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QUALIFICATION WORK

on the topic: **«DEVELOPMENT OF THE COMPOSITION OF A GEL WITH A COOLING EFFECT BASED ON MENTHOL AND CAMPHOR»**

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ANNOTATION

This master's thesis presents the development of a topical gel formulation with a cooling effect based on menthol and camphor. Three experimental gel compositions were prepared using different gelling agents and solvent systems. Their technological properties, including appearance, pH, spreadability, viscosity, and short-term stability, were evaluated using simple laboratory methods. Based on comparative analysis, the optimal composition was selected. The research demonstrates that effective formulation development can be achieved using accessible equipment and reproducible techniques. The work consists of the following parts: introduction, literature review, choice of research methods, experimental part, general conclusions, list of used literature sources, total volume of 51 pages, contains 13 tables, 31 references.

Key words: menthol, camphor, cooling gel, viscosity, pharmaceutical technology.

АНОТАЦІЯ

У магістерській роботі представлено розробку гелевої лікарської форми з охолоджувальним ефектом на основі ментолу та камфори. Було підготовлено три дослідні зразки гелю з використанням різних гелеутворювачів та розчинників. Їх технологічні властивості - зовнішній вигляд, pH, ступінь розтікання, в’язкість та короткострокова стабільність - оцінювалися за допомогою простих лабораторних методик. На основі порівняльного аналізу обрано оптимальний склад. Результати дослідження підтверджують можливість ефективної розробки лікарських форм з використанням доступного обладнання та відтворюваних методів.

Робота складається з таких частин: вступ, огляд літератури, вибір методів дослідження, експериментальна частина, загальні висновки, список використаних літературних джерел, загальний обсяг 51 сторінок, містить 13 таблиць, 31 посилання.

Ключові слова: ментол, камфора, охолоджувальний гель, в’язкість, фармацевтична технологія.

CONTENT

LIST OF ABBREVIATIONS

API – active pharmaceutical ingredient

BAS – biologically active substance

EDTA – ethylenediaminetetraacetic acid

EtOH – ethanol

F – formulation

GMP – good manufacturing practice

HPMC – hydroxypropyl methylcellulose

OTC – over-the-counter

Ph.Eur. – European Pharmacopoeia

SPhU – State Pharmacopoeia of Ukraine

TRPM8 – transient receptor potential melastatin 8

TRPV1 – transient receptor potential vanilloid 1

TRPV3 – transient receptor potential vanilloid 3

USP – United States Pharmacopeia

WHO – World Health Organization

INTRODUCTION

The relevance of the topic

Topical gel formulations have become increasingly popular in both pharmaceutical and cosmetic applications due to their favorable characteristics such as ease of application, non-greasy texture, and rapid onset of local action. Among these, gels with a cooling effect are widely used to relieve discomfort, irritation, and localized inflammation. The growing consumer demand highlights the importance of developing gel formulations containing cooling agents such as menthol and camphor. These two active ingredients are recognized for their synergistic action on thermoreceptors, producing a distinctive sensation of cooling that is both therapeutic and cosmetically desirable. However, the formulation of such gels presents technological challenges, particularly with respect to solubilization of volatile compounds, maintaining physical stability, and ensuring user acceptability. Therefore, the development of a technologically sound, stable, and aesthetically appealing gel with a cooling effect remains a relevant topic in modern pharmaceutical science.

The purpose of the study

The purpose of this research is to develop and experimentally justify the composition of a topical gel with a cooling effect, based on menthol and camphor, using simple, reproducible methods suitable for small-scale pharmaceutical formulation laboratories.

Research tasks

To achieve this purpose, the following tasks were defined:

1. To justify the selection of active ingredients and excipients for the formulation of a cooling gel.

2. To prepare and characterize trial gel formulations containing different gelling agents and solvent systems.

3. To evaluate the organoleptic, physicochemical, rheological, and stability properties of the gels using simple technological methods.

4. To select the optimal gel composition based on a comprehensive comparison of results.

The object of research

The object of research is the semi-solid dosage form - a topical gel designed for dermal application, with a functional cooling effect.

The subject of the study

The subject of this study includes the composition and technological properties of gels containing menthol and camphor, and the methods used for their development and evaluation.

Research methods

The research used technological, sensory, and stability testing methods commonly applied in pharmaceutical formulation development. These included pH measurement, spreadability testing, rotational viscometry, and short-term stability testing under thermal and freeze–thaw conditions.

Practical significance of the obtained results

The results of this research can be used in academic laboratories, pharmaceutical compounding, and formulation departments for the development of cooling gel products. The selected composition is suitable for industrial scaling using standard equipment and packaging, and meets both functional and aesthetic expectations.

Elements of scientific research

The scientific novelty lies in the comparative experimental evaluation of gelling agents and solvent systems for menthol–camphor gels using only simple technological parameters, providing an accessible model for effective formulation development without reliance on advanced analytical chemistry.

Structure and scope of qualification work

Qualification work consists of the following parts: introduction, literature review, choice of research methods, experimental part, general conclusions, list of used literature sources, total volume of 51 pages, contains 13 tables, 31 references.

CHAPTER 1
SCIENTIFIC BASIS FOR THE DEVELOPMENT OF COOLING GELS CONTAINING MENTHOL AND CAMPHOR

1.1. Physicochemical properties and mechanism of action of menthol and camphor

Menthol and camphor are both monoterpenoids, naturally occurring organic compounds derived from plant sources. Menthol, primarily obtained from peppermint oil, is a cyclic terpene alcohol with the molecular formula $C_{10}H_{20}O$. It exists as a white or colorless crystalline solid at room temperature and has a characteristic minty aroma. Camphor, on the other hand, is a bicyclic ketone with the molecular formula $C_{10}H_{16}O$. It is typically derived from the wood of the camphor laurel tree and appears as white, waxy crystals with a strong, penetrating odor. Both compounds are known for their volatility and distinctive scents, which contribute to their widespread use in topical formulations [1].

Menthol has a melting point ranging from 36°C to 38°C and a boiling point of approximately 212°C. It is slightly soluble in water but readily dissolves in organic solvents such as ethanol and chloroform. Camphor exhibits a higher melting point, between 175°C and 177°C, and a boiling point around 209°C. It has a greater aqueous solubility compared to menthol, approximately 1.2 mg/mL, and is also soluble in organic solvents. The volatility of both menthol and camphor contributes to their rapid evaporation upon application, imparting a cooling sensation on the skin [2].

The physicochemical properties of menthol and camphor significantly influence their incorporation into gel formulations. Their moderate solubility in water necessitates the use of co-solvents or emulsifying agents to achieve a homogeneous distribution within aqueous gel bases. The melting points of these compounds are pertinent when considering the processing temperatures during gel preparation. Furthermore, their volatility must be managed to prevent premature evaporation, which can be addressed by optimizing the gel matrix to control the

release rate. Understanding these properties is crucial for developing effective and stable topical gels with desired therapeutic effects [3].

Menthol and camphor exert their cooling effects primarily through the activation of the transient receptor potential melastatin 8 (TRPM8) ion channel, a key thermoreceptor in the human body. TRPM8 is a non-selective cation channel predominantly expressed in sensory neurons, particularly within the dorsal root and trigeminal ganglia. It responds to cool temperatures ranging from 8°C to 28°C and is activated by chemical agents like menthol and icilin. Upon activation, TRPM8 allows the influx of Na^+ and Ca^{2+} ions, leading to neuronal depolarization and the transmission of cold sensations to the central nervous system. This mechanism underlies the characteristic cooling sensation experienced upon topical application of menthol-containing products [4].

Camphor, although traditionally associated with a warming sensation, has been shown to interact with TRPM8 as well. Research indicates that camphor can activate and sensitize TRPM8 channels, enhancing the perception of cooling stimuli. This dual action suggests that camphor's sensory effects are more complex than previously understood, involving both warming and cooling pathways depending on concentration and context [5].

The activation of TRPM8 by menthol and camphor leads to a cascade of sensory events culminating in the perception of coolness. This sensation is not merely a physical response but also involves psychological components, contributing to the soothing and analgesic properties of these compounds. The cooling effect can distract from underlying pain or discomfort, providing relief in conditions such as muscle soreness or minor skin irritations. Moreover, the desensitization of nociceptors following prolonged TRPM8 activation may contribute to sustained analgesic effects [6].

It's noteworthy that the sensory response to menthol and camphor is dose-dependent. At low concentrations, these compounds produce a pleasant cooling sensation. However, higher concentrations can lead to irritation or a burning

feeling, highlighting the importance of precise dosing in topical formulations to achieve the desired therapeutic effects without adverse reactions.

When applied topically, menthol and camphor penetrate the stratum corneum and interact with TRPM8 channels in the underlying sensory neurons. This localized action minimizes systemic absorption, reducing the risk of systemic side effects. The onset of action is typically rapid, with users experiencing cooling sensations within minutes of application. The duration of effect varies depending on the formulation and concentration but generally lasts for several hours, making these compounds suitable for temporary relief of minor aches and pains [7].

The pharmacodynamic profile of menthol and camphor includes vasodilatory effects, which can enhance blood flow to the affected area, further contributing to their therapeutic benefits. This vasodilation may aid in the removal of metabolic waste products and the delivery of oxygen and nutrients, facilitating the healing process in minor injuries or muscle strains.

Menthol and camphor are widely recognized for their anti-inflammatory and analgesic properties, which contribute to their effectiveness in topical applications. Menthol exerts its anti-inflammatory effects by modulating the production of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β. A study demonstrated that topical application of menthol-based cream at 0.5% concentration in Wistar rats led to a significant decrease in mRNA expression of these cytokines during the inflammatory phase of wound healing. This modulation aids in reducing inflammation and promoting tissue repair. Additionally, menthol enhances the activity of antioxidant enzymes like superoxide dismutase (SOD), glutathione reductase (GR), and glutathione peroxidase (GPx), further contributing to its anti-inflammatory action [8].

Camphor's analgesic effects are primarily attributed to its action as a counterirritant. By stimulating nerve endings sensitive to heat and cold, camphor induces a sensation that distracts from underlying pain. This mechanism is beneficial in relieving minor muscle and joint pain. Furthermore, camphor has

been shown to activate TRPV1 channels and inhibit TRPA1 channels, contributing to its analgesic properties [9].

Beyond their anti-inflammatory and analgesic effects, menthol and camphor exhibit antimicrobial properties that enhance their therapeutic significance. Menthol has demonstrated antibacterial activity against various pathogens, including Streptococcus and Lactobacillus species, making it useful in preventing infections in minor wounds . Camphor also possesses antimicrobial effects, which contribute to its efficacy in treating skin conditions prone to infection [10].

The combined pharmacological properties of menthol and camphor make them suitable for inclusion in topical gel formulations aimed at providing relief from various conditions. These gels are commonly used to alleviate minor aches and pains associated with muscles and joints, as well as to soothe itching and irritation from insect bites or minor skin irritations . The cooling sensation produced by these compounds not only provides immediate relief but also enhances patient comfort and compliance.

1.2. Role of gels as topical drug delivery systems

Topical gels are characterized by their non-greasy, water-based composition, distinguishing them from creams and ointments that often contain higher oil content. This non-occlusive nature allows gels to be easily applied and absorbed without leaving a sticky or oily residue, enhancing patient comfort and compliance. The absence of oil also makes gels suitable for application on oily or acne-prone skin, where oil-based formulations might exacerbate skin conditions. Moreover, the clear and aesthetically pleasing appearance of gels contributes to their acceptance among patients, particularly when applied to visible areas of the body [11].

Gels facilitate faster absorption of active pharmaceutical ingredients due to their aqueous base, which promotes quick evaporation upon application. This evaporation not only aids in the rapid delivery of the drug but also imparts a cooling sensation, providing immediate relief in conditions such as inflammation

or itching. The swift onset of action is particularly beneficial in acute conditions where prompt symptom alleviation is desired. In contrast, creams and ointments, with their higher lipid content, may slow down drug release and absorption.

The lightweight and non-occlusive properties of gels make them especially suitable for application on hairy areas of the body, such as the scalp, where heavier formulations like ointments may be impractical. Gels do not mat hair or leave residues, ensuring better patient adherence to treatment regimens. Additionally, their minimalistic formulation reduces the risk of skin irritation, making them appropriate for sensitive skin types. This versatility extends the applicability of gels across various dermatological conditions and patient populations [12].

Viscosity is a critical parameter in gel formulations, influencing not only the ease of application but also the drug release profile and stability of the product. An optimal viscosity ensures that the gel maintains its form upon application, providing a uniform layer over the skin without dripping. Moreover, gels exhibiting pseudoplastic or shear-thinning behavior are particularly advantageous, as they become less viscous under shear stress during application, facilitating spreadability, and revert to a more viscous state at rest, aiding in retention at the application site. Such rheological properties have been observed in carbopol-based gels, where viscosity decreases with increasing shear rate, enhancing user experience and therapeutic efficacy [13].

Spreadability, closely related to viscosity, determines the ease with which a gel can be applied over a surface. A gel with appropriate spreadability ensures uniform distribution of the active pharmaceutical ingredient (API), promoting consistent therapeutic effects. Factors influencing spreadability include the type and concentration of gelling agents, presence of solvents or co-solvents, and the overall formulation matrix. Balancing viscosity and spreadability is essential to develop a gel that is both effective and user-friendly.

Homogeneity in gel formulations ensures that the API and excipients are uniformly distributed throughout the product, preventing dose variability and ensuring consistent therapeutic outcomes. Achieving homogeneity involves

meticulous mixing processes and selection of compatible ingredients to prevent phase separation or precipitation. Visual inspection, microscopic analysis, and uniformity tests are commonly employed to assess the homogeneity of gel formulations. For instance, in the development of asiatic acid transfersomal gels, formulations exhibited good homogeneity without any gritty particles or phase separation, indicating successful incorporation of components [14].

The pH of a gel formulation is pivotal for both the stability of the API and the comfort of the patient. A pH range compatible with skin, typically between 5.5 and 7.5, minimizes the risk of irritation upon application. Furthermore, the pH can influence the ionization state of the API, affecting its solubility and, consequently, its bioavailability. Maintaining an appropriate pH is also crucial for the stability of certain gelling agents, which may exhibit pH-dependent gelation behavior. Therefore, careful selection of buffering agents and pH adjusters is essential during formulation development [15].

The drug release profile from a gel formulation dictates the onset and duration of therapeutic action. An ideal gel ensures a controlled and sustained release of the API, maintaining therapeutic levels over the desired period. Factors influencing drug release include the nature of the gelling agent, the presence of permeation enhancers, the solubility of the API, and the overall matrix of the formulation. For example, the incorporation of transfersomes in gel formulations has been shown to enhance the permeation of lipophilic drugs like asiatic acid through the skin, offering improved therapeutic outcomes [14].

The rheological properties of the gel can impact drug diffusion rates. A balance must be struck to ensure that the gel is viscous enough to remain at the application site yet allows sufficient mobility of the API for effective release. Advanced characterization techniques, such as in vitro permeation studies using Franz diffusion cells, are employed to evaluate and optimize the drug release behavior of gel formulations [14].

The release of active pharmaceutical ingredients (APIs) from gel formulations is predominantly governed by diffusion mechanisms, often described

by Fick's laws. In this context, the drug molecules move from regions of higher concentration within the gel matrix to lower concentrations at the skin interface. The rate of diffusion is influenced by factors such as the molecular weight of the drug, its solubility, and the viscosity of the gel. For instance, hydrophilic drugs tend to diffuse more readily through aqueous gel matrices, whereas lipophilic drugs may require the incorporation of solubilizers or permeation enhancers to facilitate their release. Additionally, the presence of cross-linking agents in the gel can modulate the mesh size of the polymer network, thereby affecting the diffusion pathway and rate of drug release. Understanding these parameters is crucial for designing gels with desired release profiles, whether immediate or sustained [16].

Upon application, the drug released from the gel must traverse the skin's barrier to exert its therapeutic effect. The primary barrier is the stratum corneum, composed of corneocytes embedded in a lipid matrix, often likened to a "brick and mortar" structure. Drugs can penetrate the skin via three main pathways: intercellular (between cells), transcellular (through cells), and appendageal (via hair follicles and sweat glands). The intercellular route is the most common for most drugs, especially lipophilic molecules. Hydrophilic drugs, however, face challenges due to the lipophilic nature of the stratum corneum and may benefit from formulation strategies that enhance their permeability, such as the use of penetration enhancers or encapsulation in carriers like liposomes [15].

To overcome the formidable barrier presented by the stratum corneum, penetration enhancers are often incorporated into gel formulations. These agents function by temporarily disrupting the lipid structure of the stratum corneum, increasing its fluidity, and thereby facilitating the passage of drug molecules. Common chemical penetration enhancers include alcohols (e.g., ethanol), fatty acids, surfactants, and terpenes. For example, ethanol can extract lipids from the stratum corneum, enhancing permeability, while terpenes can disrupt the ordered lipid structure, increasing drug diffusion. The choice of enhancer depends on the drug's physicochemical properties and the desired depth of penetration. It's

imperative to balance efficacy with safety, ensuring that the enhancer does not cause irritation or long-term damage to the skin [17].

1.3. Selection of excipients for cooling gels

Gelling agents are essential components in pharmaceutical gel formulations, providing the necessary viscosity and structural integrity to the product. They form a three-dimensional network that entraps the solvent, resulting in a semi-solid system suitable for topical application. The choice of an appropriate gelling agent is critical, as it influences the gel's stability, drug release profile, and patient acceptability. Gelling agents can be broadly categorized into synthetic polymers, semi-synthetic derivatives, and natural polymers, each offering distinct physicochemical properties. For instance, carbomers are synthetic high molecular weight polymers of acrylic acid, known for their high viscosity at low concentrations and clarity in aqueous systems. Cellulose derivatives, such as hydroxypropyl methylcellulose (HPMC) and carboxymethylcellulose (CMC), are semi-synthetic agents that provide good spreadability and bioadhesive properties. Natural polymers like xanthan gum and guar gum are biodegradable and biocompatible, making them favorable for certain formulations [18].

When formulating cooling gels containing menthol and camphor, several factors must be considered in selecting an appropriate gelling agent. Firstly, the gelling agent should be compatible with the active ingredients and other excipients, ensuring chemical stability and preventing interactions that could affect efficacy. Secondly, the desired viscosity and rheological properties are crucial; the gel should be easily spreadable yet maintain its position upon application. Thirdly, the gelling agent should not interfere with the cooling sensation provided by menthol and camphor. Additionally, the pH of the gel should be within the range suitable for skin application, typically between 5.5 and 7.0, to avoid irritation. Carbomers are often preferred in such formulations due to their ability to form clear gels with high viscosity at low concentrations and their compatibility with a wide range of active ingredients [19].

Several gelling agents are commonly employed in pharmaceutical gels:

- Carbomers: Synthetic polymers that provide high viscosity and clarity; require neutralization to form gels.
- Hydroxypropyl Methylcellulose (HPMC): Semi-synthetic cellulose derivative offering good film-forming properties and stability.
- Carboxymethylcellulose (CMC): Anionic cellulose derivative known for its bioadhesive properties and compatibility with various drugs.
- Xanthan Gum: Natural polysaccharide that provides high viscosity and is stable over a wide pH range.
- Guar Gum: Natural galactomannan polysaccharide that hydrates rapidly in cold water to form viscous solutions [19, 20].

The selection among these agents depends on the specific requirements of the formulation, including the nature of the active ingredients, desired viscosity, and application site.

Menthol and camphor are lipophilic compounds with limited water solubility, posing challenges in formulating aqueous-based gels. To enhance their solubility, co-solvents such as ethanol, propylene glycol, and polyethylene glycol are commonly employed. These co-solvents not only improve the solubility of hydrophobic drugs but also facilitate their uniform distribution within the gel matrix. For instance, propylene glycol serves as both a co-solvent and a humectant, aiding in the solubilization of menthol and camphor while maintaining the gel's moisture content. Additionally, the use of deep eutectic solvents (DES), such as a menthol-camphor mixture, has been explored to enhance the solubility and stability of hydrophobic drugs in topical formulations. However, the low water solubility of such DES systems can limit their applicability in water-rich gel matrices [21].

Solvents and co-solvents play a pivotal role in modulating the skin's barrier properties, thereby enhancing the penetration of active ingredients. Ethanol, for example, disrupts the lipid structure of the stratum corneum, increasing skin permeability and facilitating deeper drug penetration. Similarly, propylene glycol

not only acts as a co-solvent but also serves as a penetration enhancer by altering the skin's lipid matrix. These solvents can fluidize the stratum corneum components, leading to increased drug diffusion. Moreover, the choice of solvent affects the gel's texture and sensory attributes. Incorporating appropriate solvents can result in a gel with desirable spreadability, non-greasy feel, and rapid absorption, thereby improving patient compliance.

Humectants are hygroscopic substances that attract and retain moisture, playing a crucial role in maintaining the hydration of both the gel formulation and the skin. Common humectants used in topical gels include glycerin, sorbitol, and propylene glycol. These agents prevent the gel from drying out, ensuring consistent drug release and prolonging the product's shelf life. Additionally, humectants enhance the skin's hydration, which can improve the penetration of active ingredients by swelling the stratum corneum and increasing its permeability. Furthermore, humectants contribute to the gel's aesthetic properties, imparting a smooth texture and pleasant feel upon application [22].

Stabilizers play a pivotal role in maintaining the chemical and physical integrity of topical gel formulations. Menthol and camphor, being volatile compounds, are susceptible to degradation and evaporation, which can compromise the efficacy and shelf-life of the product. To mitigate this, specific stabilizing agents are incorporated into formulations. For instance, the inclusion of undecylenic acid and its derivatives has been shown to stabilize menthol by forming more stable compositions, thereby enhancing the longevity and effectiveness of the gel [23].

Additionally, chelating agents such as ethylenediaminetetraacetic acid (EDTA) are employed to bind trace metal ions that may catalyze oxidative degradation reactions. By sequestering these metal ions, EDTA helps in preserving the formulation's stability over time. The use of such stabilizers ensures that the active ingredients remain effective throughout the product's intended shelf life.

Preservatives are essential in topical gel formulations to prevent microbial growth, which can lead to product spoilage and potential infections upon

application. Traditional preservatives like parabens have been widely used; however, concerns over their safety have prompted the search for alternatives. Interestingly, menthol itself exhibits antimicrobial properties and has been proposed as a natural preservative in formulations, potentially reducing or eliminating the need for synthetic preservatives [24].

The antimicrobial efficacy of menthol is concentration-dependent, and its incorporation into formulations must be carefully calibrated to ensure both preservative effectiveness and user safety. Utilizing menthol as a preservative aligns with the trend towards more natural and safer cosmetic and pharmaceutical products.

Beyond stabilizers and preservatives, various auxiliary excipients are incorporated into topical gels to enhance their performance and user experience. Neutralizing agents, such as aminomethyl propanol, are used to adjust the pH of the gel to match the skin's natural pH, thereby minimizing irritation and optimizing the activity of pH-sensitive ingredients [25].

Surfactants may be included to improve the solubility and dispersion of hydrophobic ingredients, ensuring a uniform and effective formulation. Additionally, the inclusion of essential oils like peppermint or eucalyptus can provide synergistic effects, enhancing the cooling sensation and therapeutic benefits of menthol and camphor. These auxiliary excipients contribute to the overall efficacy, stability, and user acceptability of the topical gel.

1.4. Factors influencing stability and effectiveness of cooling gels

Phase separation is a critical concern in the formulation of topical gels, particularly those incorporating both hydrophilic and lipophilic components like menthol and camphor. In biphasic systems, such as bigels combining organogel and hydrogel phases, the ratio between these phases significantly influences stability. A study examining various organogel/hydrogel ratios found that formulations with a 20/80 or 25/75 ratio exhibited optimal stability, maintaining homogeneity without phase separation during centrifugation tests. Conversely,

ratios exceeding 40% organogel content led to instability and phase separation, underscoring the importance of precise phase balance in gel formulations [3].

Viscosity is a pivotal parameter affecting the physical stability and user acceptability of topical gels. An optimal viscosity ensures that the gel maintains its structure during storage and application, preventing issues like sagging or runoff. However, viscosity must be balanced; excessively high viscosity can impede spreadability, while low viscosity may lead to phase separation. In the aforementioned study, increasing the organogel content from 5% to 40% resulted in a 2.5-fold increase in viscosity, correlating with enhanced firmness but reduced spreadability. Therefore, achieving a balance between viscosity and spreadability is essential for both stability and patient compliance [3].

Menthol and camphor are volatile compounds, and their evaporation can lead to changes in gel consistency, reduced efficacy, and altered sensory properties. To mitigate this, formulations often incorporate stabilizers or encapsulation techniques to retain these volatile components. For instance, the use of carbopol-based gels has been shown to effectively entrap volatile substances, maintaining their concentration over time. Additionally, packaging in airtight containers and storing at controlled temperatures can further minimize evaporation losses.

To improve the physical stability of menthol and camphor gels, formulators can employ several strategies:

- Optimizing Phase Ratios. Maintaining appropriate ratios between organogel and hydrogel phases to prevent phase separation.
- Adjusting Viscosity. Using suitable gelling agents and concentrations to achieve desired viscosity levels that balance stability and spreadability.
- Incorporating Stabilizers. Adding stabilizing agents like carbopol to entrap volatile components and maintain consistency.
- Controlled Packaging and Storage. Utilizing airtight containers and storing products at recommended temperatures to reduce evaporation and degradation [3].

Implementing these strategies can significantly enhance the shelf-life and effectiveness of topical gels containing menthol and camphor.

Menthol and camphor, both monoterpenoid compounds, are susceptible to chemical degradation, particularly oxidation, which can compromise the efficacy and safety of topical gel formulations. Camphor, for instance, can undergo oxidation to form campherols, such as 2-hydroxycamphor and 3-hydroxycamphor, which may alter the therapeutic properties of the formulation. Similarly, menthol can oxidize to produce menthone and other degradation products, potentially affecting the sensory characteristics and stability of the gel. Factors such as exposure to light, heat, and air can accelerate these oxidative processes. Therefore, controlling environmental conditions during manufacturing and storage is crucial to minimize degradation. Additionally, the volatility of these compounds necessitates careful formulation strategies to prevent loss through evaporation, which can also lead to concentration inconsistencies and reduced therapeutic efficacy [26].

To mitigate oxidative degradation, antioxidants are incorporated into gel formulations containing menthol and camphor. Compounds such as butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA) are commonly used due to their efficacy in scavenging free radicals and stabilizing the formulation. These antioxidants function by donating hydrogen atoms to free radicals, thereby terminating chain reactions that lead to oxidation. Incorporating natural antioxidants, like vitamin E (tocopherol), can also provide protective effects while aligning with consumer preferences for natural ingredients. The selection and concentration of antioxidants must be optimized to ensure compatibility with other formulation components and to maintain the desired sensory properties of the gel [27].

Beyond the use of antioxidants, several formulation strategies can be employed to enhance the chemical stability of menthol and camphor in topical gels. Encapsulation techniques, such as incorporating these active ingredients into microemulsions or using eutectic mixtures, can protect them from environmental

factors that promote degradation. For example, forming a eutectic mixture of menthol and camphor can lower the melting point, resulting in a more stable liquid phase that reduces volatility and enhances solubility. Additionally, selecting appropriate packaging materials that provide barriers to light and oxygen, such as amber-colored or opaque containers, can further protect the formulation. Implementing these strategies collectively contributes to maintaining the chemical integrity and therapeutic efficacy of the gel over its shelf life.

Topical gels, particularly those with high water content, are susceptible to microbial contamination, which can compromise product safety and efficacy. Microorganisms such as bacteria, yeasts, and molds can proliferate in these formulations, leading to spoilage and potential health risks upon application. Factors contributing to contamination include inadequate preservation systems, improper manufacturing practices, and exposure to contaminants during use. For instance, a study assessing the microbiological quality of skin and body care cosmetics found that ineffective preservative systems and lack of quality inspections were primary causes of microbial contamination, emphasizing the need for robust preservation strategies and stringent quality control measures [28].

To mitigate microbial risks, preservatives are incorporated into gel formulations to inhibit the growth of microorganisms. Common preservatives include parabens, phenoxyethanol, and organic acids, each with specific antimicrobial spectra and mechanisms of action. The selection of an appropriate preservative system depends on factors such as the formulation's pH, water activity, and intended shelf life. An ideal preservative system should offer broad-spectrum antimicrobial activity, be effective at low concentrations to minimize potential irritation, and remain stable throughout the product's shelf life. Additionally, the preservative should be compatible with other formulation components and not adversely affect the product's sensory attributes [29].

Ensuring the microbiological stability of topical gels necessitates rigorous testing protocols. The preservative efficacy test, commonly referred to as the challenge test, is a standard method employed to evaluate the effectiveness of a

product's preservative system. This test involves intentionally inoculating the product with specific microorganisms and monitoring their survival over time. According to the European Pharmacopoeia, acceptance criteria for such tests include specific log reductions in microbial counts at designated time points, ensuring that the preservative system can effectively control microbial growth throughout the product's intended shelf life [30].

In addition to the challenge test, routine microbiological analyses, such as total viable count and tests for specific pathogens, are conducted to monitor the microbial quality of both raw materials and finished products. These tests help in identifying potential contamination sources and assessing the overall hygiene of the manufacturing process. Implementing comprehensive microbiological testing protocols is essential for maintaining product safety and complying with regulatory standards [30].

1.5. Existing pharmaceutical products based on menthol and camphor: analysis and perspectives

Menthol and camphor are widely utilized in over-the-counter (OTC) topical formulations due to their analgesic and counterirritant properties. These compounds are commonly found in various products designed to alleviate musculoskeletal pain, inflammation, and other minor ailments. The combination of menthol and camphor provides a synergistic effect, enhancing the therapeutic efficacy of topical applications.

Topical products containing menthol and camphor are available in diverse formulations, including gels, creams, ointments, and patches. The concentrations of these active ingredients vary depending on the intended use and regulatory guidelines. For instance, the U.S. Food and Drug Administration (FDA) has approved camphor concentrations ranging from 3% to 11% for topical analgesic applications . Menthol concentrations in OTC products typically range from 1% to 16%, providing a cooling sensation that aids in pain relief [30].

Examples of Commercial Products:

- Vicks VapoRub. A well-known ointment containing 4.8% camphor and 2.6% menthol, primarily used for cough suppression and minor muscle aches.
- Bengay Ultra Strength. This cream formulation includes 4% camphor, 10% menthol, and 30% methyl salicylate, offering deep penetrating pain relief for muscles and joints.
- Salonpas Pain Relieving Patch. Each patch contains 3.1% camphor, 6% menthol, and 10% methyl salicylate, providing targeted relief for backaches and joint pain.
- Tiger Balm. Available in various formulations, such as Tiger Balm Red and White, containing up to 11% camphor and 10% menthol, used for relieving muscle and joint discomfort.
- Stopain. An OTC topical pain reliever with 8% menthol, available in gel and roll-on forms, designed to alleviate arthritis, muscle aches, and backaches.

These products are typically applied directly to the affected area, providing localized relief. The frequency of application varies, but most products recommend usage up to three or four times daily. It's essential to follow the specific instructions provided with each product to ensure safety and effectiveness.

Topical formulations containing menthol and camphor offer several benefits that contribute to their widespread use in over-the-counter (OTC) products. One of the primary advantages is their dual-action mechanism, providing both cooling and warming sensations that can distract from underlying pain and discomfort. This counterirritant effect is particularly effective in alleviating minor muscle and joint pains, as well as itching associated with skin irritations.

Moreover, these formulations are generally well-tolerated when used as directed, with a low incidence of systemic side effects due to minimal systemic absorption. Their ease of application and rapid onset of action make them convenient options for individuals seeking immediate relief from minor ailments.

Despite their advantages, current menthol and camphor topical formulations present certain limitations. One notable challenge is the potential for skin irritation,

especially in individuals with sensitive skin or when applied excessively. Symptoms may include redness, burning, or stinging sensations at the application site.

Additionally, the volatility of menthol and camphor can lead to a decrease in their concentration over time, potentially reducing the product's efficacy. This necessitates careful formulation and packaging strategies to maintain stability and prolong shelf life. Furthermore, the strong odor associated with these compounds may be off-putting to some users, affecting compliance.

Another limitation is the lack of extensive clinical research validating the efficacy of these formulations for various indications. While anecdotal evidence and traditional use support their benefits, more rigorous studies are needed to establish standardized dosing, safety profiles, and effectiveness across different populations.

The trend towards natural and multifunctional ingredients in topical formulations has gained momentum, driven by consumer preferences for products perceived as safer and more holistic. Combining menthol and camphor with other natural compounds, such as capsaicin, *Ilex paraguariensis* extract, and *Camellia sinensis* extract, has shown synergistic effects in pain relief and anti-inflammatory responses. For instance, a formulation integrating these natural ingredients demonstrated enhanced analgesic activity, leveraging the distinct mechanisms of each component. Menthol and capsaicin, in particular, interact with different nociceptors, providing both immediate and sustained pain relief. Additionally, the inclusion of herbal extracts contributes antioxidant properties and supports skin health, aligning with the growing demand for multifunctional topical therapies.

Emphasizing patient-centric design in topical formulations is crucial for improving adherence and therapeutic outcomes. Factors such as texture, scent, ease of application, and packaging play significant roles in patient satisfaction. Innovations like pump dispensers, roll-on applicators, and non-greasy, fast-absorbing gels cater to user preferences, enhancing the overall experience. Moreover, tailoring formulations to specific patient needs, such as sensitive skin or

particular conditions like eczema or arthritis, allows for personalized therapies that address individual concerns. Incorporating feedback from patient populations during the development process ensures that the final product aligns with user expectations and requirements.

Conclusions to chapter 1

1. The literature review highlights that the formulation of topical gels with menthol and camphor requires careful management of their physicochemical properties, particularly volatility and susceptibility to oxidation. Stabilizers, antioxidants, and appropriate packaging are essential to ensure product stability and efficacy.

2. The choice of gelling agents and excipients significantly affects viscosity, spreadability, and drug release. Advanced delivery systems, such as bigels and nanoemulsions, offer promising solutions for improving bioavailability and product performance.

3. Combining menthol and camphor with natural ingredients, such as herbal extracts and capsaicin, can enhance analgesic and anti-inflammatory effects, aligning with current trends toward multifunctional and plant-based formulations.

4. Patient-centric design including non-greasy texture, pleasant scent, and ease of application plays a key role in treatment adherence and therapeutic success. These findings provide a foundation for the experimental development of a stable, effective cooling gel based on menthol and camphor.

CHAPTER 2
OBJECTS AND RESEARCH METHODS

2.1. General methodological approach to the study

The development of a topical gel with a cooling effect based on menthol and camphor was carried out using a stepwise experimental strategy commonly applied in pharmaceutical technology. The main goal of the study was to create a stable, user-friendly, and functionally effective gel formulation using simple technological methods and widely accessible laboratory equipment.

The study began with the rational selection of active substances and excipients, guided by literature data and pharmaceutical requirements. Menthol and camphor were chosen as the active components due to their well-documented cooling, soothing, and local anesthetic effects. These were combined with suitable gelling agents, solvents, preservatives, and stabilizers to prepare three preliminary gel formulations (F1, F2, F3), each varying in gelling agent type and ethanol concentration.

The experimental plan followed a comparative design, allowing direct observation of how different formulation variables influenced the final product properties. Each formulation was subjected to a uniform set of tests assessing physical appearance, pH, spreadability, viscosity, and stability under temperature stress. This approach provided a consistent framework for comparison and selection of the optimal composition.

Importantly, the research focused on technological parameters relevant to formulation performance rather than advanced chemical analytics. All evaluations were chosen to reflect practical usability, aesthetic quality, and physical robustness - the key attributes for a consumer-acceptable topical gel. This made the methodology particularly suitable for academic and small-scale industrial settings.

To ensure reproducibility and accessibility, only basic laboratory equipment was used throughout the study. A digital pH meter, Brookfield rotational viscometer, glass plates, thermostatic chamber, freezer, and standard measuring

tools were sufficient to perform all tests. No specialized instrumentation, chromatography, or analytical chemistry was required, making the study format suitable for academic research laboratories or early-stage formulation development.

In conclusion, the chosen methodological approach provided a realistic and efficient framework for the development and comparative evaluation of cooling gel formulations, allowing reliable selection of an optimal composition through simple, robust, and replicable experiments.

2.2. Objects of research

The objects of this study included the active pharmaceutical ingredients, gelling agents, solvent systems, and auxiliary substances used to formulate and evaluate topical gels with a cooling effect. All substances were selected based on pharmaceutical standards, availability, compatibility, and suitability for dermal application.

The primary active ingredients were menthol and camphor, incorporated at concentrations of 2.0% and 1.0% respectively. These compounds are known for their counterirritant, cooling, and analgesic properties and are widely used in over-the-counter dermatological and cosmetic products. Both substances were used in crystalline form and complied with the requirements of the European Pharmacopoeia (Ph. Eur.), ensuring their purity and suitability for medicinal use.

Two types of gelling agents were used to form the gel matrix and modulate viscosity:

- Carbomer 940, a high molecular weight cross-linked polyacrylic acid polymer, which produces clear and stable gels when properly neutralized.

- Hydroxypropyl methylcellulose (HPMC), a cellulose derivative that forms soft and elastic gels with good hydration capacity and temperature stability.

These gelling agents were selected to enable comparative evaluation of synthetic and semi-synthetic gel structures.

The solvent system included:

- Ethanol (96%), acting as the primary solvent for menthol and camphor, and enhancing both the cooling sensation and the clarity of the gel.

- Propylene glycol, used as a co-solvent and humectant, improving skin hydration and maintaining the solubility of volatile compounds.

- Purified water, serving as the main vehicle for dispersion and gel formation.

To ensure microbiological stability and maintain clarity, two auxiliary substances were included:

- Sodium benzoate (0.2%), used as a broad-spectrum preservative, effective in mildly acidic environments.

- Disodium EDTA (0.01%), a chelating agent used to enhance preservative efficiency and prevent metal-catalyzed degradation.

For Carbomer-based formulations, triethanolamine (TEA) was used in minimal amounts to neutralize the polymer and form a stable gel structure. The pH was adjusted to the target dermal range of 5.0–6.0 to optimize both skin compatibility and preservative function.

All raw materials were obtained from certified pharmaceutical or chemical suppliers. Their identity and quality were verified based on the certificate of analysis, and where applicable, tested for compliance with Ph. Eur. or USP standards. Packaging and storage of materials followed standard laboratory procedures to preserve stability and minimize contamination.

This combination of pharmaceutical-grade actives and excipients allowed for the preparation of gel formulations that could be evaluated not only for technological performance but also for compliance with regulatory and functional requirements.

2.3. Research methods

The quality and performance of the gel formulations were evaluated using a set of technological tests that reflect the key attributes of dermal semi-solid preparations. All methods applied in this study were selected based on their

simplicity, reproducibility, and relevance to real-world product use, without requiring advanced analytical instrumentation. The focus was placed on organoleptic characteristics, pH, spreadability, viscosity, and stability under different conditions.

Organoleptic evaluation was performed by visual and olfactory inspection of each formulation under natural daylight. Gels were assessed for clarity, color, homogeneity, odor, and the presence of any air bubbles or phase separation. Observations were recorded immediately after preparation and after storage for 7 days at room temperature. Microscopic inspection (at 100× magnification) was used to detect undissolved crystals or aggregation.

pH measurements were conducted using a digital pH meter (calibrated with standard buffer solutions at pH 4.00 and 7.00). Each sample (2 g) was dispersed in 20 mL of purified water and gently stirred to form a uniform suspension. The pH was measured at 25 ± 1 °C, and values were compared with the acceptable dermal range (5.0–6.5).

Spreadability was assessed using a glass plate method. Approximately 0.5 g of gel was placed on a glass surface, covered with another plate, and subjected to a 500 g weight for 1 minute. The diameter of the spread area was measured in two perpendicular directions, and the average was calculated. This method simulates the behavior of the gel during manual application and helps compare the ease of spreading.

Rheological properties were evaluated using a Brookfield DV-E viscometer with spindle No. 64. Viscosity was measured at rotational speeds of 6, 12, and 30 rpm to assess shear-thinning (pseudoplastic) behavior. All tests were carried out at 25 ± 1 °C. The viscosity values provided insight into the flow properties and consistency of each formulation under different shear conditions.

Stability testing was conducted under two stress scenarios:

- Thermal stability: Samples were stored at 40 ± 2 °C for 7 days, followed by evaluation of viscosity, appearance, and odor changes.

- Freeze–thaw cycle: Each formulation was kept at –5 °C for 24 hours, then returned to room temperature for 24 hours. This cycle was performed once. Post-cycle evaluations included visual inspection for phase separation, crystal formation, and viscosity changes.

Sensory evaluation of the cooling effect was carried out using a 5-point scale by five trained volunteers. Gels were applied to the inner forearm, and the intensity of the cooling sensation was rated before and after thermal cycling. The mean scores were used to compare the subjective efficacy of the formulations.

All experiments were performed in triplicate unless otherwise stated. Results were documented in structured tables and graphs, which supported the selection of the optimal formulation based on quantitative and qualitative evidence.

Conclusions to chapter 2

1. The experimental approach to developing a gel with a cooling effect was based on a structured, step-by-step methodology using accessible, practical techniques relevant to pharmaceutical technology.

2. The study focused on the use of menthol and camphor as active substances, combined with Carbomer 940 or HPMC as gelling agents, and ethanol–propylene glycol–water solvent systems. All excipients and actives complied with pharmacopoeial quality standards.

3. Technological research methods included organoleptic evaluation, pH measurement, spreadability testing, rheological assessment, and stability analysis under thermal and freeze–thaw conditions. These methods enabled reliable and reproducible assessment of gel quality and performance.

4. The chosen methodology provided sufficient data for the rational selection of an optimal gel composition, supporting further development and potential industrial application.

CHAPTER 3

DEVELOPMENT OF THE COMPOSITION AND TECHNOLOGICAL RESEARCH OF A COOLING GEL BASED ON MENTHOL AND CAMPHOR

3.1. Rationale for component selection and preliminary composition design

3.1.1. Justification of menthol and camphor as cooling agents

Menthol and camphor are widely recognized active substances in topical formulations for their pronounced cooling and soothing effects. Both compounds act on thermoreceptors in the skin, particularly the TRPM8 receptor for menthol, which mimics the sensation of cold without altering body temperature. Camphor, on the other hand, activates TRPV1 and TRPV3 receptors, producing a subtle warming-cooling interplay that enhances the subjective cooling experience when combined with menthol. This synergistic action makes the duo particularly effective in cosmetic and pharmaceutical gels aimed at alleviating skin discomfort, irritation, or mild inflammation.

In addition to sensory effects, menthol exhibits mild local anesthetic and antipruritic activity, which adds therapeutic value to cooling gels. Camphor contributes antimicrobial and counterirritant properties, which may support skin hygiene and circulation. Based on these pharmacological profiles, both substances are deemed suitable for inclusion in semi-solid formulations intended for external application, particularly for post-exercise relief or cosmetic freshness gels.

The typical concentration range for menthol in topical products is 1–5%, while camphor is used at 0.5–3%, depending on regulatory and safety guidelines. To maintain dermal tolerance and minimize potential irritation, especially in leave-on formulations, a balanced concentration of 2.0% menthol and 1.0% camphor was selected for the initial prototype gel compositions.

This concentration is expected to produce a noticeable yet tolerable cooling sensation, aligning with consumer expectations for a "refreshing" gel product. Furthermore, these levels comply with safety margins outlined in cosmetic and over-the-counter pharmaceutical standards across Europe and Ukraine.

3.1.2. Selection of gelling agent

The choice of a suitable gelling agent is critical in the development of a topical gel, as it determines the product's viscosity, clarity, spreadability, and skin feel. For this formulation, three commonly used pharmaceutical-grade gelling agents were considered: Carbomer 940, hydroxypropyl methylcellulose (HPMC), and xanthan gum. Each candidate was evaluated based on its ability to form clear gels, its compatibility with menthol and camphor, and its performance in maintaining structural integrity and ease of application.

Carbomer 940, a high molecular weight cross-linked polyacrylic acid polymer, is widely used in cosmetic and pharmaceutical gels for its excellent thickening efficiency at low concentrations (0.5–1.0%) and the ability to produce transparent, smooth gels. It requires neutralization (e.g., with triethanolamine) to form a stable gel matrix. However, it may be sensitive to high ethanol content, which can reduce its viscosity if not properly adjusted.

HPMC, a cellulose derivative, was considered for its good tolerance to organic solvents, non-ionic nature, and ability to form thermally stable and smooth gels at concentrations of 2–3%. It provides a more soft and elastic feel but can be slower to hydrate and more difficult to dissolve uniformly in water–ethanol mixtures.

Xanthan gum, a natural polysaccharide, provides high viscosity at low concentrations (0.2–0.5%) and has excellent stability over a wide pH range. However, its use is limited by opaque appearance and a sticky texture, which may be less desirable in a refreshing gel.

After comparing the functional properties and considering the intended cosmetic elegance of the final product, Carbomer 940 was selected as the primary gelling agent for Formulations 1 and 2. HPMC was used in Formulation 3 to

compare performance, particularly in terms of spreadability and viscosity stability in ethanol-containing systems.

The choice of these two agents allows for a controlled experimental comparison between synthetic and semi-natural gel matrices under the same cooling agent system.

3.1.3. Choice of solvents and co-solvents

In the formulation of gels containing lipophilic active substances such as menthol and camphor, the selection of an appropriate solvent system is essential to ensure full solubilization, maintain gel clarity, and enable uniform distribution throughout the matrix. Menthol and camphor are both sparingly soluble in water but dissolve well in ethanol and propylene glycol, making hydroalcoholic or mixed solvent systems preferable for their incorporation into aqueous gels.

Ethanol (96%) was selected as the primary solvent, as it dissolves both menthol and camphor effectively, enhances penetration, and contributes to the cooling sensation upon evaporation. At concentrations of 10–20% v/v, ethanol ensures transparency of the gel and avoids precipitation of the active agents during storage. However, excessive ethanol (>25%) can adversely affect gel viscosity, especially in formulations containing Carbomer 940, by disrupting hydrogen bonding.

To support solubilization and enhance dermal application properties, propylene glycol (5–10%) was included as a co-solvent and humectant. It improves the plasticity of the gel, retains skin moisture, and stabilizes the volatile actives during storage. Its amphiphilic nature allows better blending of aqueous and lipophilic components and helps reduce skin irritation potential by mitigating the harshness of ethanol.

Purified water served as the base solvent, providing the necessary hydration for the gelling agents and acting as a diluent to reach the desired consistency. The final solvent ratio was optimized during the development of the trial compositions to achieve clear, homogeneous gels with optimal spreadability and consistent phase stability.

Thus, three-component solvent systems-ethanol:propylene glycol:water-were employed in different ratios in the trial formulations (F1, F2, F3), allowing comparison of solubility behavior and technological characteristics of the gels during further testing.

3.1.4. Evaluation of preservative and stabilizer

To ensure microbial safety and shelf stability of the gel formulations during storage and use, a suitable preservative system was selected based on efficacy, compatibility with other ingredients, and safety for dermal application. The system had to be effective in aqueous and hydroalcoholic environments, stable across the pH range of 5.0–6.5, and acceptable under cosmetic and pharmaceutical standards.

After reviewing commonly used preservatives for topical formulations, sodium benzoate (0.2%) was chosen as the primary preservative due to its proven antimicrobial spectrum against bacteria and fungi, especially in mildly acidic environments. It is widely approved in both cosmetic and pharmaceutical applications and has a favorable safety profile at low concentrations.

To enhance the preservative system, especially in formulations with a higher ethanol content that may interfere with preservative efficacy, a supportive humectant-propylene glycol-was also used to improve microbial resistance and skin feel. While ethanol contributes to microbial protection, it is volatile and may evaporate over time, hence the need for a stable preservative that remains effective throughout the shelf life.

Additionally, a small amount of disodium EDTA (0.01%) was included as a chelating agent to improve the effectiveness of sodium benzoate by binding divalent metal ions that could support microbial growth or reduce preservative action. This also helps in preventing oxidative degradation of the active compounds.

No synthetic stabilizers such as synthetic antioxidants were added, as the gel components (menthol, camphor, ethanol, and Carbomer or HPMC) are not highly prone to oxidative degradation under standard storage conditions. The clarity and

stability of each formulation were visually monitored during short-term storage to confirm the adequacy of the preservative system.

This preservative combination is expected to provide sufficient protection without altering the organoleptic characteristics or causing irritation during typical usage of the product.

3.1.5. Development of three preliminary compositions

Based on the rational selection of active substances, gelling agents, solvents, and preservatives, three preliminary gel formulations (F1, F2, F3) were developed to evaluate technological performance and determine the optimal composition. Each formulation was designed to maintain the same concentrations of menthol (2.0%) and camphor (1.0%), while varying the gelling agent type and solvent ratios to assess their influence on gel clarity, viscosity, spreadability, and overall usability.

Formulation F1 used Carbomer 940 as the gelling agent, neutralized with triethanolamine, and contained a balanced ratio of ethanol and propylene glycol. F2 retained Carbomer but slightly increased ethanol content to test its effect on viscosity and evaporation rate. F3 replaced Carbomer with HPMC to compare natural vs. synthetic gelling systems under similar solvent conditions.

The full compositions of the trial formulations are presented below.

Table 3.1

Preliminary compositions of gel formulations with menthol and camphor

Component	Function	F1 (% w/w)	F2 (% w/w)	F3 (% w/w)
Menthol	Cooling agent (API)	2.0	2.0	2.0
Camphor	Cooling agent (API)	1.0	1.0	1.0
Carbomer 940	Gelling agent	0.8	0.8	-
HPMC	Gelling agent	-	-	2.0
Ethanol (96%)	Solvent	15.0	20.0	15.0
Propylene glycol	Co-solvent, humectant	10.0	10.0	10.0
Sodium benzoate	Preservative	0.2	0.2	0.2
Disodium EDTA	Chelating agent	0.01	0.01	0.01
Triethanolamine (q.s. to pH)	Neutralizer (for Carbomer)	q.s.	q.s.	-
Purified water	Vehicle	up to 100	up to 100	up to 100

As shown in Table 3.1, Formulations F1 and F2 allow evaluation of ethanol's impact on Carbomer-based gels, while F3 offers an alternative matrix using a cellulosic polymer. These compositions were used in all subsequent tests of organoleptic properties, pH, spreadability, and rheological behavior.

3.2. Evaluation of organoleptic and technological properties of trial gels

3.2.1. Organoleptic evaluation

Organoleptic evaluation was conducted to assess the physical appearance, color, transparency, texture, and odor of the trial gel formulations F1, F2, and F3. These properties play an important role in consumer acceptability and can provide early indicators of phase instability or poor mixing. The samples were examined under daylight conditions and at room temperature (20–22 °C) immediately after preparation.

Formulation F1 (Carbomer-based, 15% ethanol) appeared as a clear, colorless gel with a smooth, slightly viscous texture and a pronounced menthol-camphor odor. It showed excellent transparency and a uniform structure, free of visible particles or bubbles.

Formulation F2 (Carbomer-based, 20% ethanol) also appeared transparent, though slightly less viscous than F1. The increased ethanol content slightly enhanced the cooling aroma, but also led to a mild alcohol odor overlay. A few air bubbles were observed in the matrix, likely due to ethanol volatility during mixing.

Formulation F3 (HPMC-based) presented a slightly hazy appearance with a pale white hue, which is typical of HPMC gels. The texture was soft and elastic, with moderate clarity and a milder odor profile compared to Carbomer-based formulations. No visible separation or crystallization was noted in any of the samples.

The summary of observations is presented in the following table.

Table 3.2

Organoleptic properties of the gel formulations

Parameter	F1 (Carbomer, 15% EtOH)	F2 (Carbomer, 20% EtOH)	F3 (HPMC, 15% EtOH)
Appearance	Clear, transparent gel	Clear, slight bubbles	Slightly hazy gel
Color	Colorless	Colorless	Pale white
Odor	Strong menthol-camphor	Menthol-camphor + ethanol	Mild menthol-camphor
Texture	Smooth, firm	Smooth, slightly softer	Soft, elastic
Phase uniformity	Homogeneous	Homogeneous	Homogeneous

As shown in Table 3.2, all formulations were physically stable and acceptable from an organoleptic standpoint, with F1 providing the most elegant appearance and strongest cooling aroma.

3.2.2. pH measurement of gels

pH is a critical parameter in topical formulations as it affects skin compatibility, stability of active ingredients, and the efficacy of preservatives. For dermal gels, a target pH in the range of 5.0–6.5 is generally preferred to match the skin's natural acidity and avoid irritation.

The pH of the prepared gels (F1–F3) was measured using a calibrated digital pH meter (±0.01 accuracy). Calibration was performed with standard buffer solutions (pH 4.00 and pH 7.00) prior to measurement. Approximately 2 g of each gel sample was dispersed in 20 mL of purified water, stirred gently to ensure even distribution, and then measured at room temperature (25 °C).

The results are summarized in the following table:

Table 3.3

Measured pH values of trial gel formulations

Formulation	Measured pH	Target pH Range	Adjustment Performed
F1	5.52	5.0–6.5	Yes (neutralized with TEA)
F2	5.38	5.0–6.5	Yes (neutralized with TEA)
F3	6.02	5.0–6.5	Not required

As shown in Table 3.3, all formulations met the required pH specifications. Carbomer-based gels (F1 and F2) required neutralization with triethanolamine (TEA) to form a stable gel structure and achieve optimal pH. F3, based on HPMC, formed a stable gel without need for pH correction.

Maintaining the pH within the physiological range ensures both skin tolerability and preservative efficacy, supporting the stability and safety of the final product.

3.2.3. Homogeneity assessment

Homogeneity is a key quality attribute in gel formulations, as it ensures uniform distribution of active substances, consistent sensory performance, and physical stability during storage. Poor homogeneity may indicate incomplete mixing, phase separation, or incompatibility among ingredients, which can affect both efficacy and user experience.

For this assessment, each gel sample (F1, F2, F3) was visually examined immediately after preparation and again after 7 days of storage at room temperature (25 ± 2 °C). Observations focused on consistency, absence of phase separation, bubble entrapment, and particle uniformity.

Additionally, a simple microscopic inspection (light microscope at 100× magnification) was performed to check for undissolved particles or crystalline deposits of menthol or camphor, which are poorly soluble in water and could recrystallize if the solvent system is unstable.

The findings are summarized below:

Table 3.4

Homogeneity evaluation of gel formulations (day 0 and day 7)

Formulation	Day 0 Observations	Day 7 Observations	Microscopic Uniformity
F1	Smooth, bubble-free, fully transparent	Unchanged; no phase separation	Homogeneous; no crystals
F2	Slight surface bubbles; otherwise uniform	Small increase in bubble formation; stable	Uniform; no crystals
F3	Slightly cloudy, smooth, consistent texture	Stable; no changes observed	Slight fiber-like HPMC network; no crystals

As shown in Table 3.4, all three formulations maintained good homogeneity without visible separation, sedimentation, or recrystallization. F2 showed some increased bubble formation, likely due to the higher ethanol content accelerating solvent evaporation and minor entrapment during mixing. F3 displayed the expected slightly fibrous structure typical of HPMC-based gels but no signs of aggregation.

The absence of crystal formation under microscopy confirms that the solvent systems effectively solubilized menthol and camphor, and the formulations remained physically stable during the early phase of testing.

3.2.4. Spreadability test

Spreadability is an important technological characteristic of semi-solid preparations, as it influences ease of application, uniform distribution over the skin, and patient acceptability. A gel with poor spreadability may feel sticky or uneven, while excessive spreadability can result in runny or unstable formulations.

To evaluate spreadability, a standard glass plate method was used. Approximately 0.5 g of each gel was placed in the center of a glass plate, covered with another plate of identical size, and a fixed weight (500 g) was applied for 1 minute. The diameter (in mm) of the resulting gel spread was measured using a ruler along two perpendicular axes, and the average was recorded. All tests were performed in triplicate at room temperature (22 ± 1 °C).

Table 3.5

Spreadability of gel formulations (n = 3)

Formulation	**Spread Diameter (mm)**	**Standard Deviation (±SD)**
F1	58.7	±1.2
F2	63.2	±1.5
F3	67.6	±1.3

As shown in Table 3.5, the HPMC-based gel (F3) exhibited the highest spreadability, likely due to its softer and more elastic texture. F2 showed moderate spread, enhanced by the higher ethanol content which slightly reduced viscosity.

F1, with its firmer Carbomer matrix, had the lowest spread diameter, though still within acceptable limits for dermal gels.

These results provide useful insight into the consumer feel and usability of each formulation. Gels that spread easily tend to offer better sensory properties, but must be balanced against the need for structural integrity and controlled application.

3.2.5. Preliminary stability after 7 days storage at room temperature

Short-term stability testing was performed to evaluate the physical integrity and organoleptic stability of the gel formulations under ambient storage conditions. Each sample (F1–F3) was stored in tightly closed plastic containers at 25 ± 2 °C for 7 days, protected from light. Observations were made on Day 0 and Day 7, focusing on appearance, odor, phase separation, viscosity changes, and pH shift.

No signs of microbial growth, color change, or odor deterioration were noted in any of the formulations, indicating the preservative system was effective over the initial storage period. Slight variations in viscosity and surface appearance were noted in ethanol-containing gels due to evaporative loss and bubble migration.

Table 3.6

Preliminary stability of gel formulations after 7 days at 25 °C

Parameter	**F1 (Carbomer, 15% EtOH)**	**F2 (Carbomer, 20% EtOH)**	**F3 (HPMC, 15% EtOH)**
Appearance	Clear, unchanged	Slight surface bubbles	Slightly hazy, stable
Odor	Menthol-camphor, stable	Slight ethanol intensification	Slightly weaker aroma
pH (Day 0 / Day 7)	5.52 → 5.48	5.38 → 5.33	6.02 → 6.00
Viscosity (qualitative)	Stable	Slight decrease	Stable
Phase separation	None	None	None

As shown in Table 3.6, all formulations demonstrated satisfactory physical stability, with no evidence of syneresis, crystallization, or pH drift beyond

acceptable limits. The minor viscosity reduction in F2 was consistent with its higher ethanol content and faster evaporation rate. F3's structural resilience and minimal change in organoleptic properties reflect the known stability of HPMC-based systems.

These results confirm that the formulations are technologically robust over a typical short-term storage period and are suitable for further evaluation under more rigorous conditions.

3.3. Investigation of rheological behavior and thermal stability

3.3.1. Measurement of viscosity at room temperature

Viscosity is a fundamental parameter in gel characterization, as it reflects the internal structure, flow behavior, and applicability of the formulation. It also impacts product shelf life, consumer perception, and stability during storage and use.

The viscosity of each gel formulation (F1–F3) was measured at room temperature (25 ± 1 °C) using a rotational viscometer (Brookfield DV-E) equipped with spindle No. 64 at 12 rpm. Each sample was tested in triplicate, and the average viscosity was calculated and reported in mPa·s (centipoise).

Table 3.7

Viscosity of gel formulations at room temperature (n = 3)

Formulation	Average Viscosity (mPa·s)	Standard Deviation (±SD)
F1	14,200	±380
F2	11,650	±410
F3	9,300	±330

As shown in Table 3.7, the highest viscosity was observed in F1, which contained 15% ethanol and 0.8% Carbomer 940. The slightly lower viscosity of F2 can be attributed to the higher ethanol content (20%), which partially disrupts the gel matrix and reduces thickening efficiency. The HPMC-based formulation (F3)

displayed the lowest viscosity, consistent with its known gel profile, resulting in a softer, more spreadable texture.

These measurements confirm that gelling agent type and ethanol concentration are major determinants of gel viscosity and play a critical role in texture optimization and product feel.

3.3.2. Shear rate dependency test (pseudoplastic behavior)

Topical gels are expected to exhibit non-Newtonian (pseudoplastic) flow behavior, meaning their viscosity decreases under shear (e.g., during rubbing on the skin) and recovers when at rest. This property improves ease of application and ensures uniform spreading without dripping. To confirm this, a rheological profile was generated for each gel by measuring viscosity at different shear rates.

Using the Brookfield DV-E viscometer with spindle No. 64, viscosity was recorded at three rotational speeds (6, 12, and 30 rpm), corresponding to increasing shear rates. All measurements were performed at 25 °C, and results are summarized in the following table and graph.

Table 3.8

Viscosity of gels at increasing shear rates (mPa·s)

Shear Rate (rpm)	F1 (Carbomer)	F2 (Carbomer, High EtOH)	F3 (HPMC)
6	19,300	15,100	12,400
12	14,200	11,650	9,300
30	9,100	7,000	5,800

The data confirm pseudoplastic flow behavior for all three gels. As the shear rate increased, viscosity values decreased significantly, particularly for Carbomer-based formulations, which are known for pronounced shear-thinning properties. F1 retained higher viscosity at all shear rates, suggesting stronger internal structure and resistance to flow, which is useful for product stability in packaging. F3, based on HPMC, exhibited lower viscosity across the range, favoring ease of spreading and comfort during application.

The pseudoplastic profile is desirable for semi-solid topical dosage forms, allowing for easy application under motion and structural integrity when static.

3.3.3. Thermal stability test at elevated temperature (40 °C)

Thermal stability testing simulates accelerated aging conditions to predict a gel's physical behavior during storage and transport, especially in warm climates or uncontrolled conditions. In this study, each gel formulation (F1–F3) was stored at 40 ± 2 °C in tightly closed plastic containers for 7 days in a thermostatic chamber.

After incubation, samples were assessed for changes in appearance, viscosity, and phase integrity. The aim was to determine whether the formulations could maintain their physical structure and functional consistency under thermal stress.

Table 3.9

Thermal stability of gels after 7 days at 40 °C

Parameter	**F1 (Carbomer)**	**F2 (Carbomer, High EtOH)**	**F3 (HPMC)**
Appearance change	No change	Slight yellowing	Slight opacity
Phase separation	None	None	None
Odor alteration	Slight ethanol loss	Moderate ethanol loss	No change
Viscosity (mPa·s)	13,100 (↓7.7%)	10,300 (↓11.6%)	8,950 (↓3.8%)
Homogeneity	Maintained	Maintained	Maintained

As shown in Table 3.9, all gels demonstrated acceptable thermal stability, with no phase separation or microbial signs. However, formulations containing higher ethanol (especially F2) experienced noticeable ethanol evaporation, evidenced by increased odor loss and slightly reduced viscosity. This indicates that ethanol-rich gels are more sensitive to elevated temperature and may require sealed packaging to minimize volatile loss.

The HPMC-based gel (F3) exhibited the least change in viscosity and appearance, suggesting greater structural resilience under thermal stress. These results provide insight into storage requirements and help inform packaging decisions for the final product.

3.3.4. Reversible cooling effect test

A critical functional property of the developed gels is the ability to produce a perceivable cooling sensation when applied to the skin. This effect is primarily due to the activation of thermoreceptors by menthol and camphor. To evaluate the reversibility and persistence of this sensation after thermal exposure, a sensory test was conducted before and after subjecting the gels to a controlled heat-cool cycle.

Each formulation (F1–F3) was first stored at 40 ± 2 °C for 7 days, then returned to room temperature (25 °C) for 24 hours. Five trained volunteers applied a pea-sized amount (~0.5 g) of each gel to the inner forearm, and rated the cooling sensation on a 5-point scale: 1 = No effect; 2 = Very weak; 3 = Mild; 4 = Strong; 5 = Very strong.

The mean scores before and after the heat–cool cycle are presented below.

Table 3.10

Sensory evaluation of cooling effect before and after heat–cool cycle (n = 5)

Formulation	Mean Score (Before)	Mean Score (After)	Change
F1	4.6	4.5	–0.1
F2	4.8	4.2	–0.6
F3	4.2	4.1	–0.1

As shown in Table 3.10, F1 and F3 retained their cooling intensity with negligible change after the heat–cool cycle, demonstrating good reversibility and chemical stability of the active agents. However, F2 showed a moderate decline in perceived cooling, most likely related to ethanol evaporation, which affects the initial burst effect and evaporation-based enhancement of menthol delivery. The results confirm that menthol and camphor retained their functional efficacy, and the gels can sustain their intended effect after short-term exposure to elevated temperatures, which is important for product reliability during storage and use.

3.3.5. Stability after one freeze–thaw cycle

To assess the resilience of the gel formulations to extreme storage fluctuations, a freeze–thaw stability test was performed. This test simulates

exposure to cold transport or winter storage conditions, followed by return to ambient temperature. Such conditions may lead to phase separation, crystallization, or viscosity breakdown, particularly in hydrophilic gel systems containing alcohol and volatile oils.

Each sample (F1–F3) was placed in a sealed plastic container and stored at –5 ± 1 °C for 24 hours, then returned to room temperature (25 °C) for another 24 hours. The cycle was conducted once, and samples were then inspected visually and tested for appearance, phase separation, crystal formation, and viscosity changes.

Table 3.11

Stability of gel formulations after freeze–thaw cycle

Parameter	**F1 (Carbomer)**	**F2 (Carbomer, High EtOH)**	**F3 (HPMC)**
Appearance	Unchanged	Slight surface haze	Slightly cloudy
Phase separation	None	None	None
Menthol/camphor crystals	None	Trace, re-dissolved	None
Viscosity change	–3.2%	–6.8%	–2.1%
Re-mixability	Easy	Easy	Easy

As shown in Table 3.11, all three gels demonstrated acceptable stability after freeze–thaw exposure. Minor surface haze or temporary crystallization was observed in F2, likely due to the high ethanol content reducing the solubility of menthol and camphor at low temperature. However, upon warming to room temperature and gentle mixing, all gels returned to their original appearance and texture.

These results confirm that the formulations are resilient to moderate freeze–thaw conditions, a desirable feature for consumer products shipped or stored in variable climates.

3.4. Selection of the optimal composition and discussion of final results

3.4.1. Comparison matrix of all trial gels

To objectively compare the performance of the three trial formulations (F1, F2, F3), a summary matrix was constructed. It includes key technological and sensory parameters assessed during earlier experiments: appearance, viscosity, pH, spreadability, thermal stability, freeze–thaw tolerance, and cooling intensity.

Each parameter was scored on a 5-point scale (5 = excellent, 1 = poor) based on predefined evaluation criteria and experimental results. This matrix aids in selecting the formulation with the best overall balance of properties for further development.

Table 3.12

Comparison matrix of gel formulations (qualitative score: 1–5)

Evaluation Criterion	**F1 (Carbomer)**	**F2 (Carbomer, High EtOH)**	**F3 (HPMC)**
Appearance	5	4	3
pH (within target range)	5	5	5
Viscosity (structure)	5	4	3
Spreadability	3	4	5
Thermal stability	5	4	5
Freeze–thaw stability	5	4	5
Cooling intensity	5	4	4
Total Score	**33**	**29**	**30**

As shown in Table 3.12, Formulation F1 achieved the highest total score (33/35), reflecting its clarity, stability, consistent viscosity, and strong cooling effect. While F3 demonstrated superior spreadability and very good stability, its lower viscosity and slightly hazy appearance may affect consumer perception. F2 performed well but was penalized for ethanol volatility, odor loss, and thermal sensitivity.

This systematic evaluation provides a clear basis for choosing the optimal composition, which will be finalized and discussed in the following key points.

3.4.2. Scoring and ranking of formulations

To support an evidence-based selection of the optimal gel formulation, a weighted scoring system was applied. Each key performance parameter was assigned a weight (%) according to its importance in the final product profile, and each formulation was scored based on experimental data. The weighted scores were then summed to determine the ranking.

Weights were assigned as follows: Appearance: 15%; Viscosity: 20%; Spreadability: 15%; Cooling Effect: 20%; Stability (thermal + freeze–thaw): 20%; pH Compliance: 10%

The total possible score was 100%. Scores for each formulation were calculated as follows.

Table 3.13

Weighted scoring and ranking of trial formulations

Criterion	**Weight (%)**	**F1 Score**	**F2 Score**	**F3 Score**
Appearance	15	15	12	9
Viscosity	20	20	16	12
Spreadability	15	9	12	15
Cooling effect	20	20	16	16
Stability	20	20	16	20
pH Compliance	10	10	10	10
Total Score (%)	**100**	**94**	**82**	**82**
Rank	-	**1st**	2nd	2nd

As shown in Table 3.13, Formulation F1 outperformed others due to its excellent clarity, strong structure, cooling intensity, and stability. F3, while favorable in spreadability and freeze–thaw resistance, lacked visual elegance and gel firmness. F2 was penalized for its sensitivity to ethanol loss, which affected both viscosity and user perception.

This analysis confirms F1 as the most promising composition, balancing both technological and user-oriented attributes, and thus selected for further development.

3.4.3. Selection of final formulation based on comprehensive evaluation

Based on the results of organoleptic evaluation, pH measurement, spreadability, rheological testing, and stability assessments, Formulation F1 was selected as the optimal composition for further development. This decision was supported by both qualitative observations and a quantitative scoring matrix, which confirmed F1's superior overall performance across critical parameters.

Formulation F1 is based on Carbomer 940 (0.8%) as the gelling agent, with a moderate ethanol concentration (15%) that ensures full solubilization of menthol and camphor while maintaining good viscosity and phase stability. The propagation of cooling sensation was strong and stable, and the clarity and texture of the gel were highly acceptable from both technological and aesthetic perspectives.

The preservative system (sodium benzoate and disodium EDTA) was effective under short-term and thermal stress conditions, and the gel remained homogeneous and free of phase separation or crystallization. Its pH value (5.52) was within the physiological range, ensuring good dermal compatibility and preservation efficacy.

While F2 demonstrated a stronger initial cooling aroma, it was slightly compromised by ethanol volatility and decreased viscosity under heat. F3 offered excellent spreadability and structural stability but lacked visual transparency and had a noticeably softer texture, which may not meet consumer expectations for a "refreshing" gel product.

Thus, F1 was selected as the final composition for development based on its technological balance, stability, application comfort, and visual appeal.

3.4.4. Summary of technological benefits of the optimal composition

The selected formulation, F1, demonstrated a set of technological advantages that make it highly suitable for use as a topical gel with a cooling effect. From a pharmaceutical technology perspective, F1 meets the critical requirements for product stability, functionality, and user acceptability.

Firstly, the use of Carbomer 940 provided excellent gel consistency, forming a clear and elegant product with good mechanical strength and resistance to flow at rest. This ensures product retention on the skin, minimizing run-off, while still allowing for easy spreading during application - especially when shear is applied.

Secondly, the selected solvent system (ethanol 15% + propylene glycol 10%) successfully solubilized menthol and camphor, resulting in a transparent gel matrix free from recrystallization or phase separation over short-term and thermal testing conditions. Ethanol evaporation contributed to a refreshing sensory burst, while propylene glycol improved skin hydration and preserved consistency.

Thirdly, the preservative system was simple yet effective: sodium benzoate, supported by disodium EDTA, maintained microbial integrity without altering the physical properties or odor of the product. The measured pH of 5.52 was ideal for maintaining skin compatibility and preservative function.

Furthermore, F1 exhibited reversible cooling behavior and retained performance even after thermal and freeze–thaw exposure. This indicates good shelf stability and transportation resilience, which are essential for commercial production.

Finally, the balance of spreadability, viscosity, and clarity, combined with a distinct and pleasant cooling effect, positions F1 as a strong candidate for scaling and consumer-facing use, either in cosmetic, OTC, or dermatological applications.

3.4.5. Preparation for future industrial scaling and packaging considerations

The final composition (F1) was designed with scalability and manufacturability in mind, using widely available excipients and simple technological operations that can be readily adapted for industrial production. The formulation relies on cold mixing, pH adjustment, and low-shear homogenization, which minimizes the need for complex or high-energy equipment, reducing production costs and ensuring batch-to-batch reproducibility.

Key production steps such as hydration of Carbomer, neutralization with triethanolamine, and incorporation of ethanol and actives are already well-documented in pharmaceutical and cosmetic gel manufacturing. No specialized

temperature control or vacuum equipment is required. This supports easy scale-up from laboratory batches to pilot and industrial volumes using standard mixers, storage tanks, and filling lines.

In terms of packaging, the formulation is best suited for:

- Laminate or plastic tubes (30–100 g): These offer barrier protection from moisture and oxygen, reduce ethanol evaporation, and allow hygienic dispensing.

- Airless pumps: Ideal for premium applications, preventing contamination and oxidation while enhancing shelf life.

- Wide-mouthed jars: Could be used in cosmetic contexts but require preservation strategy adjustments due to higher contamination risk.

Materials should be tested for compatibility with ethanol, especially in closure systems and inner linings. Opaque or semi-opaque packaging is preferred to protect the product from light-induced degradation and maintain its visual clarity over time.

From a regulatory perspective, the excipients used are compliant with Ph. Eur. and SPhU standards, and the formulation fits within the framework of cosmetic or non-prescription pharmaceutical products, depending on intended claims and market.

In summary, the developed gel composition offers not only functional efficacy and aesthetic appeal, but also practical feasibility for real-world production, supporting its progression from laboratory to market-ready formulation.

Conclusions to chapter 3

1. A systematic experimental workflow was applied to develop and evaluate gel formulations with a cooling effect based on menthol and camphor. The research included rational selection of excipients, preparation of trial compositions, and assessment of key technological parameters.

2. Three preliminary gel formulations (F1–F3) were developed using different gelling agents and solvent systems. Carbomer 940 and HPMC were compared in terms of appearance, viscosity, spreadability, and stability.

3. Organoleptic testing, pH measurement, rheological evaluation, thermal stress testing, and freeze–thaw cycles demonstrated that all formulations were physically stable and suitable for dermal use. However, differences in visual clarity, viscosity, and ethanol sensitivity were observed.

4. Based on quantitative and qualitative performance criteria, Formulation F1 (Carbomer 940-based gel with 15% ethanol and 10% propylene glycol) was identified as the optimal composition. It showed the best balance of clarity, cooling effect, viscosity, and storage stability.

5. The final gel composition was found to be technologically robust, suitable for industrial scale-up using standard equipment, and compatible with common packaging forms. Its properties support potential use in both pharmaceutical and cosmetic applications.

CONCLUSIONS

1. The formulation of a topical gel with a cooling effect based on menthol and camphor requires careful selection of excipients and technological parameters to ensure stability, efficacy, and user acceptability. Literature analysis confirmed that both active substances are effective thermoreceptor agonists but present challenges related to volatility and oxidation, requiring appropriate stabilizers and packaging strategies.

2. Experimental development involved the preparation of three gel compositions using different gelling agents (Carbomer 940 and HPMC) and hydroalcoholic solvent systems, allowing comparative evaluation of their physicochemical and functional properties. Only simple laboratory methods were used to assess key technological characteristics such as pH, viscosity, spreadability, and short-term stability.

3. All trial formulations demonstrated acceptable physical stability and dermal pH range. However, Formulation F1, based on Carbomer 940 with 15% ethanol and 10% propylene glycol, showed superior results in terms of clarity, viscosity retention, cooling intensity, and overall structural integrity under stress conditions.

4. The study also confirmed that consumer-oriented attributes such as gel texture, spreadability, and odor are influenced not only by the actives, but also by the type and concentration of gelling agents and solvents. These factors must be optimized alongside therapeutic efficacy to ensure patient-centered product design.

5. The final selected gel composition is suitable for industrial production using standard pharmaceutical equipment. Its formulation strategy balances functional performance, cost-effectiveness, and regulatory compliance, supporting its potential application in both cosmetic and medicinal topical preparations.

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Ф А 2.2.1-32-366

National University of Pharmacy

Faculty pharmaceutical
Department industrial technology of medicines and cosmetics
Level of higher education master
Specialty 226 Pharmacy, industrial pharmacy
Educational and professional program Pharmacy

APPROVED
The Head of Department
Industrial technology of
medicines and cosmetics

_____
Olena RUBAN

"02" September 2024

ASSIGNMENT
FOR QUALIFICATION WORK
OF AN APPLICANT FOR HIGHER EDUCATION

Reda BENMOUSSA

1. Topic of qualification work: «Development of the composition of a gel with a cooling effect based on menthol and camphor», supervisor of qualification work: Dmytro Soldatov, PhD, assoc. prof.,

approved by order of NUPh from "27" of September 2024 № 237

2. Deadline for submission of qualification work by the applicant for higher education: May 2025.

3. Outgoing data for qualification work: to develop and experimentally justify the composition of a topical gel with a cooling effect, based on menthol and camphor, using simple, reproducible methods suitable for small-scale pharmaceutical formulation laboratories

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

5. List of graphic material (with exact indication of the required drawings):
tables – 13

6. Consultants of chapters of qualification work

Chapters	Name, SURNAME, position of consultant	Signature, date	
		assignment was issued	assignment was received
1	Dmytro SOLDATOV, PhD, assoc. prof. of higher education institution of department Industrial technology of medicines and cosmetics	09.09.2024	09.09.2024
2	Dmytro SOLDATOV, PhD, assoc. prof. of higher education institution of department Industrial technology of medicines and cosmetics	18.11.2024	18.11.2024
3	Dmytro SOLDATOV, PhD, assoc. prof. of higher education institution of department Industrial technology of medicines and cosmetics	03.02.2025	03.02.2025

7. Date of issue of the assignment: «02» September 2024.

CALENDAR PLAN

№ з/п	Name of stages of qualification work	Deadline for the stages of qualification work	Notes
1	Preparation of literature review	September 2024	**done**
2	Experiment planning	October-December 2024	**done**
3	Conducting an experiment	January-March 2025	**done**
4	Registration of results	April 2025	**done**
5	Submission to the examination commission	May 2025	**done**

An applicant of higher education _____ Reda BENMOUSSA

Supervisor of qualification work _____ Dmytro SOLDATOV

ВИТЯГ З НАКАЗУ № 237

По Національному фармацевтичному університету

від 27 вересня 2024 року

Затвердити теми кваліфікаційних робіт здобувачам вищої освіти 5-го курсу Фм20(4,10д) 2024-2025 навчального року, освітньо-професійної програми – Фармація, другого (магістерського) рівня вищої освіти, спеціальності 226 – Фармація, промислова фармація, галузь знань 22 Охорона здоров'я, денна форма здобуття освіти (термін навчання 4 роки 10 місяців), які навчаються за контрактом (мова навчання англійська та українська) згідно з додатком № 1.

Прізвище, ім'я здобувача вищої освіти	Тема кваліфікаційної роботи		Посада, прізвище та ініціали керівника	Рецензент кваліфікаційної роботи
по кафедрі промислової технології ліків та косметичних засобів				
Бенмусса Реда	Розробка складу гелю з охолоджувальним ефектом на основі ментолу та камфори	Development of the composition of a gel with a cooling effect based on menthol and camphor	доц. Солдатов Д.П.	доц. Ковальов В.В.

Національний фармацевтичний університет Україна Факультет з підготовки іноземних громадян №02010936 місто Харків

Ректор

Вірно. Секретар

ФА2.8-03-317

ВИСНОВОК

експертної комісії про проведену експертизу
щодо академічного плагіату у кваліфікаційній роботі

здобувача вищої освіти

«05» травня 2025 р. № 331121121

Проаналізувавши кваліфікаційну роботу здобувача вищої освіти Бенмусса Реда, групи Фм20(4,10)англ-03, спеціальності 226 Фармація, промислова фармація, освітньої програми «Фармація» навчання на тему: «Розробка складу гелю з охолоджувальним ефектом на основі ментолу та камфори / Development of the composition of a gel with a cooling effect based on menthol and camphor», експертна комісія дійшла висновку, що робота, представлена до Екзаменаційної комісії для захисту, виконана самостійно і не містить елементів академічного плагіату (компіляції).

Голова комісії,
проректор ЗВО з НПР,
професор **Інна ВЛАДИМИРОВА**

Ф А 2.2.1-32-353

REVIEW

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

Reda BENMOUSSA

on the topic: **«Development of the composition of a gel with a cooling effect based on menthol and camphor»**

Relevance of the topic. The development of cooling gels based on menthol and camphor is highly relevant, given their widespread use in pharmaceutical and cosmetic products. These gels provide rapid relief from pain and inflammation, leveraging the synergistic effects of menthol and camphor for enhanced cooling and local anesthetic effects. The study's focus on simple, reproducible methods aligns well with current pharmaceutical trends.

Practical value of conclusions, recommendations and their validity. The work presents valuable insights into the formulation of cooling gels, including the selection of active ingredients, gelling agents, and solvents. The findings are practically applicable, providing a clear framework for small-scale production and potential industrial scaling.

Assessment of work. The study demonstrates a systematic approach to formulation, with well-structured experiments and clear data presentation. The author's technical proficiency and scientific rigor are evident throughout the work, reflecting a strong understanding of the topic.

General conclusion and recommendations on admission to defend. In general, the qualification work of the applicant deserves high marks, meets the requirements and can be submitted for official defense to the examination commission of the National University of Pharmacy.

Scientific supervisor _____ Dmytro SOLDATOV

« 15 » of May 2025

Ф А 2.2.1-32-356

REVIEW

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

Reda BENMOUSSA

on the topic: «Development of the composition of a gel with a cooling effect based on menthol and camphor»

Relevance of the topic. The development of cooling gels based on menthol and camphor is highly relevant due to their widespread use in medical and cosmetic products. These formulations provide rapid relief from pain, inflammation, and discomfort, making them popular for both over-the-counter and prescription applications. The study aligns well with current trends in pharmaceutical technology, emphasizing simple, reproducible methods suitable for small-scale production.

Theoretical level of work. The work demonstrates a solid theoretical foundation, effectively addressing the physicochemical properties of menthol and camphor, their mechanisms of action, and their impact on formulation stability. The author has clearly structured the experimental part, providing a comprehensive analysis of the factors influencing gel formulation.

Author's suggestions on the research topic. The study presents a detailed comparison of different gelling agents and solvent systems, highlighting the advantages of Carbomer and HPMC for cooling gel formulations. The author's approach to optimizing viscosity, spreadability, and sensory properties is innovative and practical, offering valuable insights for further formulation development.

Practical value of conclusions, recommendations and their validity. The research findings have significant practical value, providing clear guidance for the selection of excipients and process parameters in gel formulation. The results are directly applicable to both academic research and small-scale pharmaceutical production, demonstrating a strong alignment with industry needs.

Disadvantages of work. Some sections of the thesis could benefit from more precise language and clearer data presentation. However, these minor issues do not significantly detract from the overall quality of the work or its practical relevance.

General conclusion and assessment of the work. The qualification work of the applicant deserves high marks, meets the requirements and can be submitted for official defense to the examination commission of the National University of Pharmacy.

Reviewer _____ assoc. prof. Volodymyr KOVALOV

« 15 » of May 2025

Ф А2.2.1-91-287

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

Витяг з протоколу
засідання кафедри технологій фармацевтичних препаратів НФаУ
№ 12 від 16 травня 2025 року

Голова: завідувачка кафедри, доктор фарм. наук, проф. Рубан О. А.

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

ПРИСУТНІ: зав. каф., проф. Рубан О.А., проф. Ковалевська І.В., проф. Бобрицька Л.О., проф. Гриценко В.І., проф. Сліпченко Г.Д., проф. Кухтенко О. С., доц. Безрукавий Є. А., доц. Кутова О. В., доц. Манський О. А., доц. Ніколайчук Н. О., доц. Пуляєв Д.С., доц. Січкар А. А., доц. Солдатов Д. П., доц. Трутаєв С. І., ас. Пономаренко Т.О.

ПОРЯДОК ДЕННИЙ:

1. Про представлення до захисту в Екзаменаційну комісію кваліфікаційних робіт здобувачів вищої освіти випускного курсу НФаУ 2025 року випуску

СЛУХАЛИ: Про представлення до захисту в Екзаменаційній комісії кваліфікаційної роботи на тему: «Розробка складу гелю з охолоджувальним ефектом на основі ментолу та камфори»

здобувача вищої освіти випускного курсу Фм20(4,10д)англ-03 групи НФаУ 2025 року випуску _____Реда БЕНМУССА_____
(ім'я, прізвище)

Науковий (-ві) керівник (-ки) _к.фарм.н., доц. Дмитро СОЛДАТОВ_____

Рецензент_____к.фарм.н., доц. Володимир КОВАЛЬОВ_____

УХВАЛИЛИ: Рекомендувати до захисту кваліфікаційну роботу здобувача вищої освіти _5_ курсу _Фм20(4,10д)англ-03__групи__Реда БЕНМУССА__
(ім'я, прізвище)

на тему:__«Розробка складу гелю з охолоджувальним ефектом на основі ментолу та камфори»

Голова
завідувачка кафедри,
доктор фарм. наук, проф. _____ Олена РУБАН
(підпис)

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

Ф А2.2.1-32-042

НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ПОДАННЯ
ГОЛОВІ ЕКЗАМЕНАЦІЙНОЇ КОМІСІЇ
ЩОДО ЗАХИСТУ КВАЛІФІКАЦІЙНОЇ РОБОТИ

Направляється здобувач вищої освіти Реда БЕНМУССА до захисту кваліфікаційної роботи
за галуззю знань 22 Охорона здоров'я
спеціальністю 226 Фармація, промислова фармація
освітньо-професійною програмою Фармація
на тему: «Розробка складу гелю з охолоджувальним ефектом на основі ментолу та камфори».

Кваліфікаційна робота і рецензія додаються.

Декан факультету _____ / Микола ГОЛІК /

Висновок керівника кваліфікаційної роботи

Здобувач вищої освіти Реда БЕНМУССА виконав кваліфікаційну роботу на високому рівні, з логічним викладенням матеріалу та обговоренням, оформлення роботи відповідає вимогам НФаУ до випускних кваліфікаційних робіт та робота може бути рекомендована до захисту в ЕК НФаУ.

Керівник кваліфікаційної роботи

_____ Дмитро СОЛДАТОВ

« 13 » of May 2025 р.

Висновок кафедри про кваліфікаційну роботу

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

Завідувачка кафедри
технологій фармацевтичних препаратів

_____ Олена РУБАН

« 16 » of May 2025 року

Qualification work was defended

of Examination commission on

« ___ » _of June__ 2025

With the grade _____

Head of the State Examination commission,

DPharmSc, Professor

_____ / Volodymyr YAKOVENKO /