size distribution, optimal moisture content, and achieving the proper tablet hardness [48].

Since the evaluation of the organoleptic properties of a tableted drug is subjective in nature, it is necessary to clearly define the terms, have standards to compare with, and strictly follow the experimental conditions to obtain meaningful results.

At the latest stage of development of the pharmaceutical industry in Ukraine, considerable attention is paid to the development of medicines based on medicinal plant raw materials [42, 49].

CONCLUSIONS

1. Expanding the range and searching for effective and safe herbal medicines is one of the main directions of development of the modern pharmaceutical industry.

2. Preparations based on plant extracts used as tonics, general tonics, and medicines that stimulate nonspecific resistance of the body have a wide range of applications, especially nowadays due to the difficult environmental situation and the increase in the occurrence of various pathological conditions.

3. It is important to create new Ukrainian effective medicines with adaptogenic and tonic activity based on plant extracts in the form of pharmaceutical forms that are easy to use and stable during storage, including chewable tablets, which are characterized by better compliance compared to other solid medicines.

SECTION 2
MARKETING RESEARCH OF THE AVAILABILITY OF ADAPTOGENIC AND TONIC DRUGS ON THE PHARMACEUTICAL MARKET OF UKRAINE.
OBJECTS AND METHODS OF RESEARCH.

2.1. Market research of the pharmaceutical market of Ukraine on the availability of drugs with adaptogenic and general tonic activity

The aim of our research is to develop a Ukrainian drug based on dry extract of rhodiola and quercetin with adaptogenic and tonic activity. To achieve these objectives, we conducted marketing research of the Ukrainian market of adaptogens and general tonics.

For marketing research, we used a concept based on a step-by-step analysis of the range of drugs with adaptogenic and general tonic activity according to the following criteria: ATC classification (anatomical, therapeutic, and chemical classification), dosage forms, and country of manufacture [50-52].

The industry produces various dosage forms of adaptogens: alcohol tinctures and extracts, tablets, capsules, powders, etc. Depending on the origin, adaptogens are distinguished:

- plant-based: Rhodiola rosea, ginseng, Eleutherococcus, aralia, astragalus, goldenseal, lemongrass, sea buckthorn, ginger, etc;
- minerals of plant origin: humic substances;
- mineral origin: mumiyo;
- animal origin (including animal products): reindeer antlers (cigapan, pantocrine), bee products (apilac, etc.);
- synthetic (trecresan, bendazole, etc.).

According to the spectrum of pharmacological action, adaptogens and general tonics are divided into two groups (according to the ATC classification) [50]. The first one is broad-spectrum. Drugs of this group cause a state of nonspecific increased resistance in the body:

- vitamins (A11);
- mineral additives (A12);
- tonic agents (A13);
- miscellaneous drugs (acting on the nervous system) (N07XX10).

The second is a narrow spectrum of action. Drugs of this group create a state of specific increased resistance:

- antihypoxants (C01);
- antitoxic (V03);
- antioxidants (R05CB01; M02A X03; A11);
- geriatric (A11; V03AB26; J05AX12);
- biostimulants (A16AX10);
- immunostimulants (L03AX18 та L03AX21);
- nonsteroidal anabolic drugs (A14B);
- amino acids and their derivatives (A16AA);
- other psychostimulants and nootropics (N06BX).

An analysis of drugs with adaptogenic and tonic activity on the Ukrainian market as of 2019 [50, 52] determined that there are 75 items of drugs with adaptogenic and tonic properties (including all forms of release) on the Ukrainian pharmaceutical market.

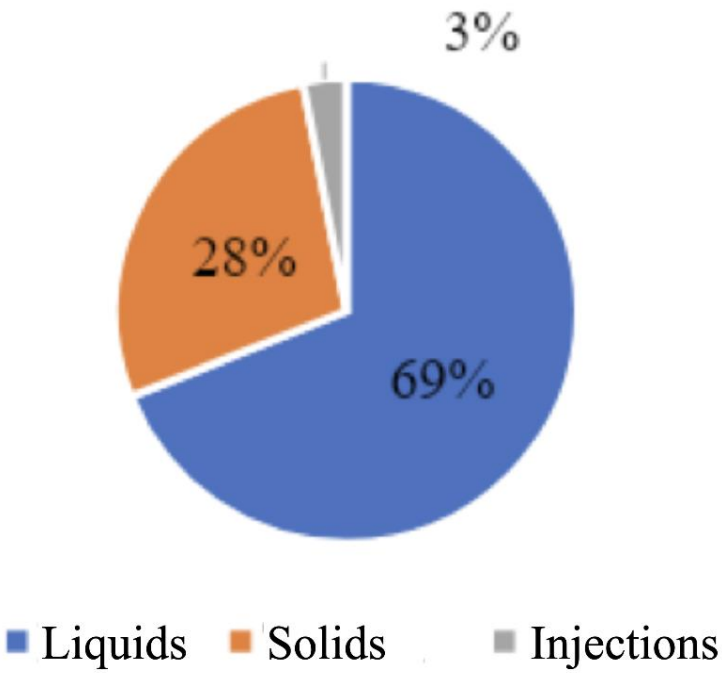


Fig. 2.1 Correlation of dosage forms with adaptogenic and general tonic activity.

As can be seen from the data presented (Fig. 2.1), the nomenclature of liquid dosage forms accounts for 69% of the total weight of drugs in this group. Solid (28%) and injectable (3%) dosage forms are present in smaller quantities.

The results of the comparative analysis of the ratio of solid dosage forms of this group are shown in Fig. 2.2.

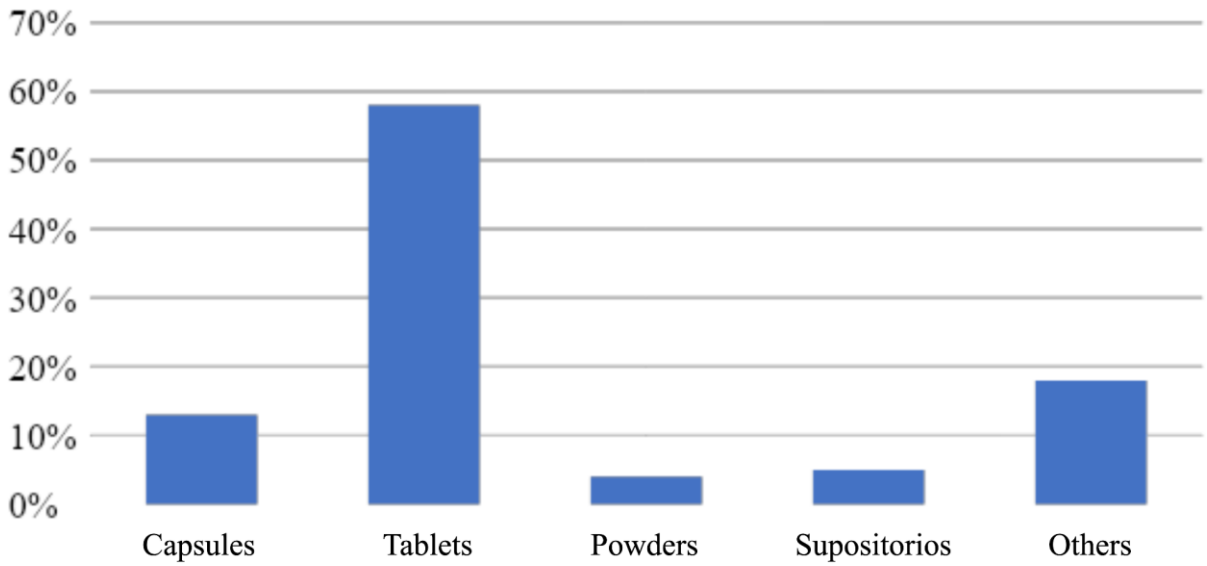


Fig. 2.2 Solid dosage forms of drugs with adaptogenic and tonic activity

The data obtained indicate the predominance of tablets among the solid dosage forms presented. However, it should be noted that there are no chewable tablets among them.

The analysis of the pharmaceutical market of Ukraine showed that the range of drugs with adaptogenic and general tonic activity is wide and varied. For the most part, the drugs of the pharmacological group under study are of plant origin and are produced by the Ukrainian industry in liquid form (tinctures, extracts, etc.). It should be noted that these dosage forms are not always convenient to use and there is a possibility of dosage errors.

Therefore, we further analyzed the distribution of drugs by country of origin. The data obtained are shown in Fig. 2.3.

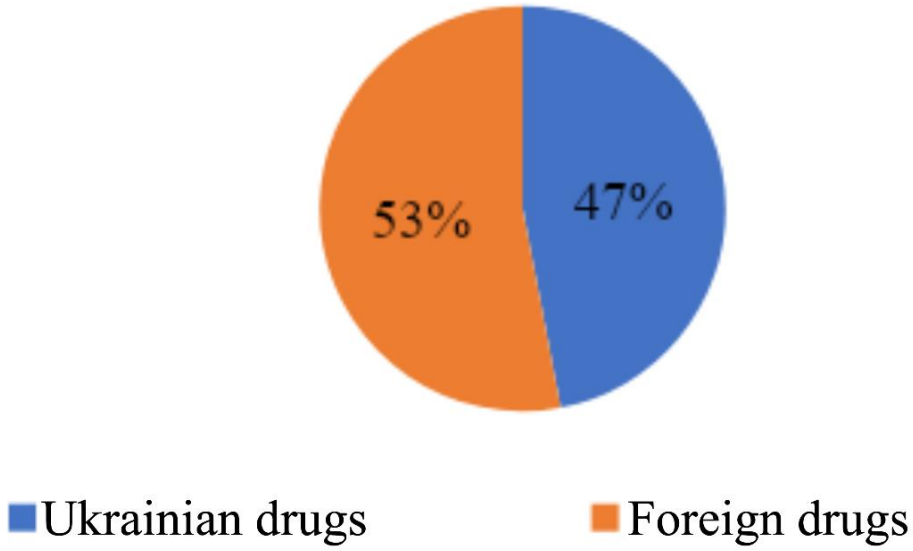


Fig. 2.3 The ratio of drugs with adaptogenic and general tonic activity by country of manufacture.

As can be seen from the data obtained, Ukrainian drugs of this group account for 47% of the Ukrainian pharmaceutical market of adaptogens and general tonics, i.e. they occupy a smaller share compared to imported drugs (53%)

of the studied group. As is well known, the cost of imported drugs is much higher than the price of Ukrainian drugs, and not all patients can afford to purchase expensive drugs.

An important aspect of pharmaceutical science and practice is not only the creation of new drugs, but also the improvement of existing ones. In this aspect, our research was aimed at improving such a well-known drug as Quertin (PJSC SIC Borshchahivskiy CPP) in order to expand the line of quercetin products. Quertin was created on the basis of quercetin granules to improve the ease of use. In addition to quercetin as an API, the product contains the following excipients: pectin, glucose monohydrate, sucrose, orange flavor, magnesium stearate, talc. The set of excipients is justified not only from the technological point of view, but also by the evidence that quercetin is best absorbed in combination with pectin and insoluble oligosaccharides [53].

Thus, it can be concluded that there is a feasibility of creating a drug of the specified pharmacological action of plant origin in a solid dosage form (chewable tablets).

A drug of natural origin with quercetin and rhodiola extract can take an important place in the implementation of a strategy for the pharmacoprophylaxis of chronic stress and reveal new opportunities for the use of quercetin drugs.

2.2. Objects of research

To achieve this goal, dry rhodiola extract and quercetin were chosen as the main objects of study.

Characterization of active pharmaceutical ingredients .

Rhodiola rosea (L.) is a perennial herb belonging to the Crassulaceae family (Fig. 2.4).

Rhodiola rosea roots contain the following BAS: phenolic glycosides, anthraglycosides, organic acids (gallic acid, caffeic acid, chlorogenic acid, oxalic

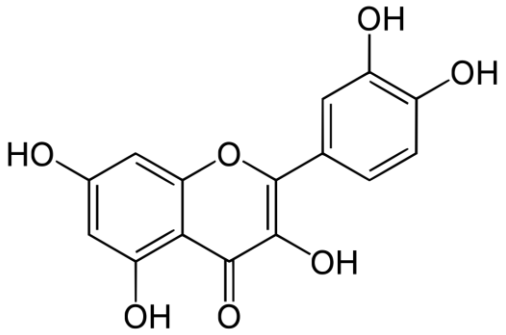
acid, citric acid, malic acid, succinic acid), flavonoids (catechins and proanthocyaninins), sterols, tertiary alcohols, unsaturated compounds and a large amount of manganese. The pharmacological properties of the "golden root" (stimulating and adaptogenic) are due to the presence of p-tyrosol, phenolic glcoside rhodioloside and rhodosin.

Fig. 2.4. Rhodiola rosea.

Rhodiola preparations are adaptogens and have a pronounced stimulating effect, significantly increasing endurance, especially increasing performance against the background of fatigue and when performing heavy physical work. In this case, energy resources are consumed economically and recovered faster [52-53]. The use of Rhodiola rosea preparations normalizes metabolic processes, improves energy metabolism in the muscles and brain. The drug has the strongest effect on muscle tissue: there is an increase in muscle strength and strength endurance, as the activity of contractile proteins increases. Rhodiola rosea preparations have a pronounced immunocorrective effect, are easily tolerated, have no identified contraindications and do not have allergenic properties [56-57].

Despite its widespread use in medicine and sports medicine, the list of Rhodiola rosea medicinal products is very limited. According to the data provided in the basic monographs on sports medicine, the main drug used for application is a 40% liquid alcohol extract 1:1 [56-57].

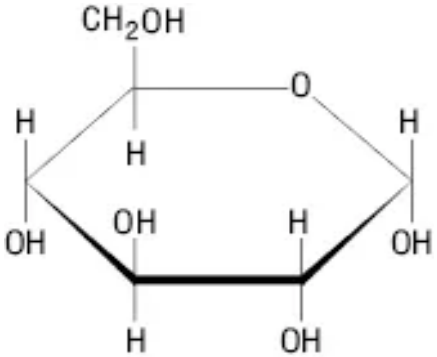
Quercetin is a lemon-yellow crystal, slightly soluble in water, diethyl ether, ethanol, chloroform, and soluble in acetic acid and alkalis.



Characterization of excipients.

Pectin (United States Pharmacopeia, USP) is an amorphous powder with a molecular weight of about 80 thousand; white or yellowish, grayish and brownish, free-flowing powder, almost odorless. The solubility of pectin depends on the degree of polymerization, esterification and molecular size.

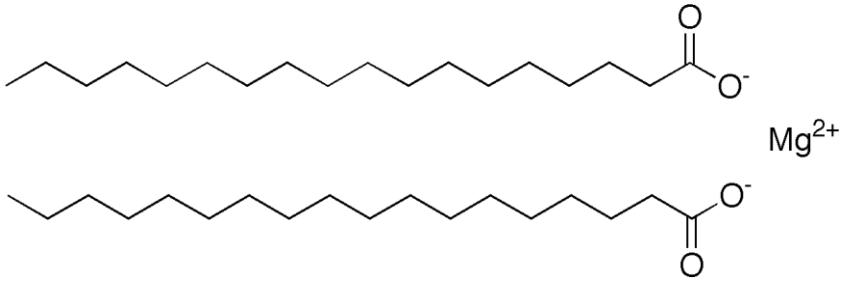
Glucose monohydrate (State Pharmacopoeia of Ukraine, SPU) is a colorless, odorless, sweet-tasting crystal or white crystalline powder.



Pressed sugar (BP, Ph Eur, USP). Three types of sugar are used in the pharmaceutical industry: spherical, pressed and confectionery. Spherical sugar is roughly spherical granules containing 62.5% to 91.5% sucrose, the rest is starch.

Talcum powder *(SPU) is a* fine white or grayish-white with a greenish tinge, odorless and tasteless crystalline flake powder that is soft, greasy and slippery to the touch. It is well adherent to the skin.

Magnesium stearate (BP, Ph Eur, USP, JP) is a fine powder of light white color with a characteristic taste and faint odor of stearic acid; it is practically insoluble in ethanol (95%), ether and water.



2.3. Research methods

In order to scientifically and practically substantiate the composition and technology of chewable tablets with dry rhodiola extract and quercetin, the main physicochemical and pharmacotechnological properties of the substance samples were studied. These properties are interrelated and can in some way affect the process of pressing and obtaining high-quality tablets.

Not only were the powders of rhodiola and quercetin dry extracts subjected to physicochemical analysis, but also the mass for granulation and tableting.

For this purpose, the following physicochemical and technological properties of the samples were determined. Thus, in accordance with the requirements of the SPU, the following studies were conducted: fractional (particle size distribution) composition; determination of volumetric parameters of powders: bulk volume, bulk density before shrinkage, shrinkage capacity, volume and density after shrinkage; fluidity, compressibility and slip, which allows easy pushing of the tablet from the matrix.

The tested chewable tablets were examined for the main quality indicators, the methods of which are given in the SPU.

Identification and quantitative testing of the active substances - dry extract of rhodiola and quercetin in the composition of the tablets was carried out by high-performance liquid chromatography (HPLC) in accordance with the conditions of SPU 1.2 (p. 60) and SPU 3.3 (p. 32) according to the methodology given.

CONCLUSIONS

1. The study of the ratio of dosage forms of drugs with adaptogenic and general tonic activity showed the preference of these drugs (34%) in the form of tinctures.

2. The analysis of the distribution of drugs by country of manufacture has shown that imported drugs of the study group (53%) outnumber Ukrainian drugs (27%). This confirms the need to create a drug of this pharmacological group in a solid dosage form.

3. The article describes the active pharmaceutical ingredients and excipients, as well as the methods of pharmacotechnological and physicochemical studies necessary for the development of the optimal composition and rational technology of chewable tablets.

CHAPTER 3
EXPERIMENTAL SUBSTANTIATION OF THE COMPOSITION AND DEVELOPMENT OF CHEWABLE TABLETS TECHNOLOGY

3.1. Investigation of pharmacotechnological properties of Rhodiola dry extract

The production of tablets begins with the study of the properties of the starting drug substances, which determine the rational method of tableting and the choice of excipients. Bulk density, flowability, degree of compaction, and compressibility are the most important factors that determine the behavior of a tableted material during compression.

The results of the analysis of the pharmacotechnological properties of the substance of the dry rhodiola extract are given in Table 1.

Table 3.1.

Indicators of pharmacotechnological properties of Rhodiola rosea dry extract (n=5; p≤0.05)

Parameters	Research data
V_0 , bulk volume before shrinkage, ml	102,0±0,02
V_0 , bulk volume after shrinkage, ml	82,0±0,02
Bulk density before shrinkage, m/V_0 , g/cm³	0,482±0,02
Bulk density after shrinkage, g/cm³	0,512±0,06
Fluidity, s/100	28,0±0,04
Weight loss during drying, %.	3,9±0,02

As can be seen from the above data, dry rhodiola extract is a low-flowing material. The moisture content of the material and the size of the particles have a significant impact on the flowability and compressibility of powders (granulates).

The data obtained from the study of the pharmacotechnological properties of the extract powder allow us to predict the composition and amount of excipients for the development of a chewable tablet formulation.

3.2. Study of physicochemical and pharmacotechnological parameters of quercetin

The drug under development contains a second active ingredient (quercetin) in addition to the active ingredient in the form of a dry rhodiola extract.

According to the professional literature on experimental clinical trials, quercetin intake significantly improves the treatment of a number of diseases of the cardiovascular, endocrine, gastroenterological and urological systems.

Therefore, the next stage of our work was to study the pharmacotechnological properties of this substance to obtain a high-quality dosage form. The data are presented in Table 2.

Table 3.2.

Indicators of pharmacotechnological properties of quercetin powder (n=5; p≤0.05)

Parameters	Results of the study
V_0 , bulk volume before shrinkage, ml	191,60±0,02
V_0 , bulk volume after shrinkage, ml	142,65±0,06
m/V_0 , bulk density before shrinkage, g/cm³	0,251±0,02
m/V, g/cm³	0,344±0,04
Fluidity, s/100	18,60 ±0,02
Weight loss during drying, %.	4,85±0,02

Studies have demonstrated such properties of quercetin as sufficient fluidity and sealing ability

Based on the results of the studies conducted on the properties of the active substances of the investigational drug, it is possible to predict the ways of obtaining a semi-product and a high-quality finished product in the production of chewable tablets.

3.3 Justification of the conditions for the granulation process

When developing the composition of excipients, we relied on the quality composition of Quertin, which is optimal for this dosage form.

We created three batches of tablet masses with rhodiola extract and quercetin, with the list of excipients remaining identical to that of Quercetin, but their quantitative content varied (Table 3).

Table 3.3.

Composition of tablet masses

Components of tablet masses	Quantitative composition					
	Quantity, %.			Quantity per tablet, g		
	Composition					
	1	2	3	1	2	3
Quercetin in terms of 100% dry matter	3,64	4,00	4,00	40,00	40,00	40,00
Dry rhodiola extract	9,09	10,00	10,00	100,00	100,00	100,00
Citrus pectin	36,36	40,00	30,00	400,00	400,00	300,00
Glucose monohydrate	33,05	26,35	36,35	363,50	263,50	363,50
Pressed sugar	14,55	16,00	16,00	160,00	160,00	160,00
Powdered flavor (orange)	0,14	0,15	0,15	1,50	1,50	1,50
Talc	2,73	3,00	3,00	30,00	30,00	30,00
Magnesium stearate	0,44	0,50	0,50	5,00	5,00	5,00

Total	100,0	100,0	100,0	1100,0	1000,0	1000,0

Today, such a granulation method as fluidized bed granulation is gaining attention. Fluidized bed granulation allows combining the operations of mixing, granulation, drying and dusting in one technological device. Therefore, this method of granulation is increasingly used in modern pharmaceutical production [2-3].

The process involves mixing powdered ingredients in a liquefied bed and moistening them with a granulating liquid while stirring them continuously.

A fluidized bed is formed when warm air directed upward lifts a layer of solid particles that begins to "boil" like liquids. The forces acting on the particles in this state are in balance. The components in the fluidized bed are mixed so effectively that the temperature over the entire height of the bed remains stable. The process in the fluidization apparatus consists of four stages [59]:

- Mixing is the first operation that affects the quality of the granulate. The uniformity of mixing depends on the aerodynamic mode of operation of the machine, the ratio of the mixture components, and the particle size;
- At the stage of adding a humectant, the mass particles clump together due to the adhesive forces of both the liquid itself and the solution formed when the surface layer of the tablet mass components is wetted with this liquid;
- During the drying stage, the lumps turn into solid granules, which are partially destroyed as a result of contact with each other and with the walls of the device. The process of granulation in the fluidized bed takes place simultaneously with the drying of the granules with heated air. Drying until the granulate is ready is carried out to the required humidity value;
- Dried granulate is powdered in the same apparatus. This operation is carried out by free application of finely ground substances to the surface of the

granules and in this way sliding and loosening agents are introduced into the tablet mass.

The resulting dried granules may have a rough surface, which will negatively affect the fluidity of the granulate. In addition, the granules can stick to the dies and punch of the tablet press, which can cause certain defects in the tablets. To avoid these undesirable phenomena, the operation of "dusting" the granulate is used.

The formation and consolidation of granules in the fluidized bed occurs due to clumping during wetting and sticking together with subsequent agglomeration.

The granulation of the obtained tablet mixtures was carried out using a fluidized bed dryer-granulator, which allows combining the operations of mixing, granulation, drying, and dusting in one equipment [2-3].

We used sugar syrup as a moisturizer.

In the process of developing the chewable tablet manufacturing process, we tried to optimize such a parameter as the order of substance introduction into the process.

Therefore, when granulating composition No. 1, we added rhodiola extract to the mass at the stage of mixing the granulate with the flavor before the powdering stage. However, the rhodiola extract caused color heterogeneity; also, due to the increased weight of the charge, the filling capacity of the matrix was at its limit.

When pelletizing compound No. 2, an increased consumption of humectant was observed. Also, the mass "hung", and it was necessary to dry it, which caused a lot of losses. As a result, agglomerates of irregular shape with poorer fluidity were formed.

The granulation process of composition No. 3 produced a granulate with good fluidity and compressibility.

3.4 Study of pharmacological and technological properties of granulate with rhodiola extract and quercetin

Subsequent studies were devoted to comparing the quality of the obtained granulates. A comparative study of the granulates was carried out according to the following indicators: bulk density, Gausner's index, fluidity, residual moisture, and fractional composition. The data are presented in Table 4.

Table 3.4.

Comparative characteristics of granulate series

No. of composition	Indicators of pharmaceutical and technological characteristics				
	Bulk density, g/cm^3	Gausner's index	Fluidity, g/s (10 mm)	Residual moisture, %.	Pressibility, H
1	0,60	1,11	4,1	4,40	165
2	0,55	1,15	3,2	4,95	234
3	0,50	1,13	3,6	4,65	295

For powdered mixtures with good fluidity, the value of the Gaussner index is in the range from 1 to 1.18 [3]. Thus, it can be concluded that all the obtained intermediates have relatively satisfactory fluidity.

It has been determined that all three formulations have quite satisfactory granulometric parameters and, as a result, may have satisfactory pharmacological and technological properties, which will be investigated in the next stages of work.

Thus, as a result of using the method of wet granulation in a fluidized bed, three compositions of granules with similar pharmaceutical and technological properties were obtained, but composition No. 3 had the best properties, as it has more uniform particle size and shape and can be subjected to tableting with the prospect of obtaining a high-quality finished product.

3.5. Study of the tableting process in the production of chewable tablets

The tableting process consists of the following basic operations: feeding the material into the die, compressing it with a punch (tableting), pushing the tablet out of the die, and discharging the tablet into a tray.

According to the composition and technology of Quercetin tablets, at the stage of obtaining the mass for tableting, the granulate is dusted with magnesium stearate and talcum powder. The amount of lubricants was selected based on their effect on the pharmacotechnological parameters of the tablet mass and tablet parameters during tableting.

Magnesium stearate has good antifriction properties, but it should not be present in large quantities in chewable tablets. According to organoleptic sensations, its maximum amount (0.5 %) was determined, which does not exceed the limit specified in the SPS (second supplement) [58].

The amount of talc was selected according to the functional purpose of this excipient - antifriction and lubrication properties.

The optimal amount of talc was chosen as 3%, as it provides the necessary technological characteristics of the mass for tableting. The selected amount of talc also meets the requirements of the SPS (second supplement) [56].

Based on our previous studies, we decided to subject all the obtained series of granulates to the pressing process to justify the choice of the optimal composition of the tablet mass.

The results of the studies showed that tablets obtained from granulate of series No. 3 have satisfactory characteristics, which confirms the previously obtained conclusions about the choice of a composition with optimal characteristics. The quality control of the finished product was carried out according to the following indicators: strength, abrasion and solubility.

The strength of the tablets according to composition No. 3 was 290-300 N. The study on the abrasion of the developed chewable tablets gave results of 0.1-0.15 % with a limit of 1 % according to the State Fiscal Service [58]. This result is fully consistent with the results of the studies on strength, which has a very satisfactory result and is 290-300 N.

3.6. Technology for the preparation of chewable tablets with rhodiola extract and quercetin

Based on the study of the physicochemical, pharmacological and technological properties of the dry extract of rhodiola and quercetin, the effect of excipients on the quality parameters of tablets, and the study of the process parameters, we have developed a technology for the production of chewable tablets by pressing with preliminary structural granulation in a fluidized bed.

The technological process includes the following operations.

1. Preparation of raw materials. The components involved in the process are weighed on scales into appropriate collections and sieved on a vibrating screen.

2. Preparation of mass for tableting.

2.1 Preparation of the humidifier. Dissolve a certain amount of sugar in the required amount of purified water.

2.2. Granulation. Granulation is carried out using a fluidized bed dryer-granulator.

2.3 Powdering of the granulate is carried out by mixing the obtained granules with the flavoring in a Turbula mixer and powdering with the calculated amounts of magnesium stearate and talc.

3. Tableting . The process of granulate tableting is carried out on a tablet press manufactured by Korsch (Germany).

4. Tablets are packaged on a Marchesini blister machine (Italy).

We have drawn up a technological scheme for the production of chewable tablets with rhodiola extract and quercetin, which is shown in Figure 3.1.

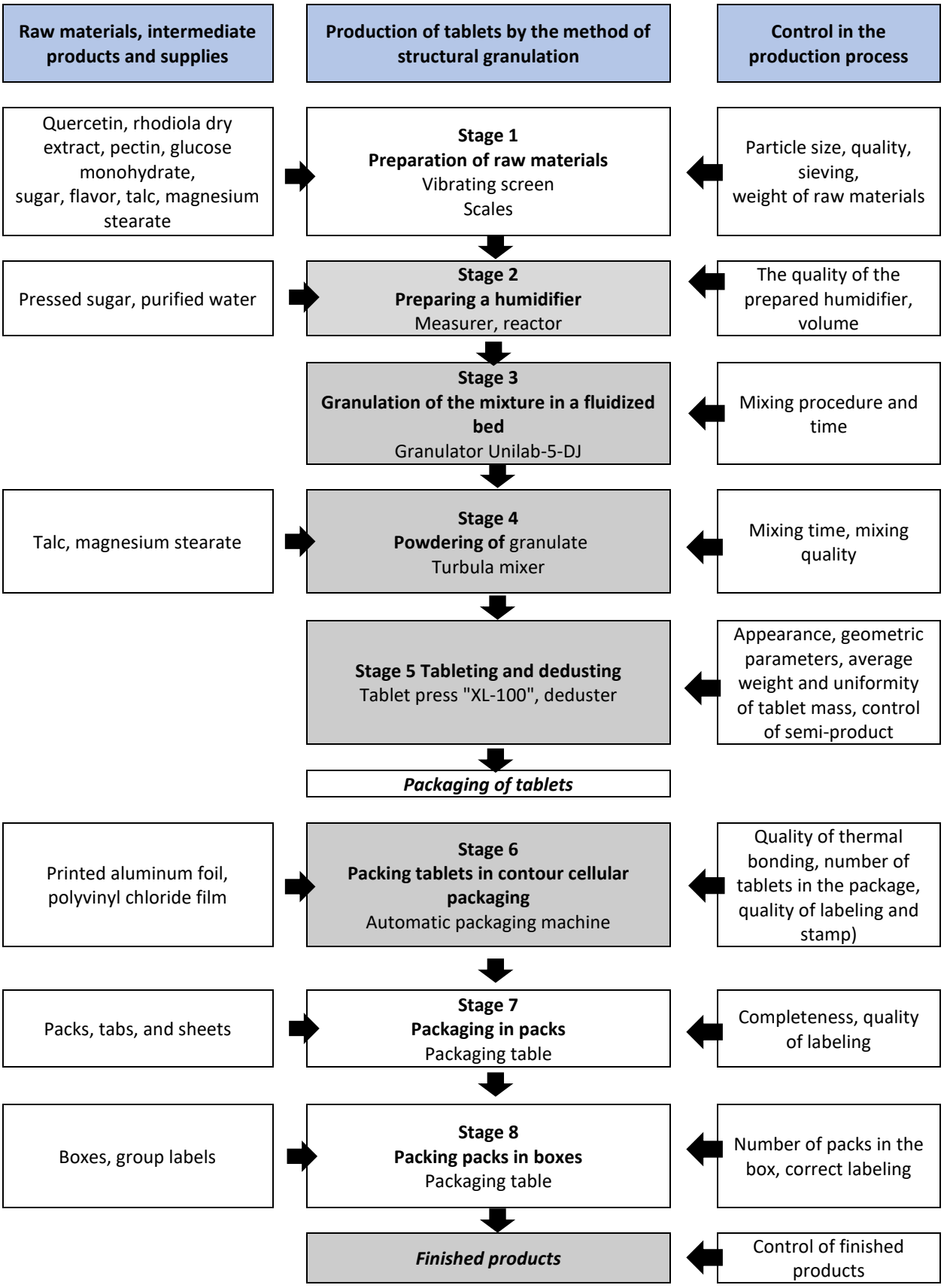


Fig. 3.1 Flow chart for the production of chewable tablets with rhodiola extract and quercetin

The main function of containers, packaging and closures is to isolate a single dosage (portion) of a medicinal product not only from other dosages, but also from the effects of so-called environmental factors: light, atmospheric air pressure, atmospheric natural gases and vapors, as well as from evaporation into the surrounding atmosphere of other drugs, chemicals and products stored in the same or neighboring premises. The correct choice of containers, packaging and closures depends on the properties of the packaged drug, the state of the surrounding atmosphere, the protective properties of packaging and closure materials and products, production conditions and the shelf life of the drug.

Storage conditions have a major impact on the stability of medicinal substances in tablets and their physicochemical properties.

When stored in dry air, tablets lose moisture, which is one of the main reasons for their cementation and complete loss of disintegration. Higher air humidity usually decreases the stability of tablets, and the disintegration time may increase or decrease.

Increased air temperature and direct sunlight also have a negative impact on the quality of the tablets. Therefore, store the tablets at room temperature in a dry, dark place.

For chewable tablets with rhodiola extract and quercetin, we chose contoured cell packaging based on PVC film and foil.

3.7. Determination of quality indicators for chewable tablets

Quality control of the manufactured tablets was performed according to the methods described in Section 2. The results of tablet quality control are presented in Table 3.5 and indicate that the obtained drug product meets the requirements of the pharmacopea in terms of pharmacotechnological parameters.

Table 3.5.

Results of quality control of the obtained capsules

Parameters under study	Acceptable values	Quality control results
Appearance	Tablets are yellowish, rounded, with a notch on one side. White inclusions are allowed	Answer.
Average weight of capsule contents and deviations from it	100 mg ± 5 (95 mg to 105 mg; no more than two individual masses deviate from the average mass by more than 5%; no individual mass should deviate from the average mass by 10% or more)	Answer.
Hardness	Not less than 55 N	292 ± 2 H
Abrasion	No more than 1% of the total	0,12%

CONCLUSIONS

1. The pharmacological, technological, physical and chemical properties of dry extracts of Rhodiola rosea and quercetin were investigated. It has been established that the moisture content of the material and the size of its individual particles have a significant effect on the fluidity and compressibility of powders (granulates).

2. The use of the method of pressing with preliminary structural granulation in the production of tablets is substantiated. The influence of lubricants on the technological process and quality indicators of tablets is determined.

3. The conditions for the granulation process in a fluidized bed were substantiated. The influence of the conditions of the pressing process on the quality of the obtained tablets was determined: height 5.9 mm, average weight 1.0 g, strength about 290-300 N.

4. Based on the experimental studies, a technology for the production of chewable tablets with a dry extract of Rhodiola rosea and quercetin was developed with the definition of critical control points for production.

5. On the basis of comprehensive studies, storage conditions ((25±2)°C at a humidity of (60±5)%) of chewable tablets for 6 months were established.

GENERAL CONCLUSIONS

1. The scientific approaches to the development of the composition and technology of chewable tablets based on dry extract of Rhodiola rosea and quercetin with adaptogenic and tonic activity are theoretically generalized and experimentally substantiated.

2. Market research of the Ukrainian pharmaceutical market on medicinal products in the group of general tonics and adaptogens has established that the vast majority of drugs with the indicated pharmacological activity are presented in the form of liquid medicinal products - 76%. The number of imported drugs exceeds the number of Ukrainian ones.

3. On the basis of bibliosemantic analysis of literature data, the prospects of creating a medicinal product in the form of chewable tablets based on dry extract of Rhodiola rosea and quercetin for the prevention of psychoemotional stress have been proved.

4. The physicochemical and technological properties of the dry extract of Rhodiola rosea and quercetin were studied, which made it possible to classify them as low-flow materials and develop approaches to the creation of a rational tablet formulation based on them.

5. The conditions for the granulation process in a fluidized bed are substantiated. An industrial technology for the production of chewable tablets by pressing with structural granulation is proposed. A technological scheme for the production of chewable tablets with dry extract of Rhodiola rosea and quercetin has been drawn up.

LIST OF REFERENCES

1. Биофармация: учеб. для студентов фармацевт. вузов и факультетов / А. И. Тихонов, Т. Г. Ярных, И. А. Зупанец [и др.]. – Харьков: Изд-во НФАУ: Золотые страницы, 2003. – 238 с.

2. Технологія ліків промислового виробництва: підруч. для студентів вищ. навч. закл.: у 2 ч. / В. І. Чуєшов, Є. В. Гладух, І. В. Сайко [та ін.]. – 2-ге вид., переробл. і допов. – Харків: НФаУ: Оригінал, 2012. – Ч. 1. – 694 с.

3. Технологія ліків промислового виробництва: підруч. для студентів вищ. навч. закл.: у 2 ч. / В. І. Чуєшов, Є. В. Гладух, І. В. Сайко [та ін.]. – 2-ге вид., переробл. і допов. – Харків: НФаУ: Оригінал, 2012. – Ч. 2. – 638 с.

4. Технологія ліків промислового виробництва: підруч. для студентів вищ. фармацевт. навч. закл. і фармацевт. ф-тів вищ мед. навч. закл. III-IV рівнів акредитації / В. І. Чуєшов, Л. М. Хохлова, О. О. Ляпунова [та ін.]. – Харків: Вид-во НФаУ: Золоті сторінки, 2003. – 719 с.

5. Дремова Н. Б. Маркетинговые исследования лекарственного обеспечения больных доброкачественной гиперплазией предстательной железы / Н. Б. Дремова, А. И. Овод // Человек и его здоровье: Курский науч.- практ. вестник. – 2006. – № 3. – С. 41–54.

6. Ковальов В. М. Фармакогнозія з основами біохімії рослин : підруч. для фармацевт. ВЗО та фармацевт. ф-тів мед. ВЗО III-IV рівнів акредитації / В. М. Ковальов, О. І. Павлій, Т. І. Ісакова. – Харків : Прапор : НФАУ, 2000. – 704 с.

7. Лекарственное растительное сырье и фитосредства : учеб. пособие для мед. (фармацевт.) вузов III-IV уровней аккредитации / под общ. ред. П. И. Середы. – Киев: Медицина, 2010. – 272 с.

8. Фармакогнозія. Лікарська рослинна сировина та фітозасоби / під ред. П. І. Середи. – Вінниця : Нова кн., 2006. – 352 с.

9. Лоскутова Е. Тенденции и структура спроса на препараты из лекарственных растений / Е. Лоскутова, О. Базаркина // Рос. аптеки. – 2003. – № 3. – С. 38–40.

10. Перинская Ю. С., Саканян Е. И. Современное состояние и перспективы разработки лекарственных средств на основе корневищ с корнями родиолы розовой (Rodiola rosea L.). Химико-фармацевтический журнал. 2014. Т. 48, № 8. С. 28–32.

11. Panossian A., Wikman G., Sarris J. Rosenroot (Rhodiola rosea): Traditional use, chemical composition, pharmacology and clinical efficacy. Phytomedicine. 2010. Vol. 17. P. 481–493.

12. Dimpfel W., Schombert L., Panossian A. G. Assessing the Quality and Potential Efficacy of Commercial Extracts of Rhodiola rosea L. by Analyzing the Salidroside and Rosavin Content and the Electrophysiological Activity in Hippocampal Long-Term Potentiation, a Synaptic Model of Memory. Front Pharmacol. 2018. Vol. 9. Article 425. URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5976749.

13. Amsterdam J. D., Panossian A. G. Rhodiola rosea L. as a putative botanical antidepressant. Phytomedicine. 2016. Vol. 23. P. 770–783.

14. Dimpfel W., Schombert L., Vega-Morales T., Wiebe J. C. Neuropharmacological Characterization of Extracts from Rhodiola rosea, Oenothera paradoxa and Paullinia cupana in Comparison to Caffeine. Pharmacology and Pharmacy. 2016. Vol. 7. P. 290–303.

15. Panossian A. G., Amsterdam J. D. Adaptogens in Psychiatric Practice. Rhodiola rosea, Schisandra chinensis, Eleutherococcus senticosus, and Withania somnifera. In: Complementary and Integrative Treatments in Psychiatric Practice / ed. by P. L. Gerbarg, P. R. Muskin, R. P. Brown. Philadelphia, USA: American Psychiatric Association Publishing, 2017. P. 155–181.

16. Domene A. M. Effects of adaptogen supplementation on sport performance. A recent review of published studies. Journal of Human Sport and Exercise. 2013. Vol. 8, N 4. P. 1054–1066.

17. Panossian A., Wikman G. Effects of Adaptogens on the Central Nervous System and the Molecular Mechanisms Associated with Their Stress-Protective Activity. Pharmaceuticals. 2010. Vol. 3. P. 188–224.

18. Архипова Э. В., Етобаева И. Г., Шантанова Л. Н., Мондодоев А. Г. Фармакотерапевтическая эффективность комплексного растительного средства «Тиреотон» при экспериментальном гипотиреозе. Фундаментальные исследования. 2015. № 1 (часть 5). С. 901–902.

19. Rhodiola rosea L.: an herb with anti-stress, anti-aging, and immunostimulating properties for cancer chemoprevention / Y. Li et al. Curr. Pharmacol. Rep. 2017. Vol. 3. P. 384–395.

20. Rhodiola rosea extracts and salidroside decrease the growth of bladder cancer cell lines via inhibition of the mTOR pathway and induction of autophagy / Z. Liu et al. Mol. Carcinog. 2012. Vol. 51. P. 257–267.

21. Куркин В. А. Родиола розовая (золотой корень): стандартизация и создание лекарственных препаратов: монография. Самара: ООО «Офорт»; ГБОУ ВПО СамГМУ Минздрава России, 2015. 240 с.

22. Степанова Э. Ф., Ширзад Б., Евсеева С. Б. Родиола розовая: состояние исследований и возможности создания космецевтических и дерматологических средств. Фармация и фармакология. 2016. Т. 4, № 5. С. 36–62.

23. Iheozor-Ejiofor P., Dey E. S. Extraction of rosavin from Rhodiola rosea root using supercritical carbon dioxide with water. J. Supercrit. Fluids. 2009. Vol. 50, N 1. P. 29–32.

24. Supercritical Carbon Dioxide Extraction of Salidroside from Rhodiola rosea L var. rosea Root / Y. X. Wu et al. Journal of the Chinese Chemical Society. 2011. Vol. 58, N 2. P. 222–227.

25. Enhancing effect of lipids and emulsifiers on the accumulation of quercetin metabolites in blood plasma after the short-term ingestion of onion by rats / K. Azuma, K. Ippoushi, H. Ito [et al.] // Biosci Biotechnol. Biochem. – 2003. – Vol. 67, N 12. – P. 2548–2555.

26. Kelly G. S. Quercetin. Monograph / G. S. Kelly // Altern. Med. Rev. – 2011. – Vol. 16, N 2. – P. 172–194.

27. Preparation, characterization, and in vitro/vivo evaluation of indion-based chewable tablets of paracetamol and ibuprofen for pediatric use / A. Helmy, S. Kady, A. Khames, A. Abdelbary // J. of American Science. – 2011. – № 7. – P. 831–844.

28. Bowman C. Administration of drugs to patients with swallowing difficulties / C. Bowman // J. of the Malta College of Pharmacy Practice. – 2007. – №12. – P. 42–45.

29. Karuna B. Taste masking to improve compliance / B. Karuna, G. Savita, S. Sushma // Internat. Research J. Of Pharm. and Applied Science. – 2013. – № 3. – P. 224–237.

30. Safety of chewable tablets for children. / Th. Michele, B. Knorr, E. Vadas, Th. Reiss // J. of Asthma. – 2002. – № 5. – P. 391–403.

31. Formulation and in vitro bioequivalence study of amoxycillin and potassium clavulanate chewable tablet /K. Mohit, Ch. ugaldas, B. Ajay, A. Vijay // Internat. J. of Pharm. and Chemical Sciences. – 2014. – Vol.3. – P. 158–167.

32. Quality Attribute Considerations for Chewable Tablets. Guidance for Industry. Draft guidance. U.S. Department of Health and Human Services FDA Pharmaceutical Quality/ CMC. – 2016. – 13 p.

33. Chewable Tablets: Is this Dosage Form Well Evaluated by Palestinian Health Professionals? /N. Z. Abdel, O. Abeer, Abu Ghosh [et al.] // The Islamic University J. – 2007. – Vol. 15, № 2. – P. 83–94.

34. Formulation and characterization of albendazole chewable tablets / V. Anusha, S. Palanichamy, M. Sugumar, M. Rajesh // Pelagia Research Library Der Pharmacia Sinica. – 2012. – № 3 (2). – P. 211–216.

35. Comparative evaluation of the in vitro efficacy of lanthanum carbonate chewable tablets /Y. Yang, S. Bykadi, A. Carlin [et al.] // J. Pharm. Sciences. – 2013. – Vol. 102. – P. 1370–1381.

36. Effect of probiotic chewing tablets on early childhood caries – a randomized controlled trial / T. Hedayati-Hajikand, U. Lundberg, C. Eldh [et al.] // BMC Oral Health. – 2015. – № 15. – 5 p.

37. Renu. Chewable Tablets: A Comprehensive Review / Renu, D. Jyoti, J. Pawan, Balvinder Singh // The Pharma Innovation J. – 2015. – № 4. – P. 100–105.

38. An update of taste masking methods and evaluation techniques / V. Sonawane, M. Saiffee, N. Shinde, [et al.]. // Scholars Research Library Der Pharmacia Lettre. – 2010. – № 2 (6). – P. 1–15.

39. Mirajkar R. Taste masking methods and agents in pharmaceutical formulations / R. Mirajkar, M. Devkar, D. Kokare // Internat. Research J. of Pharmacy. – 2012. – № 3. – P. 67–70.

40. A review: taste masking techniques in pharmaceuticals / S. B. Ahire, V. H. Bankar, P. D. Gayakwad, S. P. Pawar // Pharma Science Monitoran International J. of Pharm. Sciences. – 2012. – № l-3 (3). – P. 68–82.

41. Datrange P. Development of taste masked formulation for bitter drug / P. Datrange, S. Kulkarni, R. R. Padalkar // Research J. of Pharm., Biol. and Chemical Sciences. – 2012. – № 3. – P. 727–753.

42. Development of Guava extract chewable tablets for anticariogenic activity against Streptococcus mutans / S. Saraya, J. Kanta, N. Sarisuta [et al.]. // Mahidol University J. of Pharm. Sciences. – 2008. – № 35. – P. 18–23.

43. Formulation and evaluation of loratadine chewable tablets. / K. Kathiresan, P. Vijin, C. Moorthi, R. Manavalan // Research J. of Pharm. Biol. and Chemical Sciences. – 2010. – № 1. – P. 763–774.

44. Formulation development and evaluation of chewable tablet of albendazole by different techniques / L. Sukhbir, P. Bharat, K. Hitesh, P. Rahul // Internat. J. of Pharmacy and Pharm. Sciences. – 2012. – Vol 4. – P. 461–464.

45. Jayadev P. Formulation development and evaluation of chewable tablets containing non-sedating antihistamine / P. Jayadev, V. Vishwajith, V. Gopal // J. of Pharm. And Scenic Innovation. – 2012. – № 3. – P. 112–117.

46. Priyanka. Formulation development and evaluation of montelukast sodium chewable tablets. / Priyanka, B. Pragati Kumar // J. of Chemical and Pharm. Sciences. – 2013. – Vol.6. – P. 35–40.

47. Preparation and evaluation of pentoxifylline loaded chewable tablet for the treatment of peripheral vascular diseases / N. Upendra, B. Charu, K. Ashok, G. Neha // Scholars Research Library Der Pharmacia Lettre. – 2014. – № 6. – P. 58–64.

48. Белей Н. М., Грошовий Т. А., Белей С. Я. Сучасний стан створення, виробництва та дослідження таблетованих лікарських препаратів // Фармацевтичний часопис. 2016. № 4. С. 85-90.

49. Thombre R. Anti-bacterial activity of various medicinal plants against mixed dental flora. / R. Thombre, A. Khadpekar, A. Phatak // Research J. of Pharm., Biological and Chemical Sciences. – 2012. – Vol. 3. – P. 179–182.

50. Компендиум OnLine [Электронный ресурс]. – Режим доступа: URL: http://compendium.com.ua/

51. Мнушко З. Н. Теория и практика маркетинговых исследований в фармации / З. Н. Мнушко, И. В. Пестун. – Харьков: Изд-во НФаУ, 2008. – 307 с.

52. RxIndex – Класифікатор лікарських препаратів [Електронний ресурс]. – Режим доступу: URL http://www.rxindex.info/

53. Effect of pectin enhancement on plasma quercetin and fecal flora in rutin- supplemented mice / M. Tamura, H. Nakagawa, T. Tsushida [et al.] // J. Food Sci. – 2007. – Vol. 72, N 9. – P. S648–S651.

54. Темирбулатова А. М. Разработка состава, технологии и норм качества для БАД адаптогенного действия с экстрактом родиолы розовой: дис. канд. фарм. наук: 15.00.01 / Темирбулатова Анна Михайловна. – Пятигорск, 2007. – 134 с.

55. Dionex Corporation. Determination of Water- and Fat-Soluble Vitamins by HPLC. // Technical Note 89, LPN 2533, 2010.

56. Крендаль Ф.П., Козин С.В., Левина Л.В. Сравнительная характеристика препаратов из группы фитоадаптогенов — женьшеня, элеутерококка и родиолы розовой. – М.: ПРОФИЛЬ, 2007, – 392 с.

57. Куркин В.А. Родиола розовая (Золотой корень): стандартизация и создание лекарственных препаратов. – Самара: ООО «Офорт», 2015. – 240 с.

58. Державна Фармакопея України. Допов. 2 : введ. в дію з 1 лют. 2008 р. наказом М-ва охорони здоров’я України від 29 січ. 2008 р. № 33 / Держ. служба лікар. засобів і виробів мед. призначення. – 1-е вид. – Харків, 2008. – 617 с.

59. Фармацевтичні та медико-біологічні аспекти ліків : навч. посіб. / за ред. І. М. Перцева. – 2-е вид., перероб. та доп. – Вінниця : Нова кн., 2007. – 728 с.

APPENDIXES

Appendix A

III Міжнародна науково-практична інтернет-конференція

ПРОБЛЕМИ ТА ДОСЯГНЕННЯ СУЧАСНОЇ БІОТЕХНОЛОГІЇ

24 березня 2023 р.
м. Харків, Україна

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ
КАФЕДРА БІОТЕХНОЛОГІЇ

MINISTRY OF HEALTH OF UKRAINE
NATIONAL UNIVERSITY OF PHARMACY
DEPARTMENT OF BIOTECHNOLOGY

ПРОБЛЕМИ ТА ДОСЯГНЕННЯ СУЧАСНОЇ БІОТЕХНОЛОГІЇ

PROBLEMS AND ACHIEVEMENTS OF MODERN BIOTECHNOLOGY

Матеріали
ІІІ міжнародної науково-практичної
Інтернет-конференції

Materials
of the III International Scientific and Practical
Internet Conference

ХАРКІВ
KHARKIV
2023

Despite the focus of this work on solving applied optimization problems in agricultural biotechnology, it is also advisable to apply them to solve applied optimization problems for other complex systems. This will improve the quality of functioning of simulated systems by taking into account the structure of the studied objects and characteristics of technical means providing the studied process.

Studies of the pharmacotechnological properties of the Rhodiola rosea and Quercetin extract powder

Malak Asaad, Ruban O.

Department of Industrial Technology of Drugs of the National University of Pharmacy, Kharkiv, Ukraine

ruban_elen@ukr.net

One of the leading problems of modern medicine is the development of tools and methods to prevent the growth of pathological changes in the body, which are caused by stress reactions of various nature. Currently, the problem of both treatment and prevention of a wide range of diseases caused by chronic stress - various forms of psychosomatic pathology and neurosis is very relevant.

We decided to develop a medicinal product in the form of chewable tablets for the treatment of neuroses. Rhodiola rosea extract and quercetin were chosen as active substances. Quercetin has an antioxidant and capillary-stabilizing effect, and Rhodiola rosea extract is often used as a general tonic and adaptogen.

The production of tablets begins with the study of the properties of the original medicinal substances, which determine the rational way of tablets and the choice of excipients. The most complete conduct of the tablet material during compression reflects the mass, fluidity, degree of compaction and compressibility. Therefore, we conducted a study of the properties of the powder of dry extract of Rhodiola rosea and quercetin. In the course of the study, it was determined that the dry extract of Rhodiola rosea belongs to low-flowing materials, and quercetin has sufficient fluidity and the ability to compact. The moisture content in the material and the particle size have a significant influence on the fluidity and compaction of powders.

The data obtained from studies of the pharmacotechnological properties of the Rhodiola Rosea and Quercetin extract powder make it possible to predict the composition and amount of excipients for the development of the drug in the form of chewable tablets.

Investigation the antimicrobial activity of ethanolic extract of green tea leaves against the Gram-positive strains

Maslov O.Yu., Kolisnyk S.V., Kostina T.A., Moroz V.P., Poghosyan O.G.

National University of Pharmacy, Kharkiv, Ukraine

alexmaslov392@gmail.com

Green tea leaves are known to contain various bioactive compounds with potential health benefits, including antibacterial properties. The main components of green tea leaves responsible for this property are catechins, which are powerful antioxidants that can also exhibit antimicrobial activity.

Green tea leaves extract can be used as a natural alternative to synthetic antibiotics. Unlike synthetic antibiotics, which can lead to the development of antibiotic-resistant strains of bacteria, green tea leaves extract does not promote the emergence of resistant strains. Additionally, green tea leaves extract can be used in combination with synthetic antibiotics to enhance their effectiveness and reduce their side effects.

The aim of the study was determined the antibacterial activity of green tea leaves ethanolic liquid extract against the Gram-positive strains.

Green tea leaves of spices Chun My were taken for the study, the raw material was collected in Anhui province (China) from March to May. 10.0 g of the grinded leaves was mixed with 200 mL of 96% ethanol. Extraction was carried out within 1 hour on water bath with a condenser, then repeated two times with a new portion of the solvent. After that the obtained extracts were filtrated and concentrated using rotary evaporator to 20 mL.

The antibacterial activity was determined by the method of wells. Preparation of microorganisms` suspensions with determined concentrations of microorganisms

National University of Pharmacy

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

APPROVED
The Head of the Department of Industrial Technology of Drugs

Olena RUBAN
"_15_" __of May__ 2022

ASSIGNMENT
FOR QUALIFICATION WORK
OF AN APPLICANT FOR HIGHER EDUCATION

Malak ASAAD

1. Topic of qualification work: «Development of composition and technology of tablets with rhodiola rosea extract», supervisor of qualification work: Olena RUBAN, head of the Department of Industrial Technology of Drugs, professor.

approved by order of NUPh from "6th" of February_2023 № 35

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

3. Outgoing data for qualification work: tablets, Rhodiola, Quercetin, psycho-emotional stress, technology.

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

5. List of graphic material (with exact indication of the required drawings):

tables – 5, pictures – 5

6. Consultants of chapters of qualification work

Chapters	Name, SURNAME, position of consultant	Signature, date	
		assignment was issued	assignment was received
1	Olena RUBAN, Head of the Department of Industrial Technology of Drugs, professor	19.05.2022	19.05.2022
2	Olena RUBAN, Head of the Department of Industrial Technology of Drugs, professor	12.12.22 - 21.01.2023	12.12.22 - 21.01.2023
3	Olena RUBAN, Head of the Department of Industrial Technology of Drugs, professor	16.02.2023	16.02.2023

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

CALENDAR PLAN

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

An applicant of higher education _____ Malak ASAAD

Supervisor of qualification work _____ Olena RUBAN

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

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

Прізвище студента	Тема кваліфікаційної роботи		Посада, прізвище та ініціали керівника	Рецензент кваліфікаційної роботи
• **по кафедрі заводської технології ліків**				
Ассаад Малак	Розробка складу та технології таблеток з екстрактом родіоли рожевої	Development of the composition and technology of tablets with Rhodiola rosea extract.	проф. Рубан О.А.	проф. Ярних Т.Г.

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

№ 112732 від « 29 » квітня 2023 р.

Проаналізувавши випускну кваліфікаційну роботу за магістерським рівнем здобувача вищої освіти денної форми навчання Ассаад Малак, 5 курсу, _____ групи, спеціальності 226 Фармація, промислова фармація, на тему: «Розробка складу та технології таблеток з екстрактом родіоли рожевої / Development of the composition and technology of tablets with Rhodiola rosea 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**

11%

32%

Ф А2.2.1-32-353

REVIEW

for qualification work of the master`s level of higher education, specialty

226 Pharmacy, industrial pharmacy

Malak Asaad

on the topic: «Development of composition and technology of tablets with Rhodiola rosea extract»

Relevance of the topic. Psychoemotional disorders and stress are one of the most urgent problems of modern life. According to the literature, every 25 minutes a person feels psycho-emotional stress. Psychoemotional and cerebrovascular disorders arise as a result of age-related changes in the structure and function of the brain, chronic stress, and various pathologies. The problem of both treatment and prevention of a wide range of diseases caused by chronic stress - various forms of psychosomatic pathology and neuroses - is relevant. Chewable tablets are a convenient dosage form for the treatment of such conditions. They have many advantages compared to other dosage forms, have good bioavailability and consumer qualities. Therefore, the creation of a new drug in the form of nutritional tablets with dry extract of Rhodiola rosea and quercetin for the treatment of psycho-emotional stress is an urgent task of pharmaceutical technology.

Practical value of conclusions, recommendations and their validity. Malak Asaad reviewed the main etiopathogenetic aspects of psycho-emotional disorders, modern approaches to their treatment, theoretically substantiated the use of active pharmaceutical ingredients - dry rhodiola and quercetin. On the basis of the analysis of the results of the conducted studies, the author made conclusions on the evaluation of the pharmacotechnological properties of the studied APIs, the substantiation of the composition of excipients. Industrial technology for the

production of chewable tablets with dry rhodiola extract and quercetin for the treatment of psychoemotional stress has been developed.

Assessment of work. Qualifying work is done at a high level.

General conclusion and recommendations on admission to defend. The qualifying work meets all the requirements for qualifying papers and can be submitted for defense to the Examination Board of the National University of Pharmacy.

Supervisor of qualification work _____ Olena RUBAN

"08" April 2023

Ф А2.2.1-32-356

REVIEW

for qualification work of the master`s level of higher education, specialty

226 Pharmacy, industrial pharmacy

Malak Asaad

on the topic: «Development of composition and technology of tablets with Rhodiola rosea extract»

Relevance of the topic. According to medical statistics, psycho-emotional stress is a very common human condition today. Synthetic active pharmaceutical ingredients are more commonly used to treat such conditions. These drugs often have a wide range of side effects, and long-term use can be addictive. According to the literature, it is known that plant extracts have a wide range of pharmacological activity, can be used for a long time, and do not adversely affect the human body. In this regard, the development of new drugs that contain active pharmaceutical ingredients of plant origin is relevant.

Theoretical level of work. The literature review presents the etiology and pathogenesis of psychoemotional stress, the main directions of its treatment. On the basis of literature data, the author substantiates the use of a plant extract of Rhodiola rosea and quercetin as part of chewable capsule tablets for the treatment of this disease. The expediency of creating such a dosage form as chewable tablets is substantiated. The necessity of using excipients with different pharmacotechnological properties in the composition of the preparation has been proved.

The author's suggestions on the topic of research. For the production of tablets, the choice of the fluidized bed granulation method was justified. Based on the results of the studies, the choice of excipients is substantiated, the composition and technology for the production of chewable tablets are proposed.

Practical value of conclusions, recommendations and their validity. Scientific provisions, conclusions and recommendations formulated in the work are based on experimental data. The reliability of the results is beyond doubt.

Disadvantages of work. In the work there are unsuccessful expressions, and grammatical errors.

General conclusion and evaluation of the work. The qualification work of Malak Asaad in terms of the volume and results of research meets all the requirements that apply to qualifying works and can be submitted for defense to the Examination Board of the National Pharmaceutical University.

Reviewer _____prof. Tetyana YARNYKH

"15" April 2023

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'ЯУКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ВИТЯГ З ПРОТОКОЛУ № 9

« 21 » квітня 2023 року

м. Харків

засідання кафедри

заводської технології ліків

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

ПОРЯДОК ДЕННИЙ:

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

СЛУХАЛИ: здобувача вищої освіти5 курсу групи Фм18(4,10)англ-4 Малак АССААД про представлення до захисту в Екзаменаційній комісії НФаУ кваліфікаційної роботи на тему: «Розробка складу та технології таблеток з екстрактом родіоли рожевої». (Керівник: д.фарм.н., професор Олена РУБАН).

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

УХВАЛИЛИ: рекомендувати до захисту в Екзаменаційній комісії НФаУ кваліфікаційну роботу здобувача вищої освіти факультету з підготовки іноземних громадян групи Фм18(4,10д)англ-4 Малак АССААД на тему: «Розробка складу та технології таблеток з екстрактом родіоли рожевої».

Голова
Завідувачка кафедри ЗТЛ **Олена РУБАН**

Секретар **Тетяна ПОНОМАРЕНКО**

Ф А2.2.1-32-042

НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ПОДАННЯ

ГОЛОВІ ЕКЗАМЕНАЦІЙНОЇ КОМІСІЇ
ЩОДО ЗАХИСТУ КВАЛІФІКАЦІЙНОЇ РОБОТИ

Направляється здобувач вищої освіти Малак АССААД до захисту кваліфікаційної роботи за галуззю знань 22 Охорона здоров'я

спеціальністю226 Фармація, промислова фармація

освітньою програмою Фармація

на тему: «Розробка складу та технології таблеток з екстрактом родіоли рожевої».

Кваліфікаційна робота і рецензія додаються.

Декан факультету _____ /Світлана КАЛАЙЧЕВА /

Висновок керівника кваліфікаційної роботи

Здобувач вищої освіти Малак АССААД у процесі роботи розглянула сучасні підходи до лікування психоемоційної напруги, провела аналіз асортименту засобів для терапії даного захворювання та обґрунтувала доцільність створення нового лікарського засобу у формі жувальних таблеток для лікування психоемоційної напруги. Автором обґрунтовано оптимальний склад і розроблено технологію одержання лікарського засобу. Малак АССААД допускається до захисту даної кваліфікаційної роботи у Екзаменаційній комісії Національного фармацевтичного університету.

Керівник кваліфікаційної роботи

_____ Олена РУБАН

«08» квітня 2023 року

Висновок кафедри про кваліфікаційну роботу

Кваліфікаційну роботу розглянуто. Здобувач вищої освіти Малак АССААД допускається до захисту даної кваліфікаційної роботи в Екзаменаційній комісії.

Завідувачка кафедри

заводської технології ліків

_____ Олена РУБАН

« 21» квітня 2023 року

Qualification work was defended

of в Examination commission on

« ____ » _____2023 г.

With the grade_____

Head of the State Examination commission,

DPharm Sc. Professor

_____ / Oleg SHPYCHAK /