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Department of Industrial Technology of Drugs

QUALIFICATION WORK

on the topic: **"JUSTIFICATION OF THE COMPOSITION OF A SOFT MEDICINAL PRODUCT FOR THE TREATMENT OF HERPES INFECTION"**

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ANNOTATION

Qualification work contains 50 pages, 4 tables, 6 figures, reference list of 47 sources.

The work presents the results of studies of the development of a cream with zinc sulfate and tea tree essential oil for the local treatment of herpetic infection. Sodium alginate, xanthan gum, hydroxypropyl methylcellulose, cetyl alcohol and stearyl alcohol, beeswax, vegetable fatty oils, glyceryl stearate, glycerin and purified water were used as auxiliary substances. The selected composition of the cream is characterized by colloidal and thermal stability, optimal rheological and osmotic properties.

Keywords: cream, zinc sulfate, tea tree oil, herpes simplex virus, emulsions, pharmaceutical technology

АНОТАЦІЯ

Кваліфікаційна робота містить 50 сторінок, 4 таблиці, 6 рисунків, список літератури із 47 джерел.

В роботі представлені результати досліджень щодо розробки складу крему з цинку сульфатом та ефірною олією чайного дерева, призначеного для місцевого лікування герпетичної інфекції. В якості допоміжних речовин використовувалися альгінат натрію, ксантанова камедь, гідроксипропілметилцелюлоза, спирти цетиловий та стеариловий, віск бджолиний, рослинні жирні олії, гліцерилстеарат, гліцерин і вода очищена. Вибраний склад крему характеризується колоїдною та термічною стабільністю, оптимальними реологічними та осмотичними властивостями.

Ключові слова: крем, цинку сульфат, олія чайного дерева, вірус простого герпесу, емульсії, фармацевтична технологія

CONTENTS

LIST OF CONDITIONAL ABBREVIATIONS

AFI – active pharmaceutical ingredient

HSV – herpes simplex virus

HPMC – hydroxypropyl methylcellulose

SFU – State Pharmacopoeia of Ukraine

MP – medicinal product

DF – dosage form

INTRODUCTION

Relevance of the topic. According to scientific data, 80-100% of the world's population are seropositive against herpes simplex virus (HSV) [1-3]. Therefore, an important task of modern infectology is to improve pharmacotherapy and prevention of viral diseases caused by herpes infection.

The main therapeutic goal in the treatment of herpes infections is to selectively influence on the reproduction of HSV at different stages. At the same time, for the treatment of viral infections accompanied by external rashes, adequate antiviral therapy, in addition to systemic drugs, involves the use of topical medications, which is due to the high concentration of the HSV pathogen in the rash, painful areas of lesions and lack of local immunity [4, 5]. To date, it can be argued that synthetic agents of acyclic nucleoside groups – acyclovir, valacyclovir, famiclovir – dominate among drugs for the external treatment of herpetic rashes. However, the use of API-based drugs of synthetic nature has certain disadvantages: a sufficiently high risk of side effects, allergic reactions, disruption of normal biocenosis, etc. In addition, recently there has been an increase in virus resistance to the above drugs and an increase in the recurrence rate of herpetic infection [6, 7]. At the same time, the range of anti-herpetic drugs of natural origin, to which viral resistance develops much less frequently, is very limited.

In this regard, essential oils, particularly tea tree essential oil, are of interest. Thus, in clinical studies, tea tree oil has been shown to have anti-herpetic, anti-inflammatory and analgesic properties, and also accelerates the healing process of herpetic rashes on the lips [8].

It should be noted that the effectiveness of drugs, including topical ones, can be increased by combining several substances in the same dosage form. Combined use of antiviral drugs with different mechanisms of action causes an increase in antiviral activity and reduces or prevents the emergence of pathogen resistance. A promising therapeutic agent is zinc sulfate, which is due to the available data on the antiviral, including anti-herpetic activity of zinc compounds. Zinc ions have been shown to have an antiviral effect by preventing virus penetration by blocking the synthesis of viral protein or inhibiting the activity of viral RNA-dependent RNA polymerase [9, 10].

Thus, **the aim of the work** is to develop a composition of a cream for the treatment of herpetic infection, containing as active pharmaceutical ingredients (API) essential oil of tea tree and zinc sulfate.

In order to achieve this goal, the following tasks had to be accomplished:

● to review scientific literature on the existing problems of local treatment of herpetic rashes and the prospects for the use of essential oils and zinc compounds for this purpose, as well as to characterize the effect of excipients on the biopharmaceutical performance of drugs in soft dosage forms;

● to analyze the range of external medicines for the treatment of herpetic infection presented in the pharmaceutical market of Ukraine;

● Theoretically justify the choice of API concentrations and dosage form (DF) for the developed soft medicinal product;

● experimentally substantiate the composition of excipients and the technology of soft medicinal product based on tea tree essential oil and zinc sulfate;

● make a flowchart of the production of the developed drug with the indication of industrial equipment.

Objects of the study. Tea tree essential oil, zinc sulfate, experimental samples of soft medicinal product.

Subject of the study. Development of the composition and technology of obtaining a soft medicinal product with tea tree essential oil and zinc sulfate as active pharmaceutical ingredients.

Research methods. The following methods were used to solve the tasks set in the work: organoleptic (odor, color, homogeneity); physical and chemical (determination of pH, colloidal and thermal stability; rheological studies by rotational viscometry); pharmacotechnological (study of osmotic activity).

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

Achraf Ed Bbourh, Ruban O. A. The relevance of the development of a new drug for the treatment of herpes infection. *Problems and Achievements of Modern Biotechnology: Materials of the III International Scientific and Practical Internet Conference*, Kharkiv, 24 March 2023. Kharkiv: NUPh, 2023. P. 6–7.

Structure of the work. Qualification work is presented on 50 pages of the printed text and consists of such structural elements: introduction, literature review (section 1), experimental part (sections 2-3), general conclusions, list of the used references containing 47 sources. The work is illustrated with 4 tables and 6 figures.

SECTION 1
CURRENT ASPECTS OF DRUG DEVELOPMENT FOR THE TOPICAL TREATMENT OF HERPES INFECTION: A LITERATURE REVIEW

1.1 Current state of the treatment of herpes infection

Viruses are a special group of living organisms that can reproduce only within living cells. With their high structural diversity and adaptability, viruses cause diseases that affect all life forms. In the human population, they cause many diseases, including several that are extremely lethal and have a high epidemic potential.

Herpes infection is a group of anthropogenic infectious diseases whose causative agents are DNA-containing intracellular viruses of the family *Herpesviridae*, which includes 8 antigenic serotypes of herpes viruses: HSV (*Herpes simplex*) types 1 and 2, *Varicella zoster* virus, Epstein-Barr virus and herpes viruses types 6, 7, 8 [1]. The word "herpes" was first used by Herodotus in the 100th century BC, to refer to diseases accompanied by vesicular rashes on the skin and mucous membranes and fever. A characteristic feature of *Herpes simplex* and other viruses of the family *Herpesviridae* is the ability to extremely long existence of the virus in morphologically altered form in the cells of the host (so-called "latency"), and in case of weakened immunity the disease periodically relapses. Thus, the issue of effective antiviral therapy is relevant for every herpes infection carrier several times in the course of his life [2].

HSV can infect almost all human organs and tissues and cause acute, latent and chronic infection. HSV-1 most often affects the skin and mucous membranes of the face, eyes and mouth, while HSV-2 affects the anogenital area [3, 11].

Infection with herpes viruses can occur in different ways: airborne, hematogenous, sexual, through shared items, and during childbirth [12, 13]. In a healthy person, viral replication is under the control of the immune system, which recognizes biologically foreign agents circulating in the body, i.e. the activity of clinical manifestations of HSV is directly related to the state of the immune system [14]. Since HSV is incorporated into host cell DNA and leads to production of virus-specific proteins that inhibit T-cell immunity, function of cytotoxic lymphocytes, macrophages, natural killers, viral DNA inside cells is not inactivated. This is accompanied by persistence of viruses in the organism during the whole life, which creates conditions for parasitizing cells of immune system and causes immunodeficiency [14, 15]. Therefore, people infected with HSV-1 and HSV-2 always show some manifestations of immunodeficiency, against which different diseases may develop – HIV infection, rheumatoid arthritis, diseases of the gastrointestinal tract and others [16, 17]. In this regard, some researchers believe that the priority in the treatment of herpes infection is the treatment that can inhibit the reproduction of the virus during the acute manifestations and promote the formation of an adequate immune response with its long-term preservation.

Antiviral drugs can act at different stages in the life cycle of the virus. For example, the target for selective action of antiviral drugs can be:

- adsorption of the virus on the cell receptors;
- the penetration of the virus into the cell;
- "release" of the viral genome;
- formation of viral proteins;
- the process of virus molecule formation ("packaging");
- the exit of the virus from the cell.

Most antiviral drugs interfere with the functioning of viral enzymes or structural proteins, on which their more or less pronounced selectivity is based. Some drugs bind to cellular proteins or glycoproteins that are necessary for viral replication inside the cell or that serve as receptors for viruses. Antiviral drugs inhibit the multiplication of the virus and thus allow the immune system to "cope" with fewer cells infected by the virus. But there are antiviral drugs that merely increase the synthesis of cytokine proteins (interferons, etc.), that is, their mechanism of action is to strengthen the body's own immune response. Thus, to date, there are three main directions in the treatment and prevention of exacerbations of herpes infection: chemotherapy (use of antiviral drugs); immunotherapy (nonspecific and specific); a comprehensive method of treatment that combines immunotherapy with antiviral therapy [18]. Considering the above, anti-herpetic drugs must meet the following requirements:

- have high bioavailability;
- exhibit specific antiviral activity;
- not to damage healthy cells in the body;
- have no carcinogenic effect;
- have a dose-dependent effect;
- easily excreted from the body and does not cumulate;
- have no general toxic effects on the body, which will ensure that they can be used repeatedly over a long period of time.

Most modern anti-herpetic drugs are acyclic nucleoside derivatives – herpes virus replication inhibitors that specifically interact with the viral DNA polymerase. These include: acyclovir, valacyclovir, pencyclovir, famiclovir. Recently, especially in immunodeficient patients, high recurrence rates of herpetic infection and the growth of pathogen resistance to acyclovir have been noted [19]. To date, new drugs of this group have been synthesized – ganciclovir and penciclovir, whose mechanism of action is similar to acyclovir. Ganciclovir has high antiviral activity, but exhibits hepatotoxicity and hematotoxicity. Valacyclovir, due to its molecular modification, has higher bioavailability compared to acyclovir, which allows to reduce the number of times the drug is taken, so it is more convenient to use [18].

Despite the effectiveness of acyclic nucleoside agents, antiviral chemotherapy with these drugs is characterized by such drawbacks as the development of side effects (especially with ganciclovir and the formation of resistance of viruses to the drugs [6, 7, 18].

Herpes infection can be classified as a skin psychosomatic disease, which due to the frequency and nature of rashes (on the face, intimate areas of the skin) affect the emotional sphere of the patient and thereby create a number of medical, sociological, psychological and cosmetic problems. In this connection, anti-herpetic therapy, in addition to systemic drugs, should also include drugs for local use, which will reduce the clinical manifestations of the infection, accelerate the time of epithelialization of erosions, block reactivation of the virus in persistent foci by forming an adequate, long-term immune response [2, 18, 19].

1.2 Prospects for the use of tea tree essential oil for local therapy of herpes infection

Prospective therapeutic agents in the treatment of herpetic infection are essential oils of many essential oil-bearing plants, which is explained by their positive effect on the body's defenses, the immune system and their action directly on the immunocompetent cells. In this regard, essential oils of medicinal plants attract attention as sources for creating antiviral, immunomodeling and anti-inflammatory drugs [20, 21].

More than 2000 essential oil-bearing plants are currently known; the content of essential oils in them is determined by a number of factors and varies from 0.1 to 4.0 %. Oils include monoterpenes, mono-terpenols, terpenephenols, oxides, esters and ethers, aldehydes, ketones, aliphatic and cyclic acids. It was found that essential oils have a very complex chemical composition and contain biologically active compounds similar in structure and mechanism of action to antibiotics, antiseptics, hormones, vitamins. In addition, they inhibit the activity of pathogenic microorganisms and contribute to the penetration of antibiotics into the human cell, thus making it possible to reduce doses of chemotherapy drugs. Essential oils in mixture with medicinal substances enhance the effect of the latter by 4-10 times. Currently there is enough evidence that the components of essential oils can enhance or accelerate the penetration of substances into the skin. Such substances are called enhancers. They provide sufficient, and most importantly, precisely directed therapeutic effect, which makes it possible to reduce the dose of drugs in severe diseases [22]. For example, the volatile substance limonene, which is a component of essential oils, increases the resorption of more drugs. and hormones through the skin. Menthone and carvone (ketone monoterpenes) also have similar effects to limonene. Terpinen-4-ol and α-terpineol – (monoterpene alcohols) – accelerate skin penetration of caffeine and prednisolone. In all these cases, transdermal penetration of drugs is enhanced due to a change in lipid fluidity in the stratum corneum at physiological temperature [22, 23].

Essential oils of higher plants and, in particular, of tea tree, thyme, eucalyptus, etc. are of considerable interest in the aspect of creating anti-herpetic preparations for local application. It is known that they have a wide range of antibacterial and antifungal activity. They are also characterized by a pronounced bactericidal, antiviral, immune stimulating, anti-inflammatory, expectorant effect [24].

According to the literature, an effective essential oil against herpes simplex virus (type I and type II) is tea tree oil, which is obtained by hydrodistillation from the leaves of the tea tree (Latin *Melaleuca*). Tea tree oil has antibacterial, anti-inflammatory, antiviral and fungicidal properties. Tea tree oil contains:

- terpinen-4-ol – not less than 30.0%;
- γ-terpene – 10.0-28.0 %;
- *p*-cymene – 0.5-12.0%;
- β-myrcene – 1.0-3.0 %;
- α-terpeniol – 1.5-8.0%;

- terpinolene – 1.5-5.0%;
- limonene – 1.5-4.0% [25].

Tea tree oil is a very strong antiseptic (8 times stronger than carbolic acid and 12 times stronger than phenol). A fairly wide range of bacteria has been studied for sensitivity to tea tree oil. Most bacteria have been shown to be sensitive to tea tree oil at concentrations up to 1%, and some strains show sensitivity at higher concentrations, sometimes above 2%. As for *in vivo* activity, some studies have shown its high activity against HSV. For example, treatment of herpes virus-infected monolayer cells with tea tree oil at a concentration of 0.003% reduced HSV-1 titers by 98.1% and HSV-2 titers by 93%. A study of the activity at different stages of the replicative cycle showed the greatest efficacy at the free virus stage (i.e., before cell infection). The main antimicrobial activity correlates with 2 components of the oil, they are terpinen-4-ol and α-terpeniol. Other constituents contribute additionally: α-pinene, β-pinene, and linalool. Although tea tree essential oil has been used, for example, in Australia since the 1920s, no clinically significant cases of resistance have been identified [8, 26].

1.3 Prospects for the use of zinc compounds for local therapy of herpetic infection

Zinc, a chemical element of the minor subgroup of the second group of the periodic system, is one of the indispensable trace elements, ranking second after iron in distribution in the human and animal body and in participation in metabolic processes. Zinc belongs to the category of heavy metals; its name in literal translation from Latin (zincum) means "white plaque" [27]. [27].

In nature, zinc exists in the only stable form of the Zn ion^{2+}. Scientific data accumulated to date allow us to state that Zn is an important element for the functioning of a wide range of physiological functions of living organisms. Its average total content in the tissues of the human body is about 2-3 g, mostly in the protein-bound state. According to a rough estimate, about 10% of the genes of the entire human genome encode proteins capable of binding Zn [27]. More than 300 metalloenzymes [28] and 2,000 transcription factors [29], which require Zn to function, are currently known. Zn-containing matrix metalloproteinases (MMPs), which can hydrolyze almost all extracellular matrix proteins and determine the structural organization and regeneration of the dermis and epidermis, play an exceptional role in human skin physiology.

Zinc plays an extremely important role in human immune homeostasis. It has a versatile cell-specific effect on a wide range of immune system cells involved, among others, in the pathogenesis of skin diseases and inflammation: mast cells, platelets, macrophages, neutrophils. In some cases, Zn itself can act as an inhibitor of cellular functions, for example in relation to mast cells and platelets, while in other situations zinc deficiency leads to inhibition of the immune response [27, 30].

Zinc also has anti-inflammatory properties, which justifies the use of zinc for both the prevention and treatment of inflammatory dermatoses. The antioxidant properties of zinc are also well known. Zinc reduces UV-induced damage to cells and their genetic apparatus. To some extent, this effect is due to the action of Zn-containing enzymes and proteins involved in the elimination of active oxygen radicals [27, 31].

Zinc has a proven epithelializing property and is important in the wound healing process. This effect is mediated by several mechanisms. First of all, Zn-containing enzymes – in particular, MMPs – are required for the normal healing process. It is known that MMP activity is significantly increased during the wound healing process; these enzymes provide wound cleaning from tissue detritus, modulate the processes of cell migration and extracellular matrix reconstitution. It was shown that artificial inhibition of MMP activity leads to a significant increase in the time required for wound healing [32, 33]. In addition, zinc compounds have moderate antibacterial properties [27], since in increased concentration it inhibits the growth of a number of bacteria, and Gram-positive microorganisms are more sensitive to the inhibitory action of Zn than Gram-negative ones [34].

Zinc has antiviral properties against a number of viruses by inhibiting the enzymatic processes of viral protease and polymerase as well as virus attachment. The effect of zinc on herpes simplex virus-1 and -2 has been studied for more than 40 years (indicating the undoubted interest of researchers in this trace element), and *in vitro* studies have shown that zinc plays an inhibitory role in virtually all aspects of the virus life cycle: inhibits the function of viral polymerase, protein production and can inactivate free virus. Thus, there are data from clinical studies of the use of 0.5% suspension of zinc sulfate for the treatment of herpes lips. While in the placebo group the time to complete healing was 7-14 days, local use of zinc sulfate reduced this period to 2-4 days [10, 35, 36].

Thus, the inclusion of zinc compounds in anti-herpetic preparations for topical use will not only contribute directly to the antiviral effect, but also accelerate the processes of reparative skin healing.

1.4 Characteristics and basic principles of drug development in soft dosage forms

The most obvious advantage of using preparations for external use is the possibility of treating a range of dermatological pathologies with little effect on the body as a whole. The active ingredient in high concentration gets directly to the area where the therapeutic effect is required, while the risk of undesirable side effects is minimal.

Soft drugs in most cases are complex heterogeneous disperse systems and have specific rheological properties. The quality, efficacy and safety of these drugs depend on the type and composition of the carrier base, the dispersed state of the drug substances, the effectiveness of preservatives, production conditions, storage, etc. Therefore, general requirements for the quality of IRLs, which are regulated in the general pharmacopoeial articles, are very important. Thus, OTC medicines for topical use must be homogeneous in appearance and have specific rheological properties at a set storage temperature. They are intended to be applied to the skin, wounds and certain mucous membranes and have either a local therapeutic, emollient or protective effect, or a general therapeutic effect when the drugs penetrate the skin or mucous membranes [37, 38].

An MLS usually contains the active pharmaceutical ingredients and excipients, which must be evenly distributed in the dosage form. The excipients form a simple or complex base, which is produced separately or obtained in the process of MLS manufacturing. The base, depending on its composition, can affect the bioavailability and the therapeutic effect of the drug substance. Depending on the consistency, viscosity and elasticity, soft dosage forms can be classified into ointments, creams, gels, pastes, liniments.

Ointments are a soft dosage form for topical use, designed to be applied to the skin, wounds or mucous membranes. Ointments are divided into three groups according to their base type: hydrophobic (lipophilic), hydrophobic absorptive (emulsion) and hydrophilic.

Hydrophobic (lipophilic) ointments are prepared mainly on hydrocarbon bases (Vaseline, Vaseline oil, paraffin) and may contain other lipophilic excipients (vegetable oils, animal fats, waxes, synthetic glycerides and liquid polyalkylsiloxanes). Only small amounts of water or aqueous solutions may be introduced into their composition. Such ointments, when used, have an occlusive (preventing contact with air) effect, have a softening effect, are difficult to wash off with water and are not mixed with exudate.

Hydrophobic absorptive ointments are hydrophobic, but can absorb (emulsify) exudate when rubbed into the skin. The bases for them can be divided into two groups:

● hydrophobic bases consisting of hydrocarbons and water-in-oil emulsifiers (petroleum jelly and lanolin or wool wax alcohols) to which significant amounts of water or water solutions can be introduced to form a water-in-oil emulsion;

● hydrophobic bases, which are water-in-oil emulsions (Vaseline and aqueous lanolin). Water or an aqueous solution can additionally be introduced into their composition by emulsification.

Hydrophilic ointments are usually hyperosmolar, so they can absorb significant amounts of exudate when applied. The bases for them can be divided into two groups:

● water-soluble bases, which generally contain hydrophilic non-aqueous solvents (polyethylene glycol 400, propylene glycol, etc.) and water-soluble polymers in sufficiently high concentrations (polyethylene glycol 1500, proxanol 268, etc.);

● water-soluble bases that, in addition to water-soluble polymers and hydrophilic non-aqueous solvents, contain lipophilic substances (higher fatty alcohols, vaseline, vaseline oil, lanolin, waxes, etc.).

These bases are generally oil-water emulsions and require an oil-water emulsifier.

Creams are soft dosage forms for topical use, which are two- or multiphase dispersed systems. As a rule, creams have a less viscous consistency than ointments, although they also contain medicinal substances, oils, fats and other components. Creams are emulsions of the oil-in-water or water-in-oil type. Their composition is divided into hydrophobic (fatty) and hydrophilic (emulsion).

Hydrophobic creams are prepared on the basis of a water-in-oil or oil-water-oil emulsion stabilized with suitable emulsifiers. Hydrophobic creams use a fat base (lanolin, petroleum jelly, stearin) to which various medicinal substances are added, such as vegetable oils, vitamins, hormones, and in some cases various aromatic substances or essential oils.

Hydrophilic creams are prepared on the basis of an oil-in-water or water-in-oil-water emulsion stabilized with suitable emulsifiers. They also include colloidal dispersed systems consisting of higher fatty alcohols or acids dispersed in water or mixed water-glycol solvents, stabilized by hydrophilic surfactants (surfactants).

Gels are soft dosage forms for topical use, which are single-, two- or multiphase disperse systems with a liquid dispersion medium, the rheological properties of which are due to the presence of gel-formers in small quantities. In this dosage form gellants may additionally act as stabilizers of disperse systems: suspensions or emulsions. Such gels may be called suspension gels and emulsions, respectively. According to the type of disperse systems gels are divided into hydrophobic and hydrophilic. Hydrophobic gels (oleogels) are prepared on bases of hydrophobic solvent (Vaseline or vegetable oil, etc.) and lipophilic gel-forming agent (polyethylene, colloidal silicon dioxide, aluminum or zinc soap, etc.). Hydrophilic gels (hydrogels) are prepared on bases of water, hydrophilic mixed or non-aqueous solvent (glycerin, propylene glycol, ethyl alcohol) and hydrophilic gelling agent (carbomers, cellulose derivatives).

Pastes are a soft dosage form for topical use, which is a suspension containing significant amounts of solid dispersed phase (at least 25%), which is evenly distributed in the base. Compared with ointments, pastes have a thicker consistency, which allows them to remain on the surface longer. The base of the paste may be lanolin, Vaseline, glycerin, linseed, olive and other vegetable oils, and most often – their mixtures with each other. If the drug substances included in the paste are less than 25%, the missing amount is supplemented with indifferent powders, such as starch, talcum or zinc oxide.

Liniments (or liquid ointments) are a soft dosage form for external use, which are thick liquids or gelatinous masses that melt at body temperature and are applied by rubbing into the skin. A distinction is made between liniments-solutions are transparent mixtures of fatty oils with essential oils, chloroform, methyl salicylate, ether, turpentine, which contain various solid drug substances soluble in prescribed solvents, such as camphor, menthol, anesthesin, etc.Liniments-suspensions are two-phase systems consisting of suspensions of powdered substances insoluble in prescribed liquids; liniments-emulsions are two-phase systems, which may be an emulsion of water-oil or oil-water type. The advantages of liniments include their high biological activity, ease of application to the skin, and rapid absorption, while the disadvantages are the low stability of some of them and inconvenient transportation [38, 39].

The choice of excipient composition when developing an MLS should be made primarily by taking into account the disease or pathological condition to be treated, the type of skin on which the drug is to be applied, and the properties of the drug substance. It is also necessary to ensure that a sufficient amount of the drug substance can be delivered to the target of action, which may be located both on the surface of the skin and in other organs. In addition, it is important to minimize skin irritation and toxicity. As a rule, when developing formulations, it is necessary to carefully control the physicochemical properties of the drug product, to continuously monitor the stability of the active ingredients as well as functional excipients such as preservatives or antioxidants. For emulsions and ointments, it is important to prevent phase changes such as separation. Consideration should also be given to controlling the microbiological purity of drugs, especially in formulations containing large amounts of water; preservatives must often be added. It is recommended that viscosity and rheological properties be corrected to ensure ease of application and to give acceptable overall cosmetic properties.

The choice of a base for topical dosage forms depends on many factors, ranging from stability and compatibility, the type of disease and skin to which the drug will be applied, and biopharmaceutical factors. In general, lyophilic dosage forms such as ointments and emulsions are preferred for the treatment of diseases that are characterized by dry skin. Ointments are usually used for dry and flaky skin because they provide a moisturizing effect due to their occlusive properties. Increased hydration of the skin can also improve absorption of the medication. In addition, ointments are less irritating to sensitive skin than water-based dosage forms, but they leave a greasy feeling that patients do not like [40, 41].

Emulsion-type dosage forms, such as oil-in-water emulsions, are often preferred because of their good cosmetic properties – they are easy to apply, less viscous and greasy. However, obtaining a stable emulsion can be difficult in some cases. Liquid delivery systems, solutions or gels, are convenient to use on hairy skin areas, such as the scalp, and in some cases to use in the treatment of skin diseases in which a drying effect is desirable [42].

Analysis of the literature has shown that the most promising bases for the manufacture of soft dosage forms in terms of bioavailability, as well as achieving optimal adherence of patients to treatment, are oil-in-water emulsion type bases.

CONCLUSIONS

1. The results of the literature analysis showed that anti-herpetic therapy, in addition to systemic drugs, should include drugs for external use, which will reduce the clinical manifestations of infection by reducing the time of epithelialization of erosions.

2. Essential oils of higher plants and, in particular, of tea tree are of considerable interest in the aspect of creating anti-herpetic preparations for local application. The main activity of tea tree essential oil corresponds to terpinen-4-ol and α-terpeniol as well as α-pinene, β-pinene and linalool. Although tea tree essential oil has been used for quite a long time, no clinically significant cases of resistance have been identified.

3. Many traditional dermatological products contain zinc compounds as active substances, which is explained by the participation of zinc ions in the processes of wound healing, antioxidant protection, synthesis of collagen and elastin. There is also evidence of established anti-herpetic properties of zinc compounds.

4. Summarizes the data on soft dosage forms – classification, groups of excipients included in their composition, and the influence of the latter on the biopharmaceutical and consumer properties of soft dosage forms.

SECTION 2
CHARACTERISTICS OF THE OBJECTS AND METHODS OF RESEARCH

2.1 Analysis of the range of anti-herpetic medicines for topical application in the Ukrainian pharmaceutical market

To date, one of the most pressing issues in pharmaceutical practice is the optimal choice of one or another drug from the line of analogues presented on the pharmaceutical market. To determine the prospects for the successful introduction of a new herpetic drug to the pharmaceutical market of Ukraine, i.e. what are the potential advantages of the developed drug in comparison with analogues, we analyzed the range of dermatological drugs for treatment of herpes infection registered in the State Drug Registry of Ukraine as of the 1st quarter of 2022. [43].

It has been established that in Ukraine there are 26 registered drugs for local treatment of herpetic infection in various LF, which according to the international classification system ATC belong to the following groups:

- D06BB – Chemotherapeutic agents for topical use, Antiviral drugs;
- S01AD – antiviral agents used in ophthalmology;
- L03AX – immunostimulants [43, 44] (Table 2.1).

Table 2.1.

Drugs for local treatment of herpetic infection according to the State Register of Medicines of Ukraine

No. n/a	**Name and medicine form**	**Active ingredients**	**Manufacturer**
1	2	3	4
(D06BB) Topical chemotherapeutic agents, antiviral drugs			

1	Vratisolin, cream	Denotivir	Elfa Pharmaceutical Plant A.T., Poland
2	Epigen Intim Spray	Glycyrrhizinic acid	Cheminova International S.A., Spain B. BRAUN MEDICAL S.A., Spain
3	Acyclovir vishfa, 2.5% ointment	Acyclovir	GKP Pharmaceutical Factory LLC, Ukraine
4	Agerp, cream 5%	Acyclovir	Joint Ukrainian-Spanish enterprise "Sperco Ukraine", Ukraine
5	Lipster, cream 5%	Acyclovir	Farmak PJSC, Ukraine
6	Acyclostad®, cream 5%	Acyclovir	Stada Arzneimittel AG, Germany
7	Acyclovir Belupo, 5 % cream	Acyclovir	Belupo, Hrvatija
8	Zovirax® Duo, cream	Acyclovir	Glaxo Operations UK Limited, United Kingdom

9	Herpevir®, 2.5% ointment	Acyclovir	Kievmedpreparat, PJSC, Ukraine
10	Viroleks, cream	Acyclovir	KRKA, d.d., Novo mesto, Slovenia
11	Zovirax®, cream 5%	Acyclovir	Glaxo Operations UK Limited, United Kingdom
12	Acic®, cream 5%	Acyclovir	Salutas Pharma GmbH, Germany
13	Aflubin® penciclovir, cream 1%	Penziclovir	Novartis Pharma Productions GmbH, Germany
14	Penciclovir-phytopharmcream 1%	Penziclovir	PJSC "Fitofarm", Ukraine
15	Herpestil, cream	Penziclovir	Pharmaceutical company "Zdorovye" LLC, Ukraine
16	Priora cream	Docosanol	Fleet Laboratories Limited, United Kingdom
(S01AD) Ophthalmic drugs, antiviral drugs			

17	Oxolinum ointment	Oksolin	Ternopharm LLC, Ukraine
18	Oksolin, ointment	Oksolin	PJSC "Khimfarmzavod" "Red Star", Ukraine
19	Oksolin, nasal ointment	Oksolin	OAO Nizhpharm, Russian Federation
20	Oksolin-Darnitsa, ointment	Oksolin	Darnitsa Pharmaceutical Company, Ukraine
21	Oxolinum ointment	Oksolin	GKP Pharmaceutical Factory LLC, Ukraine
22	Oksolin, 0.25% ointment	Oksolin	Lubnifarm PJSC, Ukraine
23	Virolex, eye ointment 3%	Acyclovir	KRKA, d.d., Novo mesto, Slovenia
24	Zovirax™, 3% eye ointment	Acyclovir	Jubilant HollisterStier General Partnership, Canada
25	Virgan, eye gel, 1.5 mg/g	Ganciclovir	Farmila-Zea Farmaseutici S.p.a., Italy
(L03AX) Immunostimulants			

26	Cycloferon®, liniment 5%	Acridonacetic acid	Polysan Scientific and Technological Pharmaceutical Company LLC, Russian Federation

The main assortment of drugs in the studied segment is formed by foreign-made drugs (Fig. 2.1), and some drugs enter the market simultaneously from several manufacturers, i.e. there is a "duplication of assortment" effect.

As a result of analysis of the assortment of drugs by API composition, it was found that single-component drugs dominate – 96.3%, while combined drugs occupy only 3.7%.

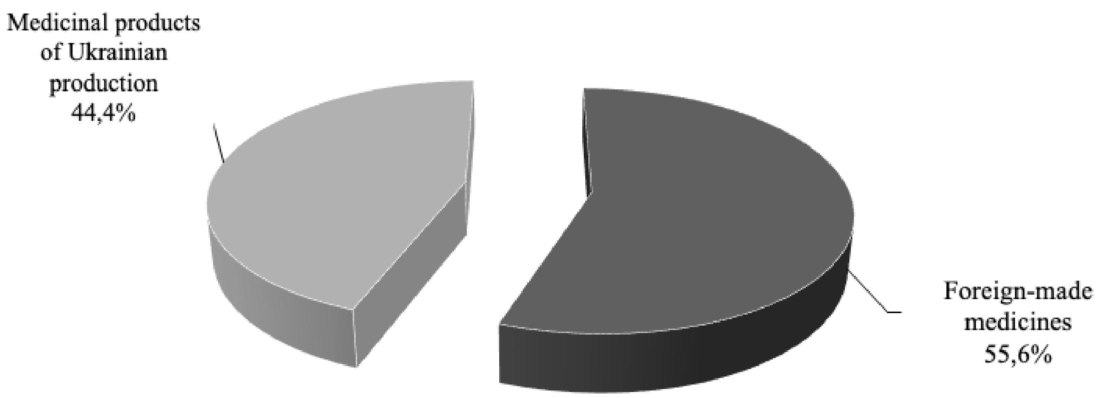


Figure 2.1. Distribution of antiviral drugs for external use of Ukrainian and foreign production

The results of the analysis of the distribution of drugs by type of LF showed that in Ukraine drugs for external treatment of herpetic infection are registered in different LFs – soft, liquid and solid, with soft LFs prevailing among them (Fig. 2.2).

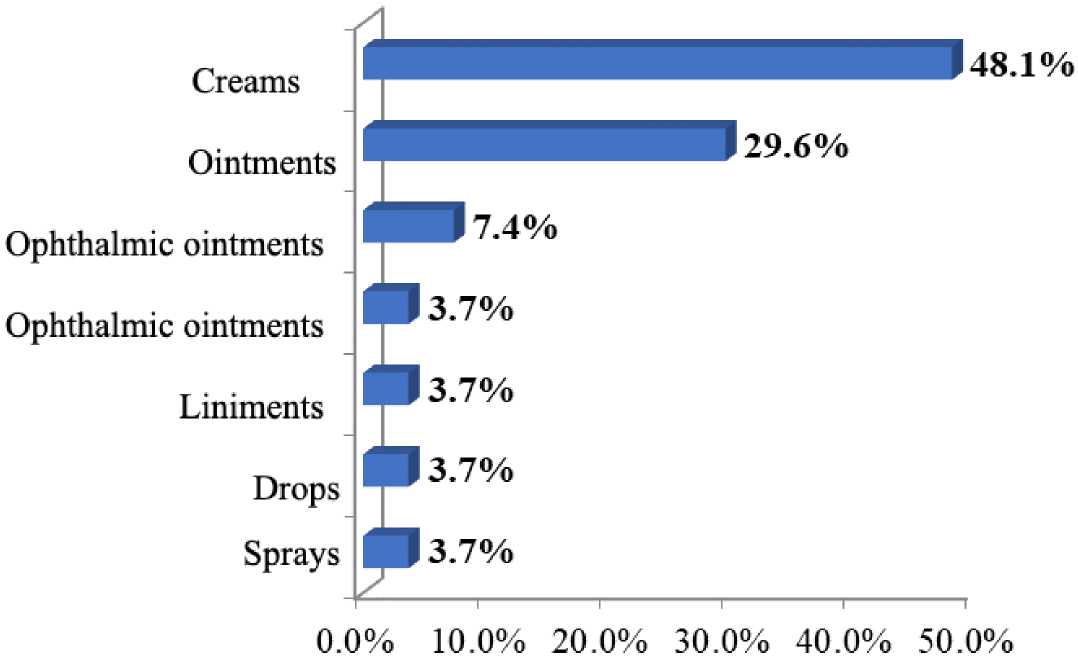


Figure 2.2. Distribution of antiviral drugs for external use by type of medcine form

Thus, we can conclude that acyclic nucleosides – inhibitors of herpes virus replication – dominate among antiviral drugs for the external treatment of herpes infection. However, as noted above, there is an increase in resistance to the above drugs, an increase in the recurrence rate of the disease, and ganciclovir also exhibits high toxicity rates. There are very few drugs of other pharmacological groups, which could provide alternative treatment regimens. The predominance of soft dosage forms, namely creams, among the drugs of the studied segment indicates both the convenience of using this type of FP (they do not spread when applied, are able to stay on the affected tissues), and their biopharmaceutical advantages (provide a long effective concentration at the site of application). All this points to the promising development of a new anti-herpetic drug for the external treatment of herpetic infection in a soft dosage form.

2.2 Objects of research

The research objects were API and model cream samples with zinc sulfate and tea tree essential oil as active ingredients.

Zinc sulfate heptahydrate ($ZnSO_4$ -$7H_2$ O) is a white crystalline powder or transparent colorless crystals, weathered in the air, very easily soluble in water, almost insoluble in alcohol 96% [45, 46].

Tea tree oil is an essential oil that is obtained by hydrodistillation from the leaves of the tea tree (melaleuca). It is a colorless or light yellow liquid with a specific odor with a hint of camphor. It is soluble in ethanol, vegetable oils, propylene glycol; poorly soluble in glycerin; insoluble in water.

Sodium alginate is a salt of alginic acid. In appearance it is a yellowish-white powder. Slowly forms a viscous colloidal solution in water; it dissolves in alcohol, organic solvents, acidic media with a pH value < 3. It is used as a thickener, gelling agent or stabilizer in cosmetic and pharmaceutical products, for example, is part of the medicine "Gaviscon" [45]. The alginate sodium of Keltone LV brand manufactured by Kelco/NutraSweet, (USA) was used in this work.

Hydroxypropyl methylcellulose (HPMC) is a white powder, tasteless and odorless, soluble in cold water and aqueous solutions of some inorganic compounds. It is used as a gelling agent. It dissolves in water in any proportions to form a transparent liquid of different viscosity, depending on the type of HPMC. It is not soluble in oils and fats [45]. In this work, we used HPMC brand Methocel K4M produced by Dow Chemical Co. Ltd.

Xanthan gum is a high molecular weight polysaccharide compound, which is a loose powder of white or cream color, odorless, almost insoluble in ethanol, soluble in cold and hot water. In pharmaceutical technology it is used as a stabilizer, thickener and emulsifier in oral and topical preparations; in cosmetic products and foodstuffs [45].

Glycerol is a triatomic alcohol $CH_2 (OH)CH(OH)CH_2 OH$, which is a syrup-like, sticky to the touch, sweet to the taste, odorless, transparent, colorless or nearly colorless, very hygroscopic liquid, absorbing moisture from air (up to 40% by weight). Glycerin is miscible with water, ethanol in any proportion, it is almost insoluble in fat oils. It is widely used in pharmaceutical practice as a humectant and softening agent, for adjustment of rheological parameters of viscous systems and their moisture-holding properties [45, 46].

Corn oil is a transparent oily liquid of light yellow color with a slight characteristic odor and slightly sweet taste. Chemically it consists of a complex of esters (triglycerides) of natural fatty acids with glycerol. It is easily absorbed by the skin. Being absorbed into epidermal cells, components of corn oil destroy free radicals at molecular level [45].

Medium chain triglycerides are a colorless or yellowish oily liquid, virtually odorless and tasteless, solidifies at 0°C. Derived from fatty oil obtained by extraction from the solid dried endosperm fraction of *Cocos nucifera* L. Soluble in all proportions at 20°C in acetone, 95% ethanol; practically insoluble in water. In emulsions, solutions and suspensions it serves as an emulsifier, solvent and suspending agent for APIs that are unstable or insoluble in aqueous media [45]. Medium chain triglycerides of Kollisolv MCT brand (BASF, Germany) were used in this work.

Refined almond oil is a pale yellow odorless liquid, pleasant in taste, insoluble in water. For therapeutic purposes it can be used as part of the external therapy of eczema, sun and household thermal burns, minor skin injuries, dry dermatitis and herpetic skin infection. It is used both in pure form and in complex remedies in concentrations of 10-50 % [45].

Coconut oil is a vegetable oil obtained from *Cocos nucifera* Linn. (palm family). It is a transparent colorless or light yellow liquid with a slight coconut odor and a pleasant soft taste. Chemically, it consists of triglycerides of fatty acids. It is soluble in ether, carbon disulfide and chloroform, in 2 parts ethanol (95%) at

60°C, practically insoluble in water. Refined coconut oil is a white or nearly white oily mass. The consistency depends on the temperature: 28-30°C – liquid, from pale yellow to colorless; 20°C – semi-solid, <15°C – solid, brittle crystalline substance. It is used as a base in production of preparations in the form of ointments [45].

Soybean oil is a composition of fatty acid glycerides: linoleic (50-57%), linolenic (5-10%), oleic (17-26%), palmitic (9-13%) and stearylic (3-6%). According to its physical and chemical properties it is a yellowish colored and odorless liquid. It is used in emulsions, as well as in many API delivery systems (liposomes, microspheres, self-emulsion systems, nanoemulsions and nanoencapsules), in cosmetic preparations, and as a food product [45].

Stearyl alcohol – flakes or granules of white color, practically insoluble in water, soluble in ethanol (96%); in the melted form it mixes well with fats, liquid and rigid paraffin, lanolin. It melts at 57-60°C, hydrophilic-lipophilic balance is 15.5. It is used in creams and ointments as a thickener (increase of viscosity of emulsions increases their stability). It also has some emollient and weak emulsifying properties and is used to increase water retention capacity in ointments [45, 46].

Cetyl alcohol is white or almost white crystalline powder, practically insoluble in water, soluble in ethanol (96%). When melted it mixes well with fats, liquid and hard paraffin, lanolin. It melts at temperature 46-52°C, hydrophilic-lipophilic balance is 15.5. It is used as emulsifier and thickener, increases stability of MLS, improves their texture and consistency. It is a weak emulsifier, but allows to reduce the amount of emulsifying agent used [45, 46].

Beeswax (yellow wax) – by origin is a natural product of wax glands of the insect *Apis mellifera* Linne (family Apidae), obtained from honeycombs and honeycombs. It looks light yellow, uniform in color, non-greasy to the touch solid mass (or small granules), translucent in a thin layer. It is soluble in fatty and essential oils, insoluble in water, partially – in 95% and hot alcohol. It can be well alloyed with fats, hydrocarbons and other waxes. Its melting point is 61-65°C. It is very viscous in fats and hydrocarbons, the presence of free alcohols in its composition leads to emulsifying properties and gives the ointment bases the ability to absorb watery skin secretions [45].

Glyceryl stearate is an ester of triatomic alcohol and stearic acid. In appearance it is white flakes with a neutral odor, which easily fuse with fatty components. The melting point is 59ºC. In creams and emulsion ointments of oil-in-water type it serves as a non-ionogenic emulsifier [45].

Stearic acid is a white or yellowish-white powder with a slight odor of grease. Its melting point is 69-70°C. Easily soluble in benzene, chloroform, ether, soluble in ethanol (95%), hexane, propylene glycol, practically insoluble in water. It is used as an emulsifying and solubilizing agent in MLS [45, 46].

2.3 Research methods

Organoleptic studies. All model samples of cream were examined for their appearance – color, texture, homogeneity and signs of phase separation. Studies were carried out by visual assessment. Homogeneity was checked in accordance with HFC requirements. The consistency of the samples was determined by smearing the samples on the skin. Also evaluated the sensation of application, including the presence of stickiness, greasiness, film after drying, etc.

The colloidal stability of the model samples was determined by centrifugation. The tested samples were sequentially centrifuged at 6000 rpm for 5 min. After the test, the absence or presence of phase separation in the samples was visually determined.

To study the thermostability of the cream samples were placed in glass tubes with a diameter of 15 mm and a height of 150 mm. Test tubes with samples of 8-10 ml were thermostatted at (42.0 ± 2.0) C for 7 days. Then they were transferred for 7 days to a refrigerator at (6 ± 2)°C. After that, the tubes were kept at room temperature for 3 days. The result was evaluated visually: if no segregation was observed in any tube, the sample was considered stable.

The degree of dispersity of the samples was *determined* by optical microscopy using an optical monocular microscope at a magnification of 400x. To determine the degree of dispersion, a sample of cream 0.05 g was taken and transferred to a slide. The sample was covered with a coverslip, fixed by light pressure, examined under a microscope and photographed.

pH value. 1.0 g of each model sample and the corresponding placebo base were dispersed in 25 ml of distilled water and the pH of the dispersion was determined using a pH meter (Mettler-Toledo) [47]. Measurements were made three times. Before testing, the pH meter was calibrated using standard buffer solutions with pH 4.0, 7.0, and 10.0.

Rheological studies were carried out on a rotary viscometer MYR VR3000" model V2R (Spain). Measurements were performed at 20ºC with shear rates from 0.1 to 50 s^{-1}. The experiment was performed three times for each sample.

The osmotic properties of the MLZ model samples were studied by equilibrium dialysis through a semipermeable membrane. For this purpose, a sample suspension was placed on cellophane film in a cylinder 50 mm in diameter (preweighed). This cylinder with the model sample was placed in another cylinder 70 mm in diameter with distilled water (100 ml) so that the film touched the water surface. At certain intervals, the mass of the inner cylinder was determined. The amount of absorbed moisture was established as a gain in mass.

Statistical analysis of the obtained data was performed using MS Excel 2010 software in accordance with the HFC requirements for statistical processing of the results of the chemical experiment [47]. The results are presented as mean value ± standard deviation. The number of repeated experiments was 3 for all experiments.

CONCLUSIONS

1. In the pharmaceutical market of Ukraine, acyclic nucleosides dominate among antiviral drugs for the external treatment of herpes infections, to which there is a growing resistance of the pathogen. There are very few drugs of other pharmacological groups that could provide alternative treatment regimens. The predominant dosage form among the drugs of this segment is cream, which indicates both the convenience of using this type of drug and its biopharmaceutical advantages. All this points to the promising development of a new anti-herpetic drug with zinc sulfate and tea tree essential oil for the external treatment of herpetic infection in a soft dosage form.

2. Information is given on the excipients that were used during the development of model cream samples: gelling agents and other hydrophilic components, fatty oils, substances with thickening and emulsifying properties.

3. The methods by which the experimental research on the development of the cream: organoleptic studies, determination of colloidal and thermal stability, pH index, rheological and osmotic properties are given.

SECTION 3
PHARMACOTECHNOLOGICAL RESEARCH ON THE DEVELOPMENT OF ANTI-HERPETIC CREAM WITH ZINC SULFATE AND TEA TREE ESSENTIAL OIL

3.1 Preparation of model cream samples

Based on the literature data on the role of zinc in maintaining skin homeostasis, its therapeutic properties, as well as taking into account the physical and chemical properties (primarily, solubility) of the most common compounds of this trace element in dermatology and cosmetology, zinc sulfate was chosen as an API. The choice of API concentration was also based on the literature data. Thus, there is evidence of successful clinical use of an anti-herpetic gel based on 1.0 % zinc sulfate under the trade name Virudermin (manufactured by Robugen GmbH, Germany), which was the basis for choosing the API concentration of 1.0 % in the developed product. The concentration of tea tree essential oil was also selected on the basis of the data presented in the literature review and was 2.0 %.

When selecting the form of a drug for external application, it is necessary to consider not only the characteristics and advantages of a particular FP, but also the specifics of the pathological process for the treatment of which the drug under development is supposed to be used. Since the drug under development is intended to treat cutaneous manifestations of herpetic infection that are accompanied by inflammation and exudation, moderate osmotic properties are desirable – to ensure the outflow of exudate from the wound. On the other hand, it is necessary for the preparation to promote reparative and epithelializing processes in the place of application, so an emulsion oil-in-water base in cream form is preferred, which has moderate osmotic activity and can also have a soft reparative effect due to the excipients included in its composition. Consequently, the research was aimed at developing a drug in the form of a cream.

We prepared 11 model cream samples containing zinc sulfate and tea tree oil as API, as well as different gelling agents (for additional thickening of dispersion medium and thus stabilization of dispersion phase) – sodium alginate, xanthan gum and hydroxypropyl methylcellulose (HPMC). The composition of model cream samples is presented in Table 3.1.

Table 3.1.

Composition of model samples of cream with zinc sulfate and tea tree oil

Ingredients	Content, %										
	Model number										
	№1	№2	№3	№4	№5	№6	№7	№8	№9	№10	№11
1	2	3	4	5	6	7	8	9	10	11	12
Zinc sulfate	1										
Tea tree essential oil	2										
Corn oil	4	4	4	4	-	-	-	-	-	-	-
Almond Oil	4	4	4	4	4	4	5	-	-	-	-
Medium chain triglycerides (Kollisolv MCT)	4	4	4	4	3	3	3	5	5	4	4
Almond Oil	4	4	4	4	4	4	5	-	-	-	-
Coconut oil	-	-	-	-	-	-	-	5	5	4	4
Soybean oil	-	-	-	-	6	6	6	5	5	4	4
Stearyl alcohol	4	5	6	6	-	-	-	-	-	-	-
Cetyl alcohol	5	6	6	7	5	4	5	7	6	6	6
Beeswax	7	8	6	6	3	4	6	7	-	-	-
Glyceryl stearate	5	6	6	6	5	5	5	5	5	5	4
Stearic acid	-	-	-	-	3	2	3	4	4	5	5
GPMC	-	-	-	-	-	-	-	-	0,1	0,1	0,1
Sodium alginate	0,35	0,35	0,35	0,35	-	-	-	-	-	-	-
Xanthan gum	-	-	-	-	0,25	0,25	0,25	0,25	-	-	-

Glycerin	5	5	5	5	5	5	5	5	5	5	5
Purified water	q.s. up to 100										

Cream samples were prepared according to the following technology. Oil phase of the cream was obtained by melting solid components (stearyl alcohol, cetyl alcohol, beeswax, glyceryl stearate, stearic acid) and then mixing them with fatty oils (corn oil, medium chain triglycerides, almond oil, coconut oil). The aqueous phase was obtained by dissolving water-soluble substances (zinc sulfate, GPMC, xanthan gum, sodium alginate, glycerol) in purified water. The aqueous phase was heated to 75-80°C for complete dissolution of all ingredients. Then the oil phase, also heated to 75-80°C, was gradually added to the aqueous phase at the same temperature while stirring. Stirring was done with a laboratory stirrer until a white homogeneous creamy mass was formed. After the cream cooled, tea tree essential oil was added while stirring and left to stir for 30 min.

In 1 hour after preparation the cream samples were subjected to evaluation of visual signs of instability. In samples № 5, 6, 7, 9 and 11 revealed signs of phase separation, so for further studies were used cream samples № 1, 2, 3, 4, 8 and 10.

3.2 Evaluation of organoleptic and physicochemical properties of model samples of cream

Pre-selected compositions of cream with zinc sulfate and tea tree essential oil were evaluated regarding their organoleptic and physicochemical properties. The results of the tests are summarized in Table 3.2.

Table 3.2

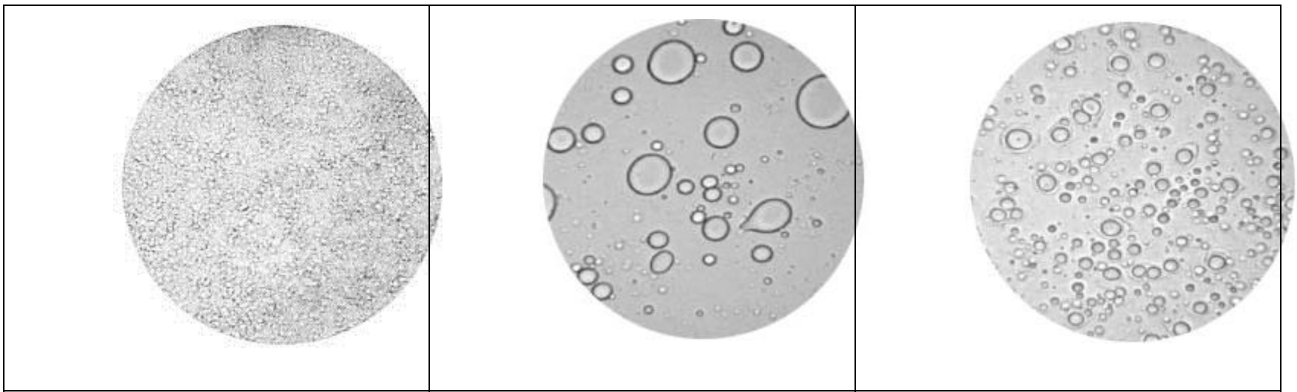
Organoleptic and physicochemical properties of cream samples

Evaluated parameter	Model number					
	№1	№2	№3	№4	№8	№10

1	2	3	4	5	6	7
Homogeneity	+	+	+	+	+	+
pH	5,64 ± 0,11	4,98 ± 0,09	5,81 ± 0,10	5,36 ± 0,14	5,66 ± 0,03	5,73 ± 0,11
Colloidal stability	Unstable; phase separation	Stable				
Thermal stability	Unstable; phase separation	Stable				
Consumer properties	+	+	+	-	+	+

Note: + – sample has good consumer properties, easily applied and distributed to the skin, quickly absorbed, does not cause discomfort after application; +/- – sample has satisfactory consumer properties, easily applied and distributed to the skin, but after application causes a feeling of tight skin; sample has unsatisfactory consumer properties, because it is hardly distributed on the skin when applied.

Thus, based on the evaluation of the 6 samples of cream selected 3 samples, which stand the test of colloid and thermal stability and at the same time have good consumer properties – these are compositions number 2, 8 and 10. It should be noted that the above compositions are made using in their composition different gel-formers, as well as other inactive ingredients, which in different ways may affect the size of particles of oil (dispersed) phase of the cream. This indicator – the size of the dispersed phase particles – is an indicator of the stability of the emulsion system: the larger the oil particles, the more heterogeneously they are distributed, the greater the risk of their coagulation and further phase separation.



№ 2	*№ 8*	*№ 10*

Figure 3.1. Microphotos of cream samples with different gelling agents: *№ 2* – sodium alginate; *№ 8* – xanthan gum; *№ 3* – HPMC

The micrographs of the three cream compositions shown in Fig. 3.1 microphotographs of three cream compositions show that in sample No. 8 large fractions of oil phase particles prevailed, while sample No. 10 was more homogeneous, and the smallest size and greatest homogeneity of dispersed phase particles were noted for sample No. 2 with sodium alginate as a gel-forming agent.

3.3 Study of rheological properties of cream samples

Objective evaluation of such properties of the model samples as extrusion ability and ease of distribution when applying the cream to the skin was carried out using the study of rheological parameters. The rheological properties of the model systems were investigated on a MYR VR3000 model V2R rotary viscometer using a TR 11 spindle. The principle of the study was the successive destruction of the structure during the transition from small shear rate gradients to large gradients and back at a constant temperature of 20ºC. Flow rheograms obtained from the experimental data are shown in Fig. 3.2.

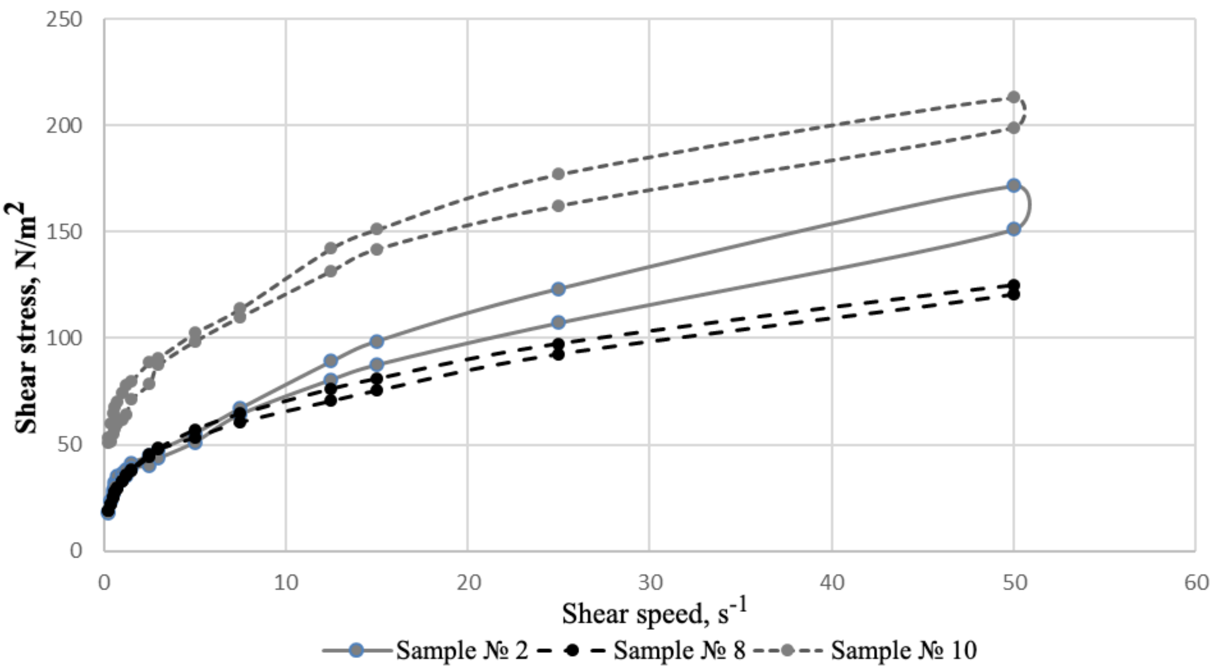


Figure 3.2. Flow rheograms of model cream samples

The results of the study of rheological parameters of model samples No. 2, 8 and 10 show that all three compositions refer to non-Newtonian fluids, the viscosity of which depends on the shear rate. It can be also stated that the systems under study have thixotropic properties because their flow rheograms show the presence of hysteresis loops – the area between the rising and falling curves. Thixotropy is the ability of a system to reduce such property as viscosity under mechanical action and restore its viscosity at rest. That is, for thixotropic systems, mechanical action reduces the viscosity of the cream, so that such cream can be easily extruded from tubes, applied and distributed on the skin when applied. The largest hysteresis loop area and, accordingly, the most pronounced thixotropic properties were established for sample No. 2.

3.4 Study of the osmotic activity of cream samples

In most cases, herpetic skin lesions are characterized by vesicles with serous or serous-hemorrhagic contents. Therefore, MLS for local treatment of herpetic infection should exhibit a certain osmotic activity in order to easily absorb secretions, but not to dry out healthy tissues and not to disturb the process of granulation and epithelization. In this regard, we investigated the osmotic properties of model samples of creams 2, 8 and 10. The studies were carried out by dialysis through a semi-permeable membrane with subsequent determination of the absorbed water by gravimetric method. Results of the studies are shown in Fig. 3.3.

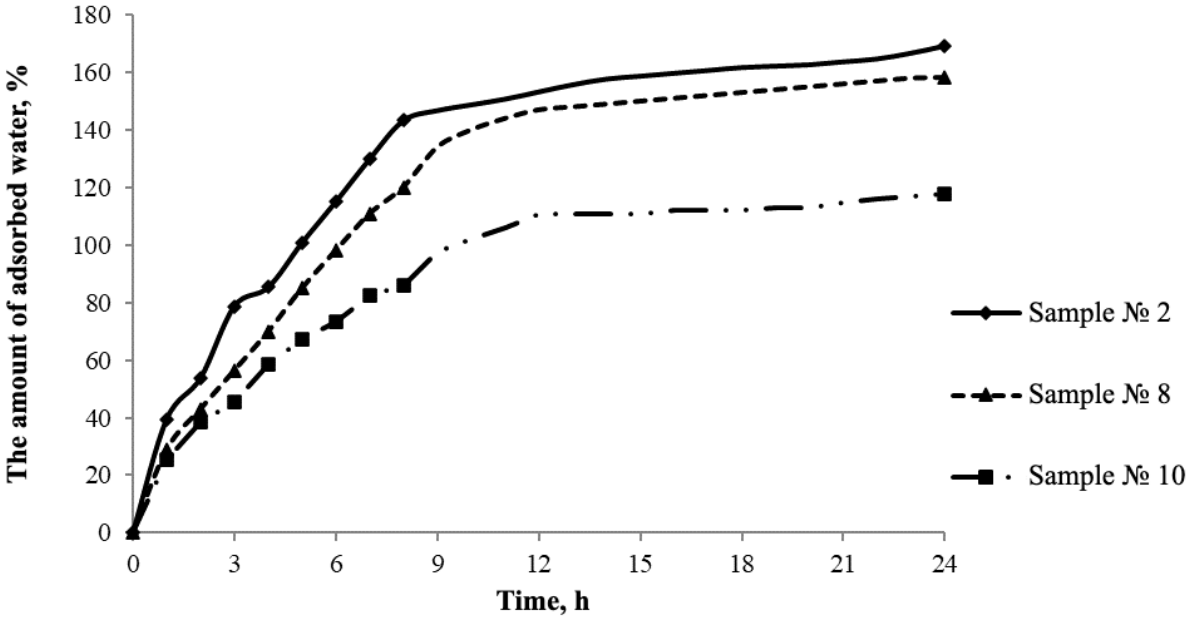


Figure 3.3. Osmotic activity of model cream samples

The analysis of the data shown in Fig. 3.3 showed that the cream samples showed moderate osmotic activity for 24 hours: the amount of absorbed liquid during this period was 169.5, 158.2 and 117.95 % for samples № 2, 8 and 10 respectively.

3.5 Composition and production technology of anti-herpetic cream with zinc sulfate and tea tree essential oil

Based on the results of the studies, the composition of sample No. 2 was chosen as the optimal composition of anti-herpetic cream with zinc sulfate and tea tree essential oil (Table 3.3).

Table 3.3.

Composition of anti-herpetic cream with zinc sulfate and tea tree essential oil

Name of ingredients	Content, %
Zinc sulfate	1,00
Tea tree essential oil	2,00
Corn oil	4,00
Almond Oil	4,00
Medium chain triglycerides (Kollisolv MCT)	4,00
Almond Oil	4,00
Stearyl alcohol	5,00
Cetyl alcohol	6,00
Beeswax	8,00
Glyceryl stearate	6,00
Sodium alginate	0,35
Glycerin	5,00

Purified water	q.s. up to 100

Under laboratory conditions the cream of the above composition is produced as described in Section 3.1. At the pharmaceutical industrial enterprise the production of this soft medicinal product is carried out by the technology consisting of 7 stages (Fig. 3.4.).

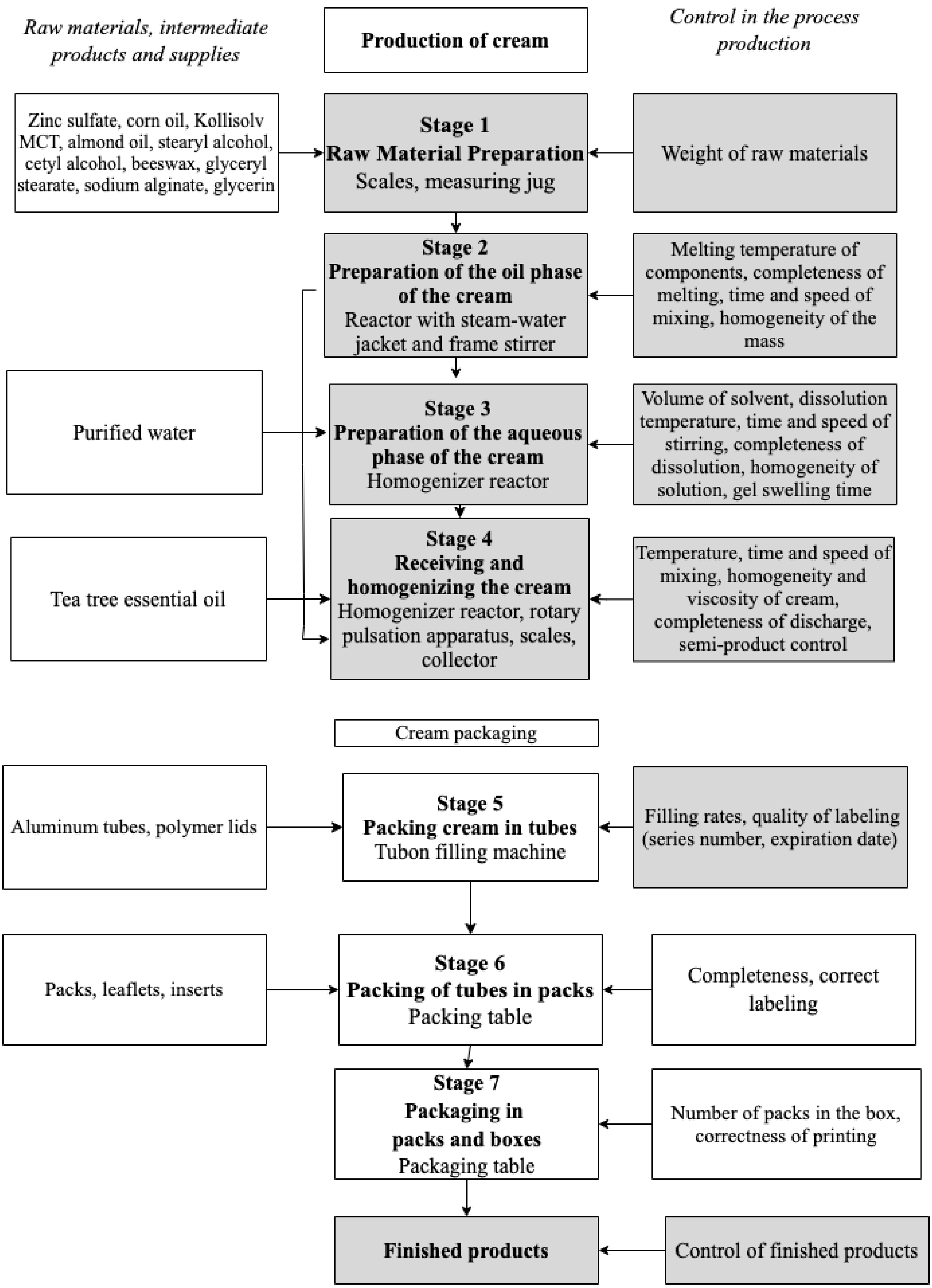


Figure 3.4 Technological scheme of the production process of cream with zinc sulfate and tea tree essential oil

Stage 1. Preparation of raw materials. Zinc sulfate and excipients (corn oil, Kollisolv MCT, almond oil, stearyl alcohol, cetyl alcohol, beeswax, glyceryl stearate, sodium alginate, glycerin) are consistently weighed on electronic scales in separate collections. Tightly closed labeled containers are transferred to stages 2-3.

Stage 2. Preparation of the oil phase of the cream. In the reactor, equipped with a steam shell and frame stirrer, load the required amount of stearyl alcohol, cetyl alcohol, beeswax, glyceryl stearate and heated under stirring to a temperature of (75 ± 5)ºC until complete melting of components.

Stage 3. Preparation of the aqueous phase of the cream. Necessary amount of purified water is loaded into homogenizer reactor and previously tested zinc sulphate is added, which is dissolved at temperature 40-45ºC and stirring during 15 ± 2 min. Check the completeness of dissolution. The solution should be transparent and contain no undissolved particles or mechanical inclusions. To the obtained solution add glycerin. Stir with a stirrer for 10 ± 2 min, and after this time with the stirrer off, add sodium alginate and stir for 5 ± 2 min until the surface of the sodium alginate is completely wetted. Check the completeness of wetting of the gelling agent. The resulting dispersion is left until complete swelling of the gelling agent. After that the contents of the reactor is stirred for 30 min under vacuum and transferred to the stage of cream production and homogenization.

Stage 4. Receiving and homogenization of cream. In the reactor homogenizer with vacuum loaded oil phase of the cream obtained at stage 2, the temperature of which is maintained at (75 ± 5) º C. Then, in the reactor homogenizer gradually with stirring turbine stirrer introduces the water phase, also heated to a temperature of (75 ± 5) º C. Stir until a homogeneous opaque mass of white color is formed. After cooling to room temperature and add tea tree essential oil, previously weighed on the scales in the collection. Homogenization is carried out by pumping the entire mass of cream through the rotary pulsation apparatus connected to the reactor. Control samples are taken from different areas of the reactor and the intermediate product – cream with zinc sulfate and tea tree essential oil in bulk – is analyzed.

Stage 5. Packing the cream in tubes. The resulting cream on the tube filling machine is packed in aluminum tubes with bushions. Check the accuracy of dosage, the performance of the machine and the correct labeling of tubes.

Stage 6. Packing of tubes in packs. Tubes with instructions for use are packed in bundles. Check the completeness of the packaging.

Stage 7. Packing the packs into boxes. Manually pack the packs in cardboard boxes. Check the correctness of the labeling.

CONCLUSIONS

1. To select the composition of the developed MLS with zinc sulfate and tea tree essential oil, 11 model cream samples were made. Five samples immediately after production showed signs of physical instability. As a result, 6 samples of cream compositions were selected for further research.

2. The results of the evaluation of organoleptic and physico-chemical properties of 6 cream samples showed that only 3 samples had colloidal and thermal stability in combination with good consumer properties. Microscopic study showed that these samples differ significantly in the dispersion of oil phase drops, which can be explained by differences in their composition of types and amounts of inactive ingredients, which can differently affect the particle size of oil (dispersed) phase of the cream.

3. All three studied cream compositions refer to non-Newtonian liquids, the viscosity of which depends on the shear rate, and are characterized by the presence of thixotropic properties. The most pronounced thixotropic properties were found for the sample made with sodium alginate as a gelling agent.

4. samples of the cream exhibit moderate osmotic activity for 24 hours, which corresponds to the intended use of the developed MLS – treatment of herpetic vesicles.

5. On the basis of studies on the totality of all studied parameters as the optimal composition of anti-herpetic cream with zinc sulfate and essential tea tree oil selected the composition of the sample with sodium alginate (№ 2). For the selected composition of the cream described production technology and compiled a flowchart indicating the necessary industrial equipment and control points in the production process.

GENERAL CONCLUSIONS

1. In the qualification work justified the composition and developed the technology of a new medicinal product for the external treatment of herpetic infection in the form of cream containing as active ingredients of zinc sulfate and essential oil of tea tree.

2. On the basis of the data of literary sources the information on modern principles of pharmacotherapy of herpetic infection is systematized. It has been established that anti-herpetic therapy, in addition to systemic drugs, should include drugs for topical use, which will reduce the clinical manifestations of infection by reducing the time of epithelialization of erosions. Zinc sulfate and tea tree essential oil are promising drugs in terms of creating new anti-herpetic drugs for local use.

3. In the pharmaceutical market of Ukraine, acyclic nucleosides dominate among antiviral drugs for external treatment of herpes infections, to which there is a growing resistance of the pathogen. There are very few drugs of other pharmacological groups that could provide alternative treatment regimens. The predominant dosage form among the drugs in this segment is cream, which indicates both the convenience of using this type of LF and the biopharmaceutical advantages.

4. Based on the results of studies of organoleptic characteristics, colloidal and thermal stability, dispersity of oil phase particles, pH index, rheological and osmotic properties the composition of auxiliaries of cream with zinc sulfate and essential oil of tea tree was selected. Proposed technology for obtaining the developed cream and compiled a flowchart of the production process with the indication of industrial pharmaceutical equipment and control points.

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APPENDIXES

Appendix A


SAPERE AUDE
НФаУ
ІІІ 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
III міжнародної науково-практичної
Інтернет-конференції

Materials
of the III International Scientific and Practical
Internet Conference

ХАРКІВ
KHARKIV
2023

The relevance of the development of a new drug for the treatment of herpes infection

Achraf Ed-Dbourh , Ruban O.
Department of Industrial Technology of Drugs of the National University of Pharmacy, Kharkiv, Ukraine
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Based on statistical data, 80-100% of the world's population are seropositive for the herpes simplex virus. Therefore, an important task of modern medicine is to improve the pharmacotherapy and prevention of viral diseases caused by herpes infection.

For the treatment of viral herpetic infections accompanied by the appearance of external rashes, adequate antiviral therapy, in addition to systemic drugs, involves the use of drugs of local (topical) action, which is due to the high concentration of the HSV pathogen in the areas of rashes, soreness of the affected areas and lack of local immunity. Synthetic agents of the group of acyclic nucleosides - acyclovir, valacyclovir, famciclovir - dominate on the market today among drugs for the external treatment of herpetic eruptions. Recently, there has been an increase in the resistance of viruses to the listed drugs and an increase in the frequency of relapses of herpes infection. The range of antiherpetic drugs of natural origin, to which viral resistance develops much less frequently, is very limited.

The aim of the work was to develop a composition of a cream for the treatment of herpes infection, which contains tea tree essential oil and zinc sulfate as active pharmaceutical ingredients. Tea tree oil has been shown in clinical studies to have anti-herpetic, anti-inflammatory, and analgesic properties, and to speed up the healing process of cold sores on the lips. Zinc ions have an antiviral effect by preventing the penetration of the virus, blocking the synthesis of the viral protein or inhibiting the activity of the viral RNA-dependent RNA polymerase.

After analyzing the literature data, it was found that the most promising bases for the manufacture of a soft dosage form for the treatment of herpes infection in terms of bioavailability, as well as to achieve optimal consumer qualities, are emulsion bases of the oil-in-water (cream).

The features of achievements and challenges of the characteristic and possibility of artificial intellect researching and perfection in health, pharmaceutics and medicine

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According to the World Health Organization (WHO), digital health is "a field of knowledge and practice related to the development and use of digital technologies to improve health". Technology and digital transformation are rapidly changing information ecosystems and the design of healthcare systems. The use of various digital technologies, such as artificial intellect and machine learning, offers great opportunities to improve health services, access to care, health workforce and health outcomes.

Although digital health has been around for a long time with technologies focused on e-health (electronic health records), the rapid growth of technology in the past few years has led to exciting new areas of digital health, including mobile health applications (mHealth) and wearable technologies. Telehealth and telemedicine, artificial intellect, advanced robotics and genomics. Digital health also includes other digital health uses such as the Internet of Things, advanced computing, and big data

Ф А 2.2.1-32-366

National University of Pharmacy

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

APPROVED
The Head of the Department of Industrial Technology of Drugs

____

Olena RUBAN
"_15_" __of May__ 2022

ASSIGNMENT
FOR QUALIFICATION WORK
OF AN APPLICANT FOR HIGHER EDUCATION

Achraf ED-DBOURH

1. Topic of qualification work: «Justification of the composition of a soft medicinal product for the treatment of herpes infection», 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: zinc sulfate, tea tree oil, Sodium alginate, xanthan gum, hydroxypropyl methylcellulose, cetyl alcohol, herpes simplex virus.

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 – 6 ____

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	18.05.2022	18.05.2022
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	15.02.2023	15.02.2023

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 __________ Achraf ED-DBOURH

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**				
Ед-Дбурх Ашраф	Обгрунтування складу м'якого лікарського засобу для лікування герпетичної інфекції	Justification of the composition of a soft medicinal product for the treatment of herpes infection	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

№ 112733 від « 29 » квітня 2023 р.

Проаналізувавши випускну кваліфікаційну роботу за магістерським рівнем здобувача вищої освіти денної форми навчання Ед-Дбурх Ашраф, 5 курсу, ______ групи, спеціальності 226 Фармація, промислова фармація, на тему: «Обґрунтування складу м'якого лікарського засобу для лікування герпетичної інфекції / Justification of the composition of a soft medicinal product for the treatment of herpes infection», 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**

2%

26%

Ф А2.2.1-32-353

REVIEW

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

226 Pharmacy, industrial pharmacy

Achraf Ed-Dbourh

on the topic: «Justification of the composition of a soft medicinal product for the treatment of herpes infection»

Relevance of the topic. The herpes simplex virus is very common among the world's population. About 80% of people are its carrier. Herpes simplex viruses can affect the quality of human life, affect almost all organs and tissues of a person and cause an acute, latent and chronic form of infection. Most often, herpes is manifested by rashes on the skin with the appearance of inflammation in the affected area. Therefore, an important task of modern pharmacy is to improve the pharmacotherapy and prevention of viral diseases caused by herpes infection. A convenient dosage form for the treatment of herpes infections is a soft dosage form, in particular, a cream. Creams have many advantages compared to other medicinal forms, have good bioavailability, are convenient to use. Tea tree essential oil and zinc sulfate were selected as active pharmaceutical ingredients. These substances have a complex effect in the treatment of herpes simplex. Therefore, the creation of a new drug in the form of a cream with tea tree essential oil and zinc sulfate is an actual task of pharmacy.

Practical value of conclusions, recommendations and their validity. Achraf Ed-Dbourh considered the main etiopathogenetic aspects of the herpes simplex virus, modern approaches to its treatment, theoretically substantiated the use of active pharmaceutical ingredients - tea tree essential oil and zinc sulfate. Based on the analysis of the results of the studies, the author made conclusions on the assessment of the pharmacotechnological properties of the studied APIs, the rationale for the composition of excipients. An industrial technology has been developed for obtaining a cream with essential oil of tea tree and zinc sulfate of the herpes simplex virus.

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 A2.2.1-32-356

REVIEW

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

226 Pharmacy, industrial pharmacy

Achraf Ed-Dbourh

on the topic: «Justification of the composition of a soft medicinal product for the treatment of herpes infection»

Relevance of the topic. According to medical statistics, almost every person is a carrier of the herpes simplex virus. For the treatment of such conditions, antibacterial and antiviral therapy based on synthetic active pharmaceutical ingredients is most often used. These drugs often have a wide range of side effects. According to the literature, it is known that some essential oils 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 for the treatment of herpes simplex virus, which contain active pharmaceutical ingredients, is relevant.

Theoretical level of work. The literature review presents the etiology and pathogenesis of herpes simplex virus, the main directions of its treatment. Based on literature data, the author substantiates the use of tea tree essential oil and zinc sulfate in creams for the treatment of this disease. The expediency of creating such a dosage form as a cream 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 cream, the choice of emulsifier and thickener was justified. Based on the studies conducted on the totality of all studied parameters, the composition of the sample with sodium alginate was chosen as the optimal composition of the antiherpetic cream with zinc sulfate and tea tree essential oil. For the selected composition of the cream, the production technology is described and a technological scheme is drawn up indicating the necessary industrial equipment and control points in the production process.

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 Achraf Ed-Dbourh 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-8 Ашраф Ед-Дбурх про представлення до захисту в Екзаменаційній комісії НФаУ кваліфікаційної роботи на тему: «Обгрунтування складу м’якого лікарського засобу для лікування герпетичної інфекції». (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 освітифакультету з підготовки іноземних громадян групи Фм18(4,10д)англ-8 Ашраф Ед-Дбурх на тему: «Обгрунтування складу м’якого лікарського засобу для лікування герпетичної інфекції».

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 Ашрафа ЕД-ДБУРХА до захисту кваліфікаційної роботи

за галуззю знань 22 Охорона здоров'я

спеціальністю226 Фармація, промислова фармація

освітньою програмою Фармація

на тему: «Обгрунтування складу м'якого лікарського засобу для лікування герпетичної інфекції».

Кваліфікаційна робота і рецензія додаються.

Декан факультету ________________________ /Світлана КАЛАЙЧЕВА /

Висновок керівника кваліфікаційної роботи

Здобувач вищої освіти Ашраф ЕД-ДБУРХ у процесі роботи розглянув сучасні підходи до лікування вірусу простого герпеса, провів аналіз асортименту засобів для терапії даного захворювання та обґрунтував доцільність створення нового лікарського засобу у формі крему для лікування вірусу герпеса. Автором обґрунтовано оптимальний склад і розроблено технологію одержання лікарського засобу. Ашраф ЕД-ДБУРХ 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 Ашраф ЕД-ДБУРХ 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 /