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# QUALIFICATION WORK

on the topic: **EMULGEL TECHNOLOGICAL PROPERTIES FOR THE DERMATITIS TREATMENT INVESTIGATION**

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## ANNOTATION

Qualification work is devoted to the improving of the composition and studying the technological properties of emulgel for the dermatitis treatment.

The work is presented on 50 pages of printed text, consists of an introduction, 3 chapters, general conclusions, a list of used sources, appendices. The list of used sources contains 35 items. The work is illustrated with 6 tables and 15 figures.

*Key words:* emulgel, dermatitis treatment, technology, Motherwort tincture, Valerian tincture.

## АНОТАЦІЯ

Кваліфікаційна робота присвячена вдосконаленню складу та вивченню технологічних властивостей емульгелю для лікування дерматитів.

Робота викладена на 50 сторінках друкованого тексту, складається зі вступу, 3-х розділів, загальних висновків, списку використаних джерел, додатків. Перелік використаних джерел містить 35 позицій. Роботу ілюстровано 5 таблицями та 15 рисунками.

*Ключові слова:* емульгель, лікування дерматиту, технологія, настоянка пустирника, настоянка валеріани.

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## LIST OF USED ABBREVIATIONS

API - Active pharmaceutical ingredients;

BAS – biologically active substances;

CMC – carboxymethylcellulose;

EF – Extemporaneous formulation;

FDA – Food and Drug Administration;

GMP – Good Manufacturing Practices;

PW – Purified Water;

RO – reverse osmosis;

SPU – State Pharmacopoeia of Ukraine;

SSD – Semisolid Dosage Forms;

TEA – Triethanolamine;

TOC – total organic carbon;

USP – United States Pharmacopeia.

# INTRODUCTION

Actuality of theme. Dermatitis, a widespread skin condition encompasses various forms of inflammatory skin conditions. In the field of clinical dermatology, the term "dermatitis" is utilized to encompass a range of skin conditions that exhibit a common inflammatory response pattern and share similar clinical presentations. Dermatitis can manifest in many forms and has various causes. It often presents with itchy, dry skin or a rash. In some cases, it may cause blistering, oozing, crusting, or flaking of the skin. Current treatments for it can be limited by factors like poor skin penetration or side effects. Emulgels, combining gel and emulsion properties, offer a promising alternative [24, 32].

Emulgels are carrier systems that represent a mixture of emulsion and gel, which are particularly significant for the delivery of hydrophobic substances. However, the proper selection of main constituents determines the stability and efficacy of emulgels. Emulgels are dual-controlled release systems, where the oil phase is utilized as a carrier for hydrophobic substances and it determines the occlusive and sensory properties of the product. Gelling agents are used to increase the consistency of composition and improve sensory properties by making these systems thixotropic. The gelling agents also impact the release of active substances from the formulation and stability of the system [24, 32].

The purpose of the study. Improving the composition and studying the technological properties of emulgel for the treatment of dermatitis.

Research tasks:

Conduct an analysis of literature data on types of dermatitis and their pathogenesis (disease mechanisms);

Design and theoretically substantiate the composition of the dermatitis gel using ingredients with established anti-inflammatory, anti-itch, and skin-barrier-repair properties.

Experimentally optimize the emulgelcomposition, considering compatibility of ingredients, physical and chemical properties of ingredients.

Estimate the stability of emulgel for the treatment of dermatitis under various storage conditions.

Investigate technological properties of the final product.

The subject of research. Emulgel for the dermatitis treatment.

Research objects. Motherwort and Valerian tinctures, purified water, lanolin and peach oil, triethanolamine, Olivem 1000, Carbopol 971, purified water.

Research methods. To achieve the goal, we used general scientific research methods: analysis, synthesis, comparison, generalisation, comparison, systematisation to process the literature data. Organoleptic, physical and technological.

Practical significance of the obtained results. Emulgel composition for the dermatitis treatment was grounded and its technological properties was investigated.

Elements of scientific research. On the basis of the conducted researches for practical realization emulgel for the dermatitis treatment was offered.

Approval of research results and publication. This work results can be used to further improve of the cream composition in order to expand the range of modern drugs for urticaria treatment. The results of the work are presented at the conference “Current issues of creating new medicines: XXX international scientific and practical conference of young scientists and students” (April 17-19, 2024, Kharkiv). Publication on the topic “Relevance of emulgel development for the dermatitis treatment” was represented.

The work is presented on 50 pages of printed text, consists of an introduction, 3 chapters, general conclusions, a list of used sources, appendices. The list of used sources contains 35 items. The work is illustrated with 6 tables and 15 figures.

# CHAPTER 1.
# FEATURES OF THE TREATMENT OF DERMATITIS. GELS

## 1.1. Dermatitis

Dermatitis, a term derived from Greek meaning "inflammation of the skin", from the words "derma" (skin) and "itis" (inflammation), a widespread skin condition encompasses various forms of inflammatory skin conditions triggered by a complex interplay of factors causing inflammation, irritation, and edema [1, 5].

Dermatitis can manifest in many forms and has various causes. It often presents with a spectrum of symptoms, from dry, itchy skin to blistering and flaking. In some cases, it may lead to blistering, oozing, crusting, or flaking of the skin [7].

It encompasses a range of inflammatory skin conditions with various contributing factors. The development of the condition entails an intricate interaction between Environmental factors, inherited disposition, and stimulation of the immunological system [7].

- Immune System Dysregulation: Atopic dermatitis, a common form, is defined by an overactive immune response to innocuous stimuli. This leads to inflammation in the skin.

- Genetic Susceptibility: Family history significantly raises the possibility of developing dermatitis. Specific gene mutations affecting proteins crucial for maintaining healthy skin barrier function have been identified.

- Environmental Influences: Environmental conditions can worsen dermatitis by altering the skin's barrier properties. Exposure to irritants (e.g., soaps, fragrances), pollutants, and tobacco smoke can disrupt the skin's delicate balance, leading to increased water loss and susceptibility to inflammation.

- Direct Irritant/Allergen Exposure: Certain types of dermatitis may be directly triggered by contact with specific substances, such as topical fluorides.

- Co-occurring Conditions: Dermatitis can coexist with other conditions that may not directly cause it but can worsen symptoms or impact quality of life. These include sleep disturbances, anxiety, depression, allergies, and asthma.

Dermatitis may manifest in many different forms, such as:

**Atopic dermatitis (AD)**

also referred to as eczema, is the most common type of eczema that affects a large percentage of people. It can begin in childhood and continue until maturity. as it impacts approximately 2% to 3% of the adult population and 25% of children. This persistent inflammatory skin condition manifests in a range of unpleasant symptoms, including intense itching, scaling, and swelling of the affected areas. Blistering may also occur in some cases. Notably, AD often exhibits a familial pattern and demonstrates a strong association with other allergic disorders such as allergies, asthma, and stress. Current research implies that the development of AD may be linked to a combination of factors, including genetic predisposition, immune dysregulation, and impaired skin barrier function that disrupts the delicate balance of moisture retention and pathogen defence [1, 7].

It manifests through a spectrum of clinical presentations, ranging from mild, localized dryness to extensive, widespread inflammation. The hallmark symptom of AD is intense pruritus (itching), which can significantly impact the quality of life for individuals. Additionally, affected skin frequently exhibits dryness, cracking, and redness (erythema). The colour of the inflamed skin can vary depending on skin tone, appearing red on lighter skin tones and potentially appearing darker brown, purple, or grey on darker skin tones. This variation in colour presentation can make diagnosis more challenging in individuals with darker skin.

The distribution of AD lesions also varies depending on age and skin tone. In adults, the hands are most commonly affected, while in children, AD typically manifests on the inner elbows, the face, scalp, and backs of the knees. It is crucial to note that in children with brown and black skin, the outer elbows and front of the knees are also frequently affected areas [1].

AD is characterized by a relapsing-remitting course, meaning individuals experience intervals of progress followed by periods of setbacks where symptoms worsen.

**Contact dermatitis (CD)**

encompasses various skin conditions defined as inflammation resulting from direct contact with a material, whether an irritating substance or allergen, can cause an allergic reaction. Typically presenting as a pink or red, itchy rash, pinpointing the exact source can pose a challenge. Anyone can experience contact dermatitis from direct contact with irritants or allergens as it affects approximately 15% to 20% of individuals at some point in their lives [5, 12].

Allergic CD initiates from a T-cell mediated immune response to seemingly harmless allergens. Upon initial exposure, sensitization occurs, with subsequent contact prompting an immune reaction leading to inflammation and rash formation. Common triggers include plants like poison ivy, oak, and sumac containing urushiol (an oily mixture of organic compounds with allergenic properties found in plants of the Anacardiaceae family), fragrances in cosmetics and perfumes, metals such as nickel in jewellery, latex in rubber products, formaldehyde in household items, and certain skincare ingredients like creams and soaps [5].

On the other hand, Irritant CD arises directly from exposure to irritants, which damage the skin barrier, provoking inflammation. Unlike allergens, irritants don't necessitate prior sensitization and can affect anyone. Examples include soaps and detergents causing dryness and irritation from frequent hand washing, solvents in cleaning products, friction from constant rubbing, and occupational exposures prevalent in industries like healthcare and construction. Workers in these professions are at heightened risk due to frequent contact with potential irritants [12, 34].

**Seborrheic dermatitis (SD)**

A prevalent inflammatory skin condition specified by greasy, yellowish, or reddish scaling on various body areas. Primarily impacting the scalp, it manifests as dandruff in adults and cradle cap in infants. SD can also manifest in other regions with high sebaceous (oil) gland activity, including the upper back and chest, the forehead and eyebrows, the hairline, the sides of the nose, the navel (belly button), and the genital area [15].

Clinically, SD presents with distinct symptoms. Scaly patches, often greasy, may be accompanied by mild inflammation (redness). In adults, the scaling on the scalp manifests as persistent dandruff, often more severe than typical dandruff. Additionally, mild inflammation, indicated by redness, may accompany the scaling.

SD affects approximately 11% of the global population, demonstrating a diverse demographic distribution. Age plays a role, with the highest prevalence observed in infants below three months of age and in adults between the ages of 30 and 60. Additionally, research suggests a higher incidence in men compared to women and in Caucasians compared to African Americans [8].

**Neurodermatitis (ND)**

often referred to as lichen simplex chronicus, is a non-life-threatening yet persistent skin condition defined as intense itching and subsequent scratching. This localized itching typically affects one or two particular body parts, most frequently Manifesting on the arms, shoulders, elbows, legs, ankles, wrists, hands, back of the neck, or scalp, and occasionally affecting the anal and genital regions, the face may also be involved. The intensity of the itch can vary, with episodes of constant scratching or more intermittent bouts. Notably, the itching often worsens during relaxation or sleep, leading to patients waking up scratching or rubbing the affected area [16, 22].

This scratching behaviour creates a detrimental cycle. By physically irritating the skin's nerve endings, scratching further intensifies the itching sensation, prompting more scratching in a continuous loop. Over time, this itch-scratch cycle can become chronic, leading to significant disruption of skin health.

Research suggests that ND affects approximately 12% of the population. Interestingly, the condition appears to be more prevalent in individuals between 30 and 50 years old, with women being twice as likely to develop it compared to men. Additionally, those with pre-existing anxiety or obsessive-compulsive disorders, as well as individuals with a family history of skin disorders like AD or CD, seem to have a higher risk of developing ND.

**Stasis dermatitis (SD)**

a non-communicable yet prevalent skin condition, primarily affects older adults. Estimates suggest that in the United States alone, 15 to 20 million individuals over 50 years of age live with this condition. This condition also holds several alternative names, such as venous eczema, varicose eczema, or gravitational dermatitis, which offer a clearer picture of the underlying physiological processes.

As we age, the one-way valves within our lower leg veins can weaken. These valves play a crucial role in propelling blood upwards towards the heart. When these valves become compromised, fluid can leak out and accumulate in the legs, leading to edema – a condition known as venous insufficiency. The pooling of this fluid in people with venous insufficiency is termed stasis

While the likelihood of experiencing venous insufficiency tends to rise as one ages, other factors can contribute to its onset. These include severe leg injuries, blood clots within the leg, or surgical procedures. Understanding these risk factors, along with the mechanisms behind stasis, is essential for effectively managing and preventing SD.

**Perioral Dermatitis (PD)**

Perioral dermatitis, also known as periorificial dermatitis, manifests as an inflammatory facial rash primarily concentrated around the mouth. This rash presents with redness, scaling, and the development of small, inflamed bumps called papules. The term "perioral" originates from the Greek words' "peri" meaning "around" and "oral" meaning "mouth," literally translating to "around the mouth." Similarly, "periorificial" utilizes "orifice" signifying an opening, effectively conveying the same location. It's important to note that these terms describe the same condition.

While PD is often mistaken for acne due to its similar appearance, it is a distinct entity. Some individuals may experience itching or burning sensations associated with the rash. In rare instances, the rash may extend beyond the perioral region, affecting the nose, eyes, and even the genitals.

PD can be further categorized as typical or granulomatous. The more common typical form presents with red papules. In Granulomatous PD, a less frequent variant, Instead of the typical appearance, the presence of yellowish bumps is observed. Children appear to be more susceptible to developing granulomatous PD compared to adults.

The diagnosis of PD is primarily based on the characteristic rash location around the mouth. While less frequent, involvement of the eyelids, nose, and rarely, the genitals, can also occur. In exceptional cases, the rash may extend to the ears, neck, scalp, trunk, and extremities.

The demographic most at risk for developing PD appears to be women between the ages of 20 and 45 who regularly use topical corticosteroids, facial creams, and other topical products. However, it is essential to note that children and men are not exempt from developing this condition.

**Complications and prevention**

While not contagious, dermatitis can lead to complications. Repeated scratching, a common symptom, can break the skin, creating cracks and open sores. These openings lead to an increased susceptibility to bacterial and fungal infections, which, though rare, can become severe if left untreated. Additionally, in individuals with brown or Black skin, dermatitis can cause affected areas to either darken (post-inflammatory hyperpigmentation) or lighten (post-inflammatory hypopigmentation). These colour changes may take months or even years to return to their original state [26].

To minimize dermatitis risk, individuals should prioritize preventative measures, particularly those that address skin dryness. This includes wearing protective clothing when handling irritants. Additionally, establishing a gentle skincare routine is crucial. This involves limiting bath or shower duration to approximately 10 minutes with lukewarm water, followed by patting the skin dry rather than rubbing. Furthermore, using fragrance-free, mild cleansers and applying moisturizer while skin remains damp are recommended practices.

Dermatitis represents a diverse category of inflammatory skin conditions that arise from a multifaceted interplay of immune system dysfunction, genetic susceptibility, and environmental triggers. These factors contribute to the diverse clinical manifestations of dermatitis, with each subtype exhibiting distinct symptomatology. Importantly, dermatitis is non-contagious. However, uncontrolled cases can lead to complications such as secondary infections and post-inflammatory hyperpigmentation.

This improved understanding of the multifactorial etiology of dermatitis paves the way for the exploration of alternative therapeutic approaches. One such avenue may lie in the development of extemporaneous formulations, tailored to address the specific needs of individual patients and dermatitis subtypes.

## 1.2. Extemporaneous formulation in dermatology

Extemporaneous formulation (EF), the practice of creating customized medications from individual ingredients, plays a unique role in dermatology. While commercially available medications are the norm in many medical fields, dermatologists continue to rely heavily on this practice [3, 30].

Traditionally, extemporaneous compounding offered a way to deliver personalized doses of medications not readily available commercially. Pharmacists played a crucial role, utilizing compounding databases to create safe and effective products tailored to individual patient needs. This practice has been particularly valuable in dermatology, where topical medications are frequently the primary treatment approach [10].

However, the landscape of medicine is constantly evolving. There has been growing apprehension about the issue of. the limited data available on the formulation and shelf life of extemporaneous preparations. Additionally, advancements in pharmaceutical development have made commercially available

medications more accessible, leading some to question the continued necessity of compounding in certain specialties.

Despite these concerns, dermatology presents a compelling case for the continued use of EFs. Unlike systemic medications, where precise dosing and potential for toxicity are paramount, topical medications offer a greater margin of safety. This, coupled with the ability to combine medications or create formulations for specific skin types, allows dermatologists to offer patients tailored treatment options. Research indicates that dermatologists frequently prescribe compounded medications, highlighting the continued relevance of this practice in the field.

Beyond traditional uses, EFs are finding new applications in the realm of clinical research. The ability to create formulations with flexible dosing and achieve sub-milligram quantities makes them ideal for early-stage clinical trials. However, this application requires a systematic approach to ensure patient safety. Rigorous stability testing and the development of matching placebos are crucial for successful implementation in research settings.

EFs hold a special position in dermatology. While concerns exist regarding their use in some medical specialties, the ability to provide patients with personalized topical treatments justifies their continued use in dermatology. Additionally, emerging applications in clinical research demonstrate the potential for this practice to contribute to the development of new medications.

### 1.3. Extemporal preparation of semisolid medicines

Extemporaneous preparation offers a unique approach to creating semisolid medications, such as creams, ointments, and gels, tailored to the specific needs of individual patients with dermatitis. This process, undertaken by compounding pharmacists or healthcare professionals, allows for adjustments in medication strength or dosage form to better suit patient preferences and treatment requirements. Common applications include topical pain relievers, hormone creams, and, particularly relevant to this chapter, dermatological preparations like gels for dermatitis treatment.

**Semisolid Dosage Forms (SSDs): Properties and Applications**

SSDs occupy a space between solid and liquid medications, offering versatility in topical applications. These formulations can be applied to various sites, including the skin, mucous membranes (nasal, corneal), rectum, vagina (often via suppositories), buccal cavity, ears, and urethra. Typically, SSDs comprise two phases: an oil and a water component. One phase forms the continuous, external matrix, while the other is dispersed within it. Notably, active ingredients can be incorporated into either or both phases [5].

Ideally, an SSD should possess a smooth texture, free of grittiness. Additionally, desirable characteristics include being non-hygroscopic (non-absorbent), non-dehydrating, non-staining, and non-greasy (non-oily). However, it is important to acknowledge that achieving all these qualities may not always be possible. For instance, Ointments are often characterized by their staining and greasy properties. Since these medications come into direct contact with the skin, they should be formulated to minimize the risk of irritation, sensitization, or disruption of normal skin function.

The release behavior of a SSD are influenced by several factors, particle size of the dispersed phase, the medication's flow properties, and the interfacial tension existing between the two phases.

**Topical versus Transdermal Delivery**

It is crucial to distinguish between topical and transdermal applications of SSDs. Topical formulations are designed to exert their effect on the skin's surface and do not penetrate further. They are commonly used to treat various dermatological conditions such as acne, infections, wounds, and eczema. In contrast, transdermal SSDs are specifically designed to penetrate the skin and enter the bloodstream. This approach is often used for conditions requiring sustained medication delivery, for instance, pain relief. Additionally, transdermal formulations can be utilized for birth control and nicotine replacement therapy.

By understanding the properties and applications of SSDs, alongside the benefits of extemporaneous preparation, this section lays the groundwork for a

detailed exploration of this approach in the context of dermatitis treatment. Subsequent sections can delve into specific aspects such as:

- Commonly used active ingredients for compounded semisolid medications in dermatitis treatment.
- Selecting appropriate excipients to achieve desired characteristics in the final product.
- Detailed compounding procedures for various semisolid dosage forms.
- Strategies to optimize stability and extend the shelf life of compounded medications.

**Types of SSDs**

Topical and transdermal medications are available in various semisolid forms, each with unique properties and applications. Here's an overview of the most commonly encountered types:


Pic 1.1 SSDs classification

Ointments: These oil-based formulations offer a thick consistency, ideal for occlusive and emollient effects. They are suitable for treating dry, scaly conditions such as eczema and provide a protective layer on the skin. Ointments come in various categories, including hydrocarbon or oleaginous bases (oil-based for long-lasting action), water-miscible bases (emulsions for controlled absorption), absorbent bases (for water-soluble or oil-soluble actives), and water-soluble bases (non-greasy and easily washable).

Creams and Lotions: Creams, like ointments, exhibit an opaque appearance but featuring a greater proportion of water and a reduced amount of oil. This translates to a lighter, less greasy feel and easier spreadability. Creams can be categorized as either oil-in-water or water-in-oil based emulsions. Lotions, which contain an even higher water content, represent the lightest among these topical options. Some lotions may incorporate alcohol for specific purposes.

Pastes: Offering the thickest consistency among these forms, pastes consist of a blend of powder and ointment. While they can be applied topically or transdermally, their application challenges, particularly on larger areas, restrict their application to localized conditions, such as athlete's foot [20].

Gels: These aqueous colloidal suspensions have a liquid phase trapped within a polymeric matrix. Typically, clear or translucent, gels offer smooth consistency that facilitates their application over extensive areas. They are suitable for both topical medication distribution and lubrication purposes.

Jellies: Similar in consistency to gels, jellies are strictly for topical use. They are formulated with water, active ingredients, emulsifiers, gelling agents, and preservatives, and find applications in treating issues such as vaginal dryness.

Poultices (Cataplasms): This topical dosage form involves applying medication to a cloth or dressing before placing it on the affected area. Poultices are traditionally used for conditions such as abscesses or sunburn, and can also offer relief from soreness, discomfort and inflammation and swelling [13].

Suppositories: As a transdermal option, suppositories have a melting or dissolving external membrane at body temperature, facilitating the release and The uptake of the active component. They are placed inside the body cavities like the vagina or rectum.

Medicated Plasters: These typically combine water, plaster, and an active component. Upon application to the skin, the plaster hardens, delivering a slow and gradual release of medication over a period of time. Salicylic acid plasters are an example, used for treating skin and plantar warts [2].

Rigid Foams: This distinct medication delivery mechanism incorporates gas bubbles dispersed in a liquid containing the active ingredient and excipients. Topical foams offer versatility in delivering various medications, including antimicrobials, corticosteroids, and sunscreens.

Glycerogelatins: Designed for prolonged release, glycerogelatins combine the active ingredient with glycerin and gelatin [33].

**Advantages of SSDs**

Semisolid dosage forms offer several advantages that make them a valuable option for patients and healthcare professionals:

- Simplified Administration: Topical application of SSDs is generally easier for many patients compared to oral medications, potentially improving medication adherence. This external application also minimizes the risk of gastrointestinal side effects often associated with oral medications.
- Reduced Systemic Exposure: Topical formulations deliver medication directly to the affected area, minimizing systemic exposure and the potential for systemic side effects. This is particularly beneficial for treating dermatological conditions.
- Bypassing First-Pass Metabolism: Orally administered medications undergo first-pass metabolism in the liver, which can significantly impact their efficacy and predictability. The transdermal delivery of medications through SSDs bypasses this first-pass effect, leading to more consistent and predictable the drug uptake into the bloodstream.
- Controlled Release: Certain transdermal SSD formulations offer controlled release mechanisms. This ensures a steadier level of medication in the bloodstream, reducing fluctuations that can contribute to side effects and improve the overall therapeutic effect.

## 1.4. General characteristics of gels

Gels occupy a unique space within topical dermatological treatments, they offer a valuable dosage form due to their unique properties. they can be defined as

semi-solid systems and from a structural standpoint, gels are essentially a colloidal system where a three-dimensional network of interconnected molecules or particles restricts the movement of a liquid component. This results in a material with a jelly-like consistency that appears solid but is primarily composed of liquid. Gels often exhibit thixotropy, meaning they can become more fluid when agitated and then return to a gel state upon resting. This structure offers advantages for both the medication and the patient [25, 31].

Pic 1.2 Gel textures

For medications, the gel matrix provides protection from environmental factors such as light, moisture, heat, and oxygen. This safeguards the active ingredients and promotes stability. Additionally, the gel can shield medication from potential degradation caused by the patient's natural physiological environment, such as the acidity of the skin.

From the patient's perspective, gels offer several benefits. They can mask unpleasant tastes or odors associated with certain medications. Gels are also known for their smooth, spreadable texture, making them convenient for topical application. This ease of use is particularly important for treating dermatological conditions, where discomfort may already be present. Furthermore, the gel structure minimizes the risk of irritation or other unwanted side effects often associated with topical medications [29, 31].

The term "gel" itself is derived from the word "gelatin", which reflects the material's gel-like consistency. Both "gel" and "jelly" have roots in the Latin word

"gelu" meaning "frost," further emphasizing the characteristic transformation of a liquid into a solid-like state. However, unlike a solid, a gel retains some liquid characteristics and exhibits elasticity. The formal classification of gels emerged in the late 19th century as a way to categorize semi-solid materials based on their observable properties rather than their molecular makeup [11, 29].

On a more technical level, a gel can be described as a two-component system. One component is a network of gelling agents, which can be inorganic particles or natural polymers (large molecules). The other component is a continuous liquid phase. These gelling agents form cross-links, either through chemical bonds (chemical gels) or through weaker, reversible interactions (physical gels). Examples of these interactions include hydrogen bonding, electrostatic forces, and hydrophobic interactions. The United States Pharmacopeia (USP) defines a gel as a semisolid system containing a dispersion of either small inorganic particles or large organic molecules, all interpenetrated by a liquid. For inorganic gels, these particles form a three-dimensional network, while organic gels involve the dispersion of large molecules throughout the liquid phase [11, 19, 32].

The visual appearance of gels can vary. Some gels are transparent like water, while others may appear cloudy. This variation is often due to the degree of dispersion of the gelling agents within the liquid component. If the gelling agents are not fully dissolved or form aggregates, they can scatter light, resulting in a cloudy appearance. The concentration of gelling agents in a topical gel formulation is typically low, usually ranging from 0.5% to 2%, with additional inactive ingredients included to optimize the gel's properties.

**Advantages of Gels**

Gels offer several advantages as a topical dosage form for treating dermatological conditions. These advantages contribute to improved drug delivery and patient experience.

- Enhanced Cutaneous and Percutaneous Delivery: Gels facilitate optimal delivery of medication through the skin (cutaneous) or deeper layers (percutaneous). This allows for targeted treatment of skin conditions.

- Bypassing Gastrointestinal Issues: Gels circumvent potential challenges associated with oral medication administration. These challenges include difficulties with absorption due to gastrointestinal pH, enzymatic breakdown in the gut, and potential interactions with food and beverages.
- Alternative to Oral Medication: Gels can serve as a suitable alternative route for medication administration when oral administration is not ideal or feasible.
- Avoiding First-Pass Effect: Topical gels bypass the first-pass effect, where a medication undergoes initial metabolism by the liver after oral ingestion, potentially reducing its overall effectiveness.
- Minimizing Systemic Exposure: By delivering medication directly to the affected area, gels minimize systemic exposure and potential side effects associated with medications absorbed into the bloodstream.
- Non-invasive and Patient-Friendly: Gels offer a non-invasive and generally well-tolerated method of medication delivery, improving patient compliance with treatment regimens.
- Controlled Release: Gels can be formulated to provide sustained and controlled release of medication over time, reducing the frequency of application and potentially enhancing treatment efficacy.
- Versatility in Applications: Gels can be formulated as both topical and oral suspensions, offering flexibility for different treatment needs. Aluminum hydroxide gel, for example, is a common oral gel formulation used for treating gastrointestinal issues.
- Localized Effects: Gels often provide localized action, delivering medication directly to the affected area and minimizing potential side effects associated with systemic absorption.

**Gels classification**

Gels can be categorized based on several key characteristics, including the nature of their components, the solvent used, their physical behavior, and their flow properties (rheology).

**By Colloidal Phases:**

- Inorganic Gels (Two-Phase System): These gels consist of a dispersed phase of relatively large inorganic particles that form a three-dimensional network throughout the gel structure. The type of force responsible for linking these particles determines the overall stability and properties of the gel. Due to the larger particle size, these systems can be less stable and may require thixotropic properties, meaning they exhibit a gel-like state at rest but become more fluid with agitation [31, 32].
- Single-Phase System: In contrast, single-phase gels consist of large, dissolved organic molecules (natural or synthetic polymers) dispersed throughout a continuous liquid phase. These entangled polymer chains can become physically intertwined or linked by weak interactions like van der Waals forces [32].

**By Nature of Solvent:**

- Hydrogels (Water-Based): These are the most common type of gel, where water acts as the continuous liquid phase. Examples include bentonite magma, gelatin gels, and gels containing cellulose derivatives, carbopol, and poloxamer.
- Organogels (Non-Aqueous Solvent): These gels utilize a non-aqueous solvent as the continuous phase. Examples include Plastibase (low molecular weight polyethylene dissolved in mineral oil), Olag gels (aerosol gels), and dispersions of metallic stearates in oils.
- Xerogels (Dried Gels): These are gels with a very low solvent content, produced by processes like evaporation or freeze-drying. The remaining gel framework can often swell and be reconstituted when exposed to fresh liquid. Examples include tragacanth ribbons, acacia tears, beta-cyclodextrin, dried cellulose, and polystyrene.

**By Rheological Properties:**

Gels typically exhibit non-Newtonian flow behavior, meaning their viscosity is not constant and can change under applied stress. Common gel types based on their flow properties:

- Plastic Gels: These gels, like Bingham bodies or flocculated suspensions of aluminum hydroxide, exhibit a yield value. This means they require a certain amount of stress to initiate flow. Above this yield value, the gel structure deforms and begins to flow [29].
- Pseudoplastic Gels: Examples include dispersions of tragacanth, sodium alginate, and sodium carboxymethylcellulose (Na CMC). These gels exhibit a decrease in viscosity with increasing shear rate (applied stress). Unlike plastic gels, they do not have a yield value. This behavior arises from the shearing action on the long polymer chains within the gel. As the stress increases, the entangled chains become aligned in the direction of flow, releasing solvent from the gel matrix and reducing its overall viscosity.
- Thixotropic Gels: These gels possess weak inter-particle bonds that can be broken down by shaking or agitation. The resulting fluid state can then revert back to a gel as the particles collide and re-form bonds. This reversible gel-sol-gel transformation is often observed in colloidal systems with non-spherical particles that can form a network-like structure. Examples include kaolin, bentonite, and agar gels.

**By Physical Nature:**

- Elastic Gels: Gels formed by materials like agar, pectin, guar gum, and alginates exhibit elastic behavior. These fibrous molecules are linked at specific points by weak bonds like hydrogen bonds and dipole-dipole interactions. Additionally, the presence of free carboxylic acid groups (-COOH) allows for further cross-linking through ionic interactions between adjacent polymer chains. Examples include alginate and Carbopol gels.
- Rigid Gels: These gels are formed from macromolecules with strong covalent bonds within their framework. Silica gel is a prime example, where silicic acid molecules are linked by Si-O-Si bonds, creating a rigid polymer structure with a network of pores.

**Gelling Agents**

Gelling agents are hydrocolloidal substances that impart a thixotropic consistency to gels, serving as solidifiers, stabilizers, and thickening agents in pharmaceutical formulations. While there is no universal gelling agent currently available, there has been significant progress in the development of natural products for various applications. The pharmaceutical industry has shown a growing interest in gelling agents of natural origin due to their safety, biodegradability, and availability, offering advantages over synthetic counterparts. These natural gelling agents can be tailored for specific purposes in drug delivery systems, competing effectively with synthetic excipients. The increasing focus on naturally derived gelling agents has sparked interest in discovering, extracting, and purifying compounds from natural sources, making them valuable candidates for a wide range of pharmaceutical preparations, particularly in novel drug delivery systems [11, 23, 32].

Gelling agents serve to increase the thickness or viscosity of a formulation, thereby enhancing the nasal retention time and reducing the likelihood of spillage from the nasal cavity due to gravity and mucociliary clearance. These agents help maintain the medication in the nasal passage for a longer period, allowing for better absorption and increased efficacy.

They are biodegradable substances, naturally occurring polymers found in all living organisms. These gels have no harmful impact on the environment or human health, being biocompatible and non-toxic. Typically composed of repeating monosaccharide units, these plant-derived materials are primarily carbohydrates, ensuring the safety of gels and their lack of adverse effects.

These natural gelling agents are widely available in many countries due to their versatile applications across various industries. An ideal gelling agent must possess specific characteristics, including thixotropic behavior, non-greasiness, emollient properties, and non-staining attributes. It should form a stable solid-like structure during storage, easily dispersing upon exposure to shear forces like shaking or squeezing. Additionally, the gelling agent should allow for efficient drug

incorporation, not interact chemically or physically with the drug, facilitate drug diffusion and release, be cost-effective to manufacture, remain stable under various conditions, and ensure the non-toxicity of both the gelling agent and its degradation products.

Table 1.1.

**Gelling Agents and Their Subtypes**

| **Gelling Agents** | **Subtypes** | **Examples** |
|---|---|---|
| Polymeric gelling agents | Synthetic polymers | Carbomer, Poloxamer, Polyvinyl alcohol, Polyacrylamide, Polyethylene and its co-polymers. |
| | Semisynthetic polymers | Hydroxypropyl cellulose, carboxymethylcellulose, and hydroxyethyl cellulose. |
| | Natural polymers | Proteins, Gelatin, Collagen, Pectin, Gellum Gum, Xanthine, Cassia tora, Guar Gum, Alginic acid, Agar, Tragacanth, Sodium or Potassium, Carrageenan, Polysaccharides. |
| Inorganic substances | --------- | Bentonite, Aluminum hydroxide, Surfactants Brij-96, Cetostearyl alcohol. |

Carbopol homopolymers: acrylic acid crosslinked with allyl sucrose or allyl pentaerythritol.

Carbopol copolymers: acrylic acid and C10-C30 alkyl acrylate crosslinked with allyl pentaerythritol.

Carbopol interpolymers: carbomer homopolymer or copolymer that contains a block copolymer of polyethylene glycol and a long chain alkyl acid ester.

Gelling agents can be classified into two primary categories: aqueous and non-aqueous. Aqueous gelling agents encompass cellulose and its derivatives, gums, clays, and PEGs and their modifications, which are water-soluble and form gels

when combined with a dispersing medium. In contrast, non-aqueous gelling agents include polyethylene, organic compounds, organoclays, and silica, which are not soluble in water and form gels through various mechanisms, such as melting or dissolution in non-aqueous solvents. This classification highlights the diverse properties and applications of gelling agents, which are essential tools in the development of pharmaceutical formulations [11, 32].

Table 1.2.

**Carbopol® Polymer Products** [21]

| **Carbopol Polymer** | **Polymerization Solvent** | **Carbomer Product Type** | **Viscosity, cP (0.5 wt% at pH 7.5)** |
|---|---|---|---|
| 71G NF | Ethyl Acetate | Homopolymer | 4,000 - 11,000 |
| 971P NF | Ethyl Acetate | Homopolymer | 4,000 - 11,000 |
| 974P NF | Ethyl Acetate | Homopolymer | 29,400 - 39,400 |
| 980 NF | Cosolvent (made using cyclohexane and ethyl acetate) | Homopolymer | 40,000 - 60,000 |
| 981 NF | Cosolvent | Homopolymer | 4,000 - 10,000 |
| 5984 EP | Cosolvent | Homopolymer | 30,500 - 39,400 |
| ETD 2020 NF | Cosolvent | Interpolymer | 47,000 - 77,000 1.0 wt% |
| Ultrez 10 NF | Cosolvent | Interpolymer | 45,000 - 65,000 |
| 934 NF | Benzene | Homopolymer | 30,500 - 39,400 |
| 934P NF | Benzene | Homopolymer | 29,400 - 39,400 |
| 940 NF | Benzene | Homopolymer | 40,000 - 60,000 |
| 941 NF | Benzene | Homopolymer | 4,000 - 10,000 |
| 1342 NF | Benzene | Copolymer | 9,500 - 26,500 1.0 wt% |

Gelling agents exhibit varying solubility characteristics, with some like Acacia and Tragacanth being more soluble in cold water, while others such as Bentonite and Gelatin show better solubility in hot water. Typically used in concentrations ranging from 0.5% to 10%, these agents necessitate a neutralizer or pH-adjusting chemical to form the gel once wetted in the dispersing medium. Hydration of gelling agents usually takes 24-48 hours for complete hydration and attainment of maximum viscosity and clarity. The viscosity of the resulting gel layer typically falls within the range of approximately 1000 cps to about 100,000 cps, highlighting the diverse properties and applications of gelling agents in pharmaceutical formulations [11, 32].

## 1.5. Marketing analysis of gels

Topical dermatology drugs can be formulated into various dosage forms, including liquids, solids, and semisolids, with the latter being the most prevalent, accounting for approximately 80% of the global market. Semisolid formulations encompass a diverse range of products, including creams, emulsions, ointments, pastes, and gels, which have the ability to adhere to the application surface for a reasonable duration, allowing for controlled release to a specific area. These formulations primarily target surface action on the skin, but they can also be used for transdermal drug delivery, bypassing first-pass hepatic metabolism and gastrointestinal degradation. Semisolid drugs can be applied not only to the skin but also to other epithelial and mucosal membranes, such as the cornea, nasal mucosa, rectal tissue, vaginal tissue, and the external lining of the ear [9].

As the topical dermatology market continues to grow, there is increasing interest in formulations for skin conditions, particularly semisolid products. The 2017 Nice Insight Pharmaceutical Equipment Survey revealed that more respondents reported their companies manufacturing semisolid dosage forms in 2017 (50%) than in 2016 (45%). Semisolid dosage forms were the third most

common dosage forms manufactured after liquids and oral solid dosage forms, with the gap between their rankings narrowing.

Table 1.3.

**Some marketed formulations of Emulgels**

| **Marketed product** | **Active pharmaceutical ingredient** | **Manufacturing company** | **Indication** |
|---|---|---|---|
| Miconaz-H emulgel | Miconazole nitrate, Hydrocortisone | Medical union pharmaceuticals | Fungal infection |
| Voltaren emulgel | Diclofenac diethyl ammonium | Novartis pharma | Osteoarthritis |
| Diclobar emulgel | Diclofenac diethyl amine | Barakat pharma | Osteoarthritis |
| Excex gel | Clindamycin, Adapalene | Zee Laboratories | Acne |
| Pernox gel | Benzoyl peroxide | Cosme Remedies Ltd. | Acne |
| Lupigyl gel | Metronidazole, Clindamycin | LupinPharma | T. vaginalis infection |
| Clinagel gel | Clindamycin phosphate, Allantion | StiefelPharma | Acne and pimples |
| Zorotene gel | Tezarotene | Elder Pharmaceuticals | Psoriasis and Acne |
| Cloben G gel | Clotrimazole, Beclomethasone | Indoco Remedies | Skin infections |
| Avindo gel | Azithromycin | CosmePharma Lab. | Acne vulgaris |
| Accent gel | Aceclofenac | Intra Labs India Pvt. Ltd. | Sensitivity and plaque |

| | | | |
|---|---|---|---|
| Topinate gel | Clobetasol propionate | SystopicPharma | psoriasis, itching and dermatitis |

In terms of equipment demand for processing semisolid dosages, there is a stronger demand for mixers, stirrers, and blenders (45%), heating and cooling equipment (43%), and homogenising equipment (41%) compared to form-fill-seal equipment (37), milling equipment (34), and size reduction equipment (32).

**Conclusions to Chapter I**

Dermatitis is a complex and multifaceted skin condition that affects millions of people worldwide. The various forms of dermatitis, such as atopic, contact, seborrheic, neurodermatitis, stasis, and perioral dermatitis, each have distinct symptomatology and require tailored treatment approaches. A comprehensive exploration of dermatitis treatment's features was conducted, with a particular focus on the use of gels as a topical dosage form. Gels offer several advantages as a topical dosage form for treating dermatological conditions, including enhanced cutaneous and percutaneous delivery, bypassing gastrointestinal issues, minimizing systemic exposure, and providing controlled release of medication.

Understanding the multifactorial nature of dermatitis is crucial for paving the way for alternative therapeutic approaches. One such avenue may lie in the development of extemporaneous formulations, tailored to address the specific needs of individual patients and dermatitis subtypes. Extemporaneous formulation plays a unique role in delivering personalized topical medications, addressing specific skin types, and combining medications for optimal treatment.

The importance of understanding dermatitis's multifactorial nature was emphasized, highlighting the potential for alternative therapeutic approaches. One such avenue may lie in the development of extemporaneous formulations, tailored to address the specific needs of individual patients and dermatitis subtypes. Extemporaneous formulation, particularly in dermatology, plays a unique role in

delivering personalized topical medications, addressing specific skin types, and combining medications for optimal treatment.

The versatility of gels allows for the incorporation of various active ingredients, including corticosteroids, antibiotics, and anti-inflammatory agents, to address the diverse needs of dermatitis patients. The use of natural gelling agents further enhances their safety and biocompatibility, making them a preferred choice for dermatological applications.

The investigation of natural emulgel technological properties for dermatitis treatment is about to be explored in depth, covering specific research objectives and methodologies. A comprehensive overview of the experimental design, materials and methods, and data analysis approaches used to evaluate the efficacy and safety of emulgels in dermatitis treatment will be provided, aiming to foster a deeper understanding of the investigation's rigor and scientific validity.

# CHAPTER II
# RESEARCH OBJECTS AND METHODS

## 2.1. Theoretical justification of the extemporaneous gel composition for the treatment of allergic dermatitis

The development of dermatitis treatment is a critical area in modern pharmacy and medicine, as the prevalence of this skin condition continues to rise due to various environmental and lifestyle factors. Emulgels, which are a type of semi-solid dosage form, have emerged as a promising solution for dermatitis treatment due to their unique properties that combine the benefits of both emulsions and gels. they are characterized by their ability to deliver both hydrophilic and lipophilic drugs to the skin, making them highly versatile in treating a wide range of dermatological conditions. In the case of dermatitis, emulgels can be formulated with anti-inflammatory, antipruritic, and reparative agents to provide a comprehensive treatment approach [24, 27].

The use of herbal extracts in dermatitis treatment has gained significant attention due to their potential therapeutic benefits and reduced side effects compared to traditional pharmaceutical treatments. Motherwort Tincture and Valerian Tincture are two such herbal extracts that have shown promising results in the treatment of various skin conditions, including dermatitis.

Leonurus cardiaca, also known as motherwort, has been used in traditional medicine for centuries due to its anti-inflammatory, antispasmodic, and analgesic properties. It contains various biologically active substances (BAS), including alkaloids, flavonoids, and tannins, which have been shown to have a positive impact on inflammatory skin conditions.

Valerian tincture, on the other hand, is derived from the root of the Valerian plant and has been used for its sedative and anxiolytic effects. It contains valepotriates, which have been shown to have anti-inflammatory properties, making it a potential candidate for dermatitis treatment [6, 28].

When formulated into an emulgel, these two herbal extracts can provide a synergistic effect, enhancing their therapeutic properties and improving their delivery to the skin. The emulgel's formulation can provide a controlled release of the active compounds, ensuring their prolonged contact with the skin and enhancing their efficacy.

The use of herbal extracts in dermatitis treatment offers a more natural and holistic approach to managing skin conditions. By combining the anti-inflammatory and analgesic properties of Motherwort Tincture with the anti-inflammatory effects of Valerian Tincture, this emulgel can offer a comprehensive solution for dermatitis treatment, addressing both the inflammation and pain associated with this condition.

The selection of an appropriate emulsion-oitment base is crucial for the effectiveness of dermatitis treatment. emulgels with a peach oil and lanoline base have gained attention due to their potential therapeutic benefits.

| | | |
|---|---|---|
| Rp.: | Tincturae Leonuri | 2 ml |
| | Tincturae Valerianae | 2 ml |
| | Aquae purificatae | 10 ml |
| | Lanolini anhydrici | 30,0 |
| | Olei Persicoru | 30,0 |

Peach oil is a rich source of essential fatty acids, vitamins, and antioxidants that have been shown to improve skin hydration, elasticity, and barrier function. It also has anti-inflammatory properties, making it an ideal addition to the emulgel formulation. The natural oils and emulsifiers that provide additional benefits to the skin can also further enhanced the emulgel formulation for dermatitis treatment.

Olivem 1000 is a natural emulsifier derived from olive oil that has been shown to improve the stability and texture of emulsions. It is also known for its moisturizing and skin-conditioning properties, making it a popular choice for cosmetic and pharmaceutical applications.

Carbopol, a commonly used thickener in pharmaceutical applications, was chosen for this emulgel formulation. When dispersed in water, Unlike cellulose

derivatives, the formation of gels with Carbopols requires neutralization using alkalis, triethylamine, or aminomethylpropanol, depending on specific product characteristics. Carbopols of different grades and their resulting gels exhibit variations in concentrations used, emulsifying and suspending capabilities, degree of purification, application scope, gelation speed, transparency, resistance to electrolytes, temperature stability, and tolerance to mechanical stress. For that Carbopol 971 NF was selected for administration of the emulgel of Motherwort Tincture and Valerian Root Tincture and Peach oil.

Triethanolamine (TEA) is used as a pH adjuster to ensure the stability and compatibility of the emulgel formulation. It also helps to maintain the pH of the skin, which is crucial for the health and function of the skin barrier.

So the full emulgel composition will be:

Table 2.1.

**Emulgel composition for allergic dermatitis**

| | |
|---|---|
| Motherwort tincture | 2ml |
| Valerian tincture | 2ml |
| Peach oil | 30,0 |
| Olivem 1000 | 6,0 |
| TEA | to pH 5.0 |
| Carbopol 971 | 0,7 |
| Water purified | to 74,0 |

## 2.2. Characteristics of research objects

The focus of this research was an emulgel designed for alleviating allergic dermatitis. The active ingredients incorporated were Tincturae Leonuri and Tincturae Valerianae. Additionally, Peach oil, Olivem 1000 and Triethanolamine were included for their beneficial properties. To complete the emulgel formulation, purified water and Carbopol 971 were used as excipients.

**Motherwort tincture**

Pic. 2.1. Tincturae Leonuri (left), Leonurus cardiaca plant (right)

Motherwort tincture, a natural remedy derived from the aerial parts of the Leonurus cardiaca plant. It has a long history of use in traditional medicine, particularly in European and Chinese herbal traditions, for its various therapeutic properties.

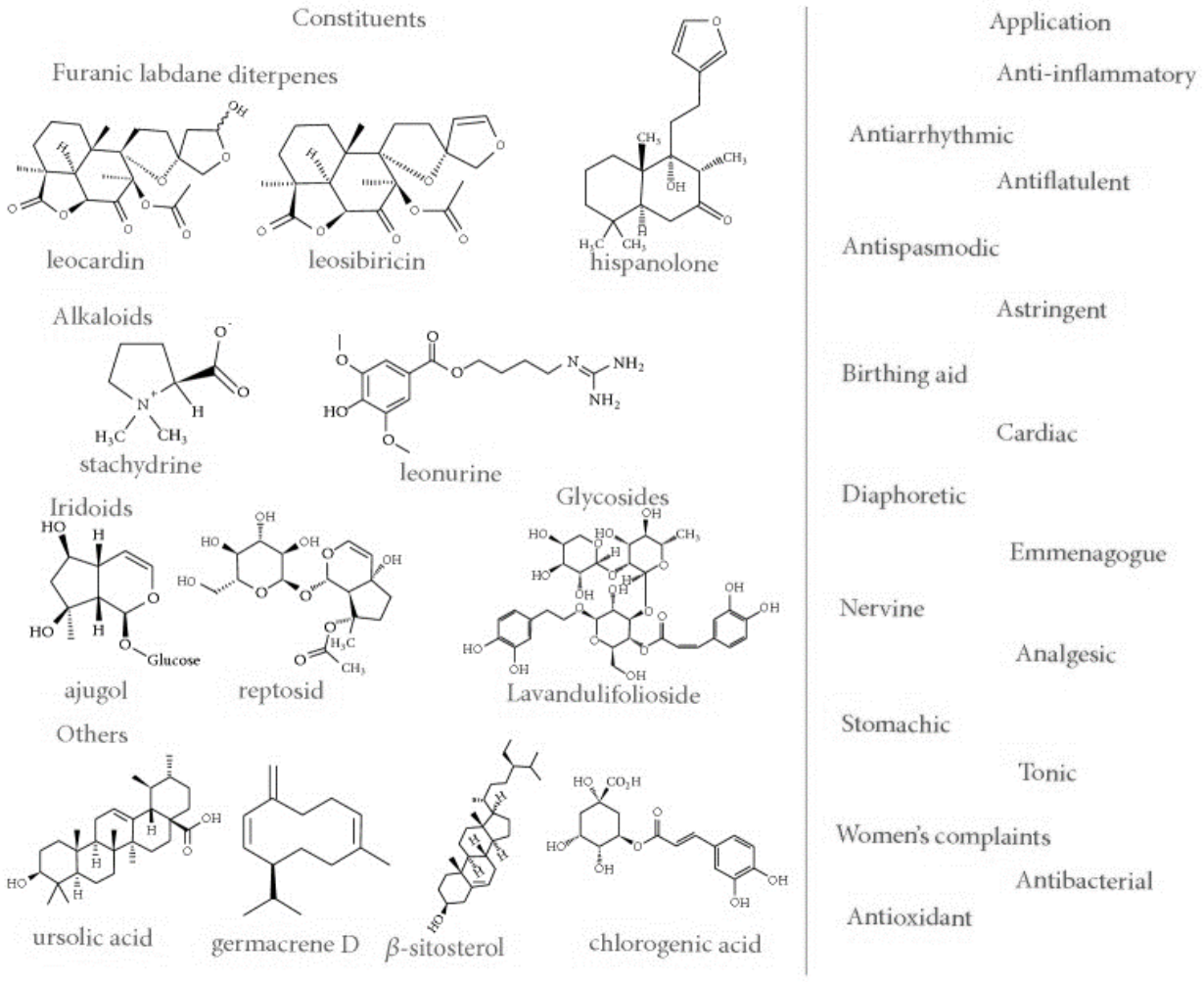
Tincturae Leonuri may be used in skin gels for irritation. Its anti-inflammatory effects help with redness, swelling, and itch. Furthermore, it antioxidant compounds can promote skin healing and protect against oxidative damage, making it suitable for skincare products targeting sensitive or irritated skin.

The makeup of Leonurus cardiaca is composed of various compounds, such as furanic diterpenes (labdanes), alkaloids (including stachydrine), sterols, iridoids, flavonoids, ursolic acid, minerals, and other substances.

The Leonurus cardiaca extract contains several compounds, including a major chlorinated iridoid glucoside (7-chloro-6-desoxy-harpagide), chlorogenic acid, ferulic acid, cichoric acid, caffeic acid, lavandulifolioside, isoquercitrin, verbascoside, and rutoside.

Additionally, stachydrine has been detected in various parts of Leonurus cardiaca. The essential oil of Leonurus cardiaca leaves revealed the presence of caryophyllene (39.8%), α-humulene (34.8%), α-pinene (5.6%), β-pinene (0.5%), limonene (0.4%), linalool (0.7%). Furthermore, the ursolic acid present in the leaves has been quantified to be 0.26%. Additionally, various active compounds have been quantified in both the raw material and medicinal preparation of Leonurus cardiaca, including chlorogenic acid, harpagide, ajugol, rutin, galiridoside, harpagide acetate,

galiridoside, lavandulifolioside, ajugoside, verbascoside, isoquercitrin, hyperoside, and apigenin-7-O-glucoside [18].




Pic. 2.2. Composition and applications of Leonurus cardiaca

The anti-inflammatory properties of Leonurus cardiaca, specifically its component leonurine, were investigated in mice with Escherichia coli-induced mastitis. The results indicated that leonurine alleviated histopathological changes, decreased the levels of proinflammatory cytokines, increased the anti-inflammatory cytokine IL-10, and inhibited the expression of nitric oxide synthase and cyclooxygenase-2. This effect is thought to be mediated by the inhibition of toll-like receptor 4 expression, nuclear factor-kappa B activation, and the phosphorylation of mitogen-activated protein kinases, extracellular signal-regulated kinase, and Jun N-terminal kinase.

Furthermore, the potential anti-inflammatory effects of leonurine were demonstrated in rat models of acute gouty arthritis. These findings support its use as an inhibitor of COX-2, microsomal prostaglandin E synthase-1, and 5-lipoxygenase, thereby showing antiarthritic effects. Moreover, leonurine was found to reduce inflammation induced by monosodium urate crystals by decreasing interleukin-1β and tumor necrosis factor-alpha production, highlighting its potential as an anti-inflammatory agent.

The antioxidant capacity of Leonurus cardiaca extract was assessed using ABTS, DPPH, and ferric reducing antioxidant power assays, yielding antioxidant capacity values ranging from 350±20 to 455±17 μM Trolox/g. This highlights the extract's ability to scavenge free radicals and suggests its potential as a valuable source of antioxidants for various applications [18].

The anti-inflammatory effects of Leonurus cardiaca help with redness, swelling, and itch. Also, its antioxidant compounds can promote skin healing and protect against oxidative damage, making it suitable for skincare products targeting sensitive or irritated skin and for skin conditions like dermatitis.

**Valerian tincture**

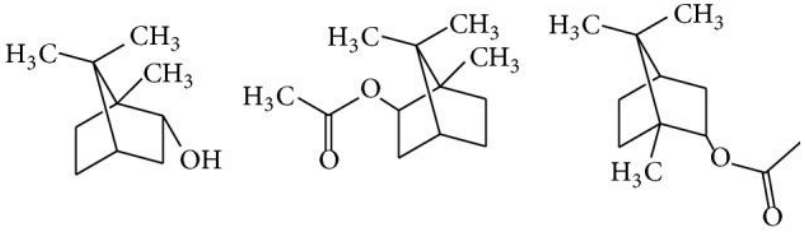
Pic. 2.3. Tincturae Valerianae (left), Valeriana officinalis plant (right)

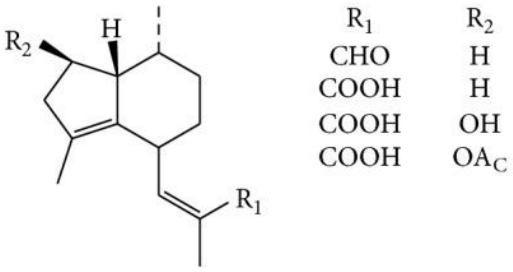
Valerian tincture, a derived from the Valeriana officinalis plant, Valerian tincture have a history in traditional medicine for its sedative effects, Valerian tincture interacts with GABA receptors in the brain, offering anxiolytic and sedative

benefits that can aid in managing stress-related dermatitis and supporting skin healing.

Commonly used in topical formulations for dermatitis and eczema, it may relieve itching, redness, and inflammation while soothing skin sensitivity, making it a valuable addition to skincare products for sensitive or irritated skin types.

Valerian contains various known compounds such as alkaloids (actinidine, chatinine, shyanthine, valerianine, and valerene), Gamma-aminobutyric acid (GABA), Valeric acid, Isovaleric acid, Iridoids (including valepotriates such as isovaltrate and valtrate), Sesquiterpenes found in the volatile oil (valerenic acid, hydroxyvalerenic acid, and acetoxyvalerenic acid), Flavanones (hesperidin, 6-methylapigenin, and linarin), and Isovaleramide may form during the extraction process [4, 6, 28]




Pic. 2.4. Major essential oil constituents from Valeriana officinalis

Valerian root has been found to have a multitude of effects on the body. One of its key components, iridoids, may function as anti-inflammatory agents and inhibit the expression of specific genes. Research conducted on mice has indicated

that valerian root can alleviate pain in the body through the action of flavonoids, which inhibit the production of nitric oxide.

**Peach oil**

Pic. 2.5. Peach oil

Peach oil is a fatty oil extracted through cold-pressing seeds of plants from the olive subfamily Prunoideae, including common peach (Prunus persica), common apricot (Armeniaca vulgaris), domestic plum (Prunus domestica), and plum (Prunus divaricata). It is a transparent oily liquid with a light yellow color, a faint or distinct odor, and a pleasant oily taste. The oil does not dry in the air.

Peach oil is used as a solvent for the production of various injection solutions, such as chrysanol, camphor, deoxycorticosterone acetate, diethylethylbestrol propionate, ergocalciferol, progesterone, retinol acetate, sinestrol, and testosterone propionate. It is also used in the production of suspensions like bioquinol and bismoverol. Furthermore, peach oil is an ingredient in spermacetate ointment, emulsions, tetracycline ointment, and dental paste. It is also recognized as a gentle laxative medicinal substance.

**Olivem 1000**

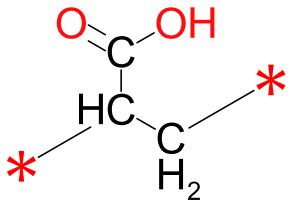
A multifunctional ingredient derived from olives, serving as a nonionic oil-in-water self-emulsifying agent without polyethylene glycol (PEG). Comprising fatty

acids akin to the skin's lipid composition, it can form liquid crystal structures resembling the organization of the stratum corneum.

Pic. 2.6. Olivem 1000, a natural emulsifier

This emulsifier deeply moisturizes, commonly found in products for sensitive skin, night creams, daily moisturizers, after-sun care, baby products, and hair conditioning creams. The recommended usage ranges from 1.5 to 3% for lotions, serums, and gels, and 3.5 to 8.5% for creams.

**Carbopol 971P NF Polymer**




Pic. 2.7. Carbopol 971P structural formula:

Carbopols constitute high molecular weight polymers of acrylic acid, which are chemically cross-linked with polyalkenyl alcohols or divinyl glycol. The primary distinction among these polymers lies in the type of substituent, crosslink density, and the presence of hydrophobic comonomers. Consequently, carbomers are categorized into five groups: [21]

Carbopol homopolymer: This polymer consists of acrylic acid that is cross-linked with allyl saccharose or allyl pentaerythrolol.

Carbopol polymer: This polymer is derived from acrylic acid and C10-C30 alkyl acrylate, cross-linked with allyl pentaerolite.

Interpolymer: This carbomer is a homopolymer or copolymer containing a block of a copolymer of polyethylene glycol and an ester with a long chain alkyl substituent.

The diversity in the structure and composition of Carbopols enables their use in various pharmaceutical and cosmetic applications, where they can provide thickening, gelling, and stabilizing properties. The specific type of Carbopol used in a formulation can significantly impact the rheological behavior, drug release profile, and overall performance of the product.

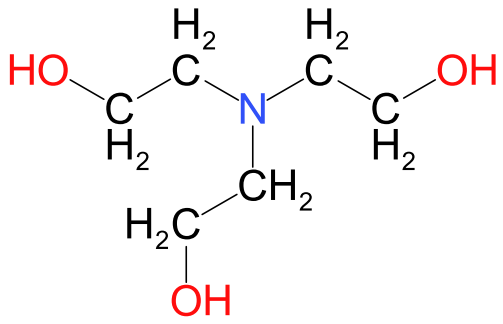
Carbopol 971, along with other carbopol resins, is recognized for its non-toxic nature and the ability to significantly expand upon hydration with a suitable solvent. This expansion capability enables these resins to incorporate substantial quantities of an active drug without any adverse impact on the drug release rates from the processing variables. The inherent properties of Carbopol 971, make it suitable for use in pharmaceutical applications where controlled drug release and stability are critical factors. These resins contribute to the development of reliable and effective formulations, ensuring consistent drug delivery and patient safety.

Carbopol 971P NF polymer is suitable for creating gels with low viscosity, lotions, and liquids that exhibit excellent clarity. When used at topical levels ranging from 0.5% to 3% by weight, this polymer can enhance the formulation of gels, providing stability and clarity. Moreover, it offers emulsion stabilization properties, particularly beneficial for maintaining the stability of lotions. Incorporating it in gel formulations not only helps achieve desired viscosity levels but also contributes to the overall quality and appearance of the product, ensuring a stable and visually appealing end result.

**Triethanolamine (TEA)**

A colorless, viscous organic compound with the formula N(CH2CH2OH)3, plays a diverse role in various industrial and consumer products. This molecule

possesses a unique chemical structure, combining properties of both tertiary amines and triols (molecules with three alcohol groups). While pure TEA is colorless, slight yellowing may occur due to impurities [14].




Pic. 2.8. Triethanolamine structural formula:

The primary application of triethanolamine lies in the creation of surfactants, particularly emulsifiers. This functionality makes TEA a common ingredient in a wide range of formulations. In these applications, TEA neutralizes fatty acids, regulates and buffers pH levels, and aids in solubilizing oils and other water-insoluble ingredients. Additionally, TEA salts can offer advantages over alkali metal salts, exhibiting greater solubility and leading to less alkaline products compared to those formed with alkali metal hydroxides [14, 17].

The pharmaceutical industry also utilizes TEA. Notably, it serves as the active ingredient in some ear drops for treating earwax impaction. Beyond this specific use, TEA's pH-balancing properties make it a valuable component in various cosmetic products, including cleansers, lotions, eye gels, moisturizers, shampoos, and shaving creams. It's important to note that TEA is a relatively strong base, with a 1% solution reaching a pH of around 10. This is significantly higher than the natural pH of human skin, which typically falls between 5.5 and 6.0 [21].

**Purified water**

Purified water serves as a crucial excipient in the manufacturing of non-parenteral pharmaceutical formulations and is also employed in various other

pharmaceutical applications, such as the cleaning of specific equipment and non-parenteral product-contact components. To ensure its suitability for these purposes, purified water must adhere to stringent standards of ionic and organic chemical purity and be safeguarded against microbial contamination.


Pic. 2.9. USP Purified Water (USP-PW)

The production of purified water typically involves the use of drinking water as the source or feed water. To maintain its purity, this water must be shielded from recontamination and microbial proliferation throughout the production process. Common methods for producing purified water comprise ion exchange, ultrafiltration, reverse osmosis (RO), distillation and electrodeionization processes.

The purified water produced is subjected to rigorous quality testing, ensuring that it meets or exceeds the standards set forth by the United States Pharmacopeia (USP) for Purified Water (USP-PW). Every batch of purified water undergoes testing for sterility, endotoxin levels, conductivity, pH, and total organic carbon (TOC) to ensure its compliance with these standards [35].

The manufacturing facility where this water is produced is fully compliant with current Good Manufacturing Practices (cGMP) and is registered with the Food and Drug Administration (FDA) as a medical device manufacturer. Additionally, the facility is certified to ISO 13485 standards, further attesting to its commitment to quality and safety in the production of purified water for pharmaceutical applications.

### 2.3. Research methods

Description. The appearance, organoleptic properties of the samples (color, smell, consistency) were controlled. Model samples were examined for signs of physical instability (delamination, discoloration).

Appearance, color and smell. The appearance, color and smell were determined by examining samples of the ointment applied to a glass slide.

Determination of the stability of the ointment

To check the stability and quality of the ointment, the method of stratification - centrifugation was used.

Determination method: 5.0 samples of the ointment are placed in test tubes, which are installed in the centrifuge holder.

At the first stage, centrifugation is carried out for 10 minutes at a rotation speed of 500 rpm. After 10 minutes, remove the test tubes and, with sufficient lighting, check the ointment samples for delamination. In the event of a change in the homogeneity of the ointments – their separation into separate components – the height of the separated fractions is measured and their appearance is described.

At the second stage, centrifugation is carried out for 10 minutes, and the speed of rotation of the centrifuge is 1000 rpm. After the end of time, the same measurements and determinations as in the first stage are carried out. At further stages, only the number of revolutions is increased - 2000, 3000 rpm and so on. The number of revolutions is increased until delamination occurs in all samples of ointments. Based on the results of these studies, conclusions are made about the comparative stability or instability of ointments.

Determination of thermal stability. To conduct the test, take 5-6 test tubes (diameter - 15 mm, height - 150 mm). 10 ml of the test samples are added to the test tubes and placed in a thermostat (temperature 40-40$^{o}$C) for 1 week, then transferred to a refrigerator (temperature 10-12$^{o}$C) for 1 week, after which they are kept for 3 days at room temperature temperature Stability is determined visually by the absence of delamination in the tested samples.

Optical microscopy. Microscopy of the gels was carried out using a Granum R-40 laboratory microscope with a built-in digital video camera at magnifications of 40, 100, and 400 times.

Determination of the pH of ointments is necessary to control the behavior of medicinal substances and bases during storage. A change in pH indicates a change in their physical and chemical properties. To determine the pH of ointments, a portion of the product is poured with 50 ml of purified water at a temperature of 50-60°C and shaken on a vibrator for 30 minutes. The obtained extract is filtered and titration of the potentiometer is carried out according to the SPU method [37].

## Conclusions to chapter 2

The characteristics of API, auxiliary substances and the range of methods necessary for improving the composition and studying the technological properties of emulgel for the treatment of dermatitis were represented.

# CHAPTER 3.
# EMULGEL CONTAINING MOTHERWORT AND VALERIAN TINCTURES TECHNOLOGICAL PROPERTIES INVESTIGATION

## 3.1. Emulgel containing motherwort and valerian tinctures composition substantiation and characteristic

In the extemporaneous formulations, an emulsion ointment is used for the treatment of dermatitis containing Motherwort and Valerian tinctures, purified water, lanolin and peach oil. This composition refers to emulsion systems, where APIs dissolved in a liquid opposite in properties to the base. In order to increase the ease of use and bioavailability, we suggest replacing the water/oil lanolin anhydrous emulsifier with Olivem 1000 with the addition of Carbopol 971 gelling agent and (triethanolamine) TEA.

Motherwort and Valerian tinctures have anti-inflammatory, antioxidant and soothing properties that make them suitable for use in gels, particularly for dermatitis treatment. By incorporating these tinctures into an emulgel formulation, it is possible to enhance their skin penetration and stability, while also reducing any undesirable side effects.

**Emulgel composition :**

Motherwort tincture 5ml
Valerian tincture 5ml
Peach oil 30,0
Olivem 1000 3,0
TEA to pH 5.0
Carbopol 971 1,0
Water purified to 100,0

**Characteristic:** The given medicine is a emulgel (ointment emulsion) containing Motherwort and Valerian (aromatic) tinctures water soluble substances, Peach oil, emulsifier Olivem 1000, Carbopol 971, TEA and purified water.

### 3.2. Emulgel technological process stages

**1. Preparatory works:**

1.1. Prescription pharmaceutical expertise

1.2. Calculations

1.3. Preparation of auxiliary materials, active and additional substances

**2. Emulgel technology:**

2.1. Weighing out Peach oil 30,0 in porcelain cup.

2.2. Weighing out Olivem 1000 0,5.

2.3. Heating Peach oil to 75ºC on water barh and adding emulsifier Olivem 1000. Mixing.

2.4. Measuring 56 ml of water purified and transferring it to a auxiliary glass botle.

2.5. Weighing out Carbopol 971 and adding to water purified

2.6. Heating water purified

2.7. Adding hot water purified to Peach oil, Olivem 1000 and mixing 1-2 min.

2.8. Removing emulgel from water bath and homogenizing 2 min.

2.9. Adding TEA to pH 5.0 and mixing until complete cooling.

3. Quality control: written control, physical control (deviation in weight), organoleptic control, questionnaire control.

4. Package. Marking (labeling).

5. Delivery control.

### 3.3. Determination of emulgel stability indicators

An appearance, color, odor, application, pH and stability were determined in the prepared samples of the cream for 32 days.

**Table 3.1.**

**Organoleptic quality indicators of the emulgel samples**

| Research term | Appearance | Color | Odor | Stratification (thermostability) | pH |
|---|---|---|---|---|---|
| 1 day | homogeneous emulgel of a soft consistency | white | light specific | not observed | 5.1 |
| 5 days | homogeneous emulgel of a soft consistency | – “– | – « – | not observed | 5.1 |
| 32 days | homogeneous emulgel of a soft consistency | – “– | – « – | not observed | 5.2 |

Based on the research conducted, it is possible to set a storage period of up to 30 days.

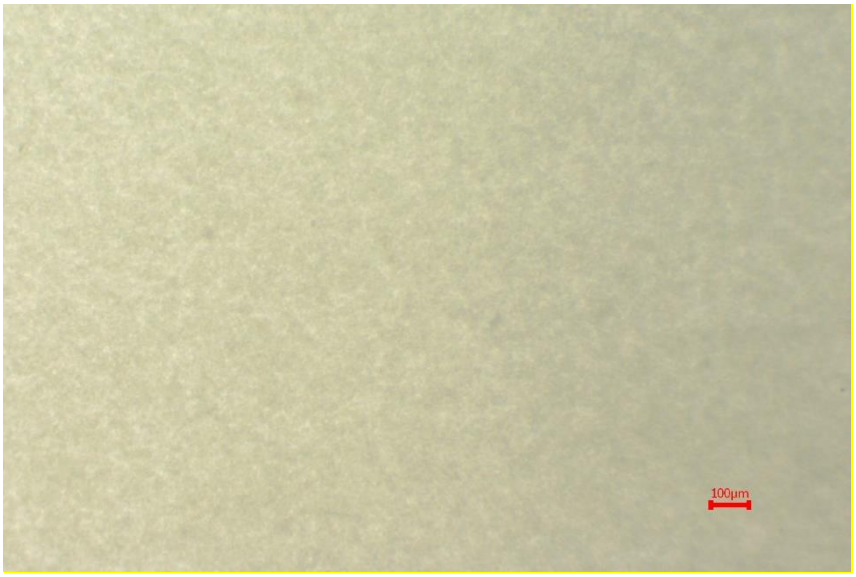



Fig. 3.1. Gel sample at x40 magnification

Microscopic research and measurement of the linear dimensions of gel particles was carried out using a Granum R-40 laboratory microscope with a built-in DCM 310 digital camera and achromatic lenses with 4x, 10x, 40x magnification. The use of this equipment made it possible to visualize the particles and carry out their morphometric analysis using the Toup View 3.7 program. To prove the homogeneity of the gel, its microscopy was performed according to the method given in section 2, the results are presented on fig. 3.1. and 3.2.

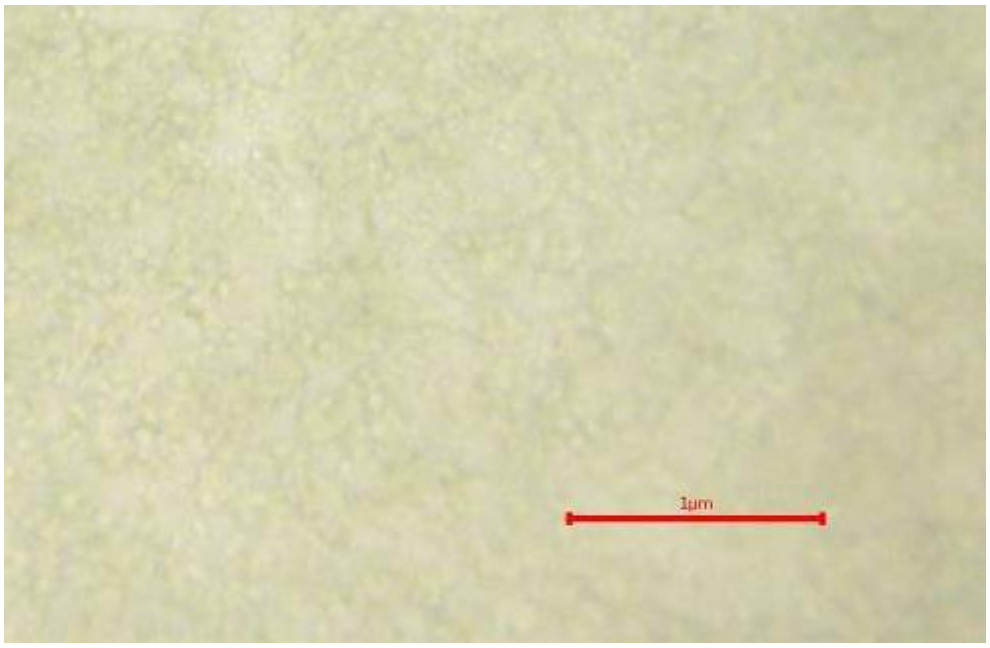



Fig. 3.2. Gel sample at x400 magnification

The resulting emulsion was stable for 32 days, and no signs of delamination were detected, as proved by optical microscopy.

### 3.4. Determination of emulgel pH

The pH value is an important indicator that affects the stability of gel systems during storage, the nature of component interactions, as well as the biological activity and therapeutic effectiveness of the drug.

Measurement of the pH of 10% aqueous solutions of experimental emulgel samples after 32 days of storage was carried out by the potentiometric method.

**Table 3.2.**

**Determination of emulgel pH**

| m | n | $X_i$ | $X_{cp}$ | $S^2$ | $S_{cp}$ | P | t(P, n) | Confidence interval | | | ε_, % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 2 | | 3 | 4 | 5 | 6 | 7 | 8 | | | 9 |
| 6 | 5 | 5,26 | 5,2017 | 0,0022 96667 | 0,0196 | 0,95 | 2,78 | 5,2017 | ± | 0,0544 | 1,0456 |
| | | 5,19 | | | | | | | | | |
| | | 5,16 | | | | | | | | | |
| | | 5,25 | | | | | | | | | |
| | | 5,14 | | | | | | | | | |
| | | 5,21 | | | | | | | | | |

As a result of the research, it was established that the hydrogen index is 5.20±0.0544.

## Conclusions to chapter 3

1. Theoretically proved composition of emulgel containing motherwort and valerian tinctures for the dermatitis treatment.

2. The technology of the emulgel, containing Peach oil, TEA, Olivem 1000, Carbopol 971 and purified water, was experimentally chosen.

3. Organoleptic quality indicators of the emulgel samples was observed.

4. By the method of sieve microscopy proved the uniform distribution of gel particles and the absence of insoluble particles.

5. When determining the pH of the gels, it was established that the pH value is in the range of 5.14-5.26.

## GENERAL CONCLUSIONS

1. Theoretically justified and experimental proved the emulgel composition and technology for the dermatitis treatment.
2. An analysis of the literature on types of dermatitis and mechanisms of its development was carried out.
3. Modern approaches to the treatment of dermatitis, in particular allergic dermatitis, were analyzed.
4. On the basis of comprehensive research, the composition of the emulgel base was chosen for the dermatitis treatment.
5. The composition and technology of the emulgel are theoretically and experimentally substantiated, taking into account the physical and chemical ingredients included in its composition.
6. Term of storage for 30 days at refrigerator was proven.
7. Technology of the emulgel for the dermatitis treatment was proposed.

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# APPENDICES

# Appendix A

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ`Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

## АКТУАЛЬНІ ПИТАННЯ СТВОРЕННЯ НОВИХ ЛІКАРСЬКИХ ЗАСОБІВ

МАТЕРІАЛИ
XXX МІЖНАРОДНОЇ НАУКОВО-ПРАКТИЧНОЇ
КОНФЕРЕНЦІЇ МОЛОДИХ ВЧЕНИХ ТА СТУДЕНТІВ

17-19 квітня 2024 року
м. Харків

Харків
НФаУ
2024

## Continuation of Appendix A

УДК 615.1

**Редакційна колегія**: проф. Котвіцька А. А., проф. Владимирова І. М.
**Укладачі**: Зуйкіна Є. В., Боднар Л. А., Сурікова І. О.,

Актуальні питання створення нових лікарських засобів: матеріали XXX міжнародної науково-практичної конференції молодих вчених та студентів (17-19 квітня 2024 р., м. Харків). – Харків: НФаУ, 2024. – 475 с.

Збірка містить матеріали міжнародної науково-практичної конференції молодих вчених та студентів «Актуальні питання створення нових лікарських засобів», які представлені за пріоритетними напрямами науково-дослідної роботи Національного фармацевтичного університету. Розглянуто теоретичні та практичні аспекти синтезу біологічно активних сполук і створення на їх основі лікарських субстанцій; стандартизації ліків, фармацевтичного та хіміко-технологічного аналізу; вивчення рослинної сировини та створення фітопрепаратів; сучасної технології ліків та екстемпоральної рецептури; біотехнології у фармації; досягнень сучасної фармацевтичної мікробіології та імунології; доклінічних досліджень нових лікарських засобів; фармацевтичної опіки рецептурних та безрецептурних лікарських препаратів; доказової медицини; сучасної фармакотерапії, соціально-економічних досліджень у фармації, маркетингового менеджменту та фармакоекономіки на етапах створення, реалізації та використання лікарських засобів; управління якістю у галузі створення, виробництва й обігу лікарських засобів; суспільствознавства; фундаментальних та мовних наук.

УДК 615.1

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# Continuation of Appendix A

XXX Міжнародна науково-практична конференція молодих вчених та студентів
«АКТУАЛЬНІ ПИТАННЯ СТВОРЕННЯ НОВИХ ЛІКАРСЬКИХ ЗАСОБІВ»

## RELEVANCE OF EMULGEL DEVELOPMENT FOR THE DERMATITIS TREATMENT

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**Introduction.** Dermatitis, a widespread skin condition encompasses various forms of inflammatory skin conditions. In the field of clinical dermatology, the term "dermatitis" is utilized to encompass a range of skin conditions that exhibit a common inflammatory response pattern and share similar clinical presentations. Dermatitis can manifest in many forms and has various causes. It often presents with itchy, dry skin or a rash. In some cases, it may cause blistering, oozing, crusting, or flaking of the skin. Current treatments for it can be limited by factors like poor skin penetration or side effects. Emulgels, combining gel and emulsion properties, offer a promising alternative.

Emulgels are carrier systems that represent a mixture of emulsion and gel, which are particularly significant for the delivery of hydrophobic substances. However, the proper selection of main constituents determines the stability and efficacy of emulgels. Emulgels are dual-controlled release systems, where the oil phase is utilized as a carrier for hydrophobic substances and it determines the occlusive and sensory properties of the product. Gelling agents are used to increase the consistency of composition and improve sensory properties by making these systems thixotropic. The gelling agents also impact the release of active substances from the formulation and stability of the system.

**Aim.** To study the relevance of developing an emulgel with tinctures of Motherwort and Valerian for the dermatitis treatment.

**Materials and methods.** To achieve this goal, we used general scientific research methods: analysis, synthesis, comparison, generalisation, comparison, systematisation to process the literature data.

**Research results.** In the extemporaneous formulations, an emulsion ointment containing Motherwort and Valerian tinctures, purified water, lanolin and peach oil is used for the treatment of dermatitis. This composition refers to emulsion systems, where APIs dissolved in a liquid opposite in properties to the base. In order to increase the ease of use and bioavailability, we suggest replacing the water/oil lanolin anhydrous emulsifier with Olivem 1000 with the addition of Carbopol 971 gelling agent and (triethanolamine) TEA.

Motherwort and Valerian tinctures have anti-inflammatory, antioxidant and soothing properties that make them suitable for use in gels, particularly for dermatitis treatment. By incorporating these tinctures into an emulgel formulation, it is possible to enhance their skin penetration and stability, while also reducing any undesirable side effects.

**Conclusions.** Emulgels offer a novel approach to enhancing skin penetration and reducing side effects. The focus on natural ingredients with anti-inflammatory, soothing, and moisturizing properties highlights a shift towards more holistic and effective dermatitis management and demonstrates a strategic approach to creating a stable and suitable semi-solid medicinal form. That's why developing emulgel with Motherwort and Valerian tinctures for the dermatitis treatment is a pressing task.

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**Appendix B**


МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

# СЕРТИФІКАТ УЧАСНИКА

Цим засвідчується, що

**Youness Chouati, Oliinyk S.V.**

**Scientific supervisor: assoc. prof. Kovalov V.V.**

брав(ла) участь у роботі

XXX Міжнародної науково-практичної конференції молодих вчених та студентів

**«АКТУАЛЬНІ ПИТАННЯ СТВОРЕННЯ НОВИХ ЛІКАРСЬКИХ ЗАСОБІВ»**

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