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QUALIFICATION WORK

on the topic: **«DEVELOPMENT OF THE COMPOSITION OF HARD GELATIN CAPSULES WITH ANTI-INFLAMMATORY ACTION BASED ON BLACK ELDERBERRY EXTRACT»**

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ANNOTATION

This study presents the development of hard gelatin capsules containing black elderberry (*Sambucus nigra*) dry extract with anti-inflammatory action. Several formulation variants were prepared and evaluated for powder flow, compatibility, capsule uniformity, and disintegration. The optimal composition demonstrated good technological characteristics and short-term stability under laboratory storage conditions. The findings support the use of elderberry extract in natural anti-inflammatory capsule formulations.

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 50 pages, contains 19 tables, 32 references.

Key words: hard gelatin capsules, black elderberry, anti-inflammatory, formulation development, pharmaceutical technology.

АНОТАЦІЯ

У роботі представлено розробку твердих желатинових капсул із сухим екстрактом чорної бузини (*Sambucus nigra*), що мають протизапальну дію. Було підготовлено та оцінено декілька варіантів складу за показниками плинності, сумісності компонентів, однорідності капсул та часу розпаду. Оптимальний склад продемонстрував добрі технологічні характеристики та короткочасну стабільність при зберіганні в лабораторних умовах. Отримані результати підтверджують перспективність використання екстракту бузини у складі натуральних протизапальних капсул.

Робота складається з таких частин: вступ, огляд літератури, вибір методів дослідження, експериментальна частина, загальні висновки, список використаних літературних джерел, загальний обсяг 50 сторінок, містить 19 таблиць, 32 посилання.

Ключові слова: тверді желатинові капсули, чорна бузина, протизапальний засіб, розробка складу, технологія ліків.

CONTENT

LIST OF ABBREVIATIONS

API – active pharmaceutical ingredient

COX – cyclooxygenase

GMP – good manufacturing practice

HPLC – high-performance liquid chromatography

LOD – loss on drying

MS – mass spectrometry

NF-κB – nuclear factor kappa B

Ph.Eur. – European Pharmacopoeia

ROS – reactive oxygen species

SPhU – State Pharmacopoeia of Ukraine

TNF-α – tumor necrosis factor alpha

WHO – World Health Organization

INTRODUCTION

The relevance of the topic

Inflammatory conditions are among the most prevalent health problems globally, contributing to chronic disease progression, immune system dysregulation, and reduced quality of life. Herbal medicines have gained increasing attention as safe and effective alternatives to synthetic anti-inflammatory agents. Among these, black elderberry (*Sambucus nigra L.*) has demonstrated significant therapeutic potential due to its antioxidant, anti-inflammatory, and immunomodulating effects.

Capsule dosage forms are widely used in modern pharmaceutical practice for delivering herbal extracts. They offer precise dosing, ease of administration, and protection of sensitive substances from environmental degradation. Hard gelatin capsules, in particular, provide an effective vehicle for dry herbal powders and are compatible with conventional encapsulation techniques at both laboratory and industrial scales.

The development of a scientifically justified and technologically stable formulation of black elderberry extract in hard gelatin capsules is both relevant and practically important. It addresses the need for natural anti-inflammatory products with high patient acceptability and reliable performance.

The purpose of the study

The purpose of this study was to develop the composition of hard gelatin capsules containing black elderberry extract with anti-inflammatory activity, and to evaluate their technological properties and short-term stability.

Research tasks

To achieve this goal, the following tasks were set:

1. To select suitable excipients compatible with the active ingredient and capsule form;

2. To prepare several capsule formulation variants and evaluate their powder flow properties;

3. To perform capsule filling and assess weight uniformity, disintegration, and moisture content;

4. To carry out short-term stability testing under laboratory storage conditions.

The object of research

The object of research was a solid oral dosage form - hard gelatin capsules containing black elderberry extract as the active pharmaceutical ingredient.

The subject of the study

The subject of research was the composition, technological characteristics, and stability of capsule formulations containing plant-derived anti-inflammatory substances.

Research methods

Experimental methods included preformulation testing, flowability assessment, pharmacopeial quality control of the capsules, and short-term stability analysis under controlled temperature and humidity.

Practical significance of the obtained results

The results of this study can be used as a scientific and practical basis for developing natural anti-inflammatory supplements in capsule form. The validated methodology and data may also support future preclinical evaluation and industrial scale-up.

Elements of scientific research

The novelty of the study lies in the development and optimization of a hard gelatin capsule composition using black elderberry extract, a plant substance with high therapeutic relevance.

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 50 pages, contains 19 tables, 32 references.

CHAPTER 1

BLACK ELDERBERRY EXTRACT AND ITS APPLICATION IN ANTI-INFLAMMATORY PHARMACEUTICAL FORMS

1.1. Botanical and chemical characteristics of black elderberry (*Sambucus nigra L.*)

Sambucus nigra L., commonly known as black elderberry, is a deciduous shrub or small tree belonging to the Adoxaceae family. It typically grows to a height of 3 to 8 meters, with a bushy appearance and multiple stems arising from the base. The plant features pinnate leaves composed of 5 to 7 serrated leaflets, each measuring approximately 5 to 12 centimeters in length. The bark is light gray when young, becoming darker and furrowed with age. In late spring to early summer, black elderberry produces flat-topped clusters (corymbs) of small, creamy-white, hermaphroditic flowers, which later develop into glossy, dark purple to black berries in the autumn [1].

Black elderberry is native to most of Europe, extending into parts of Western Asia and North Africa. It thrives in a variety of habitats, including hedgerows, woodlands, and riverbanks, and is commonly found in both rural and urban settings. The plant prefers moist, fertile soils and can tolerate a range of pH levels, although it favors slightly alkaline conditions. Its adaptability allows it to grow at various altitudes, from lowland areas up to mountainous regions, depending on the local climate. In Sicily, for example, S. nigra is widespread but exhibits a discontinuous distribution, favoring hedges, riparian woodlands, forest margins, and clearings [2].

The widespread distribution and adaptability of black elderberry have contributed to its long-standing use in traditional medicine and its incorporation into various cultural practices across different regions. Its presence near human settlements and sacred places suggests intentional cultivation and utilization throughout history [3].

Black elderberry (*Sambucus nigra L.*) is renowned for its rich chemical composition, which includes a diverse array of bioactive compounds contributing to its therapeutic potential.

Flavonoids, particularly rutin and quercetin, are prominent in elderberries. Rutin, a glycoside combining quercetin and rutinose, is abundant in elderberry fruits, with concentrations reported at 813.08 μg/100 g dry weight. This compound is a significant contributor to the antioxidant activity of elderberries, acting as a free radical scavenger and exhibiting protective effects against oxidative stress. Additionally, phenolic acids such as chlorogenic acid and gallic acid are present, further enhancing the fruit's antioxidant properties [4].

Anthocyanins are another vital group of compounds in elderberries, responsible for their characteristic dark purple color. These water-soluble pigments, primarily cyanidin-3-glucoside and cyanidin-3-sambubioside, are present in significant amounts, ranging from 560 to 1347 mg/100 g fresh weight, depending on the cultivar and ripeness. Anthocyanins contribute not only to the visual appeal but also to the health benefits of elderberries, including anti-inflammatory and antioxidant effects [5].

The chemical composition of elderberries is influenced by various seasonal and environmental factors. Intrinsic factors such as the plant's genetic makeup and the degree of fruit ripeness play a role, while extrinsic factors include growing conditions, altitude, light exposure, temperature, and rainfall. For instance, elderberries cultivated in well-organized orchards have been found to possess higher polyphenolic content compared to those grown in the wild. Postharvest factors like drying methods, storage conditions, and extraction techniques also affect the stability and concentration of bioactive compounds [6].

Understanding the chemical composition of black elderberry is crucial for its application in pharmaceutical formulations, as the concentration and stability of these bioactive compounds directly impact the efficacy and quality of the final product.

The therapeutic potential of black elderberry (*Sambucus nigra L.*) is largely attributed to its rich composition of bioactive compounds, including flavonoids, anthocyanins, and phenolic acids. These constituents exhibit significant anti-inflammatory properties, making elderberry a valuable candidate for pharmaceutical applications.

Flavonoids, such as quercetin and rutin, are abundant in elderberry and have been extensively studied for their anti-inflammatory effects. These compounds modulate inflammatory pathways by inhibiting enzymes like cyclooxygenase (COX) and suppressing pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukins (IL-1β, IL-6). For instance, a study demonstrated that elderberry flower extract, rich in flavonoids, significantly reduced the levels of these cytokines in both in vitro and in vivo models, highlighting its anti-inflammatory efficacy [7].

Anthocyanins, particularly cyanidin-3-glucoside and cyanidin-3-sambubioside, are responsible for the deep purple color of elderberries and contribute to their anti-inflammatory activity. These compounds inhibit the nuclear factor kappa B (NF-κB) pathway, a key regulator of inflammatory responses. Research indicates that elderberry extracts containing these anthocyanins can effectively reduce inflammation by modulating this pathway.

Phenolic acids, such as chlorogenic acid, also play a crucial role in the anti-inflammatory effects of elderberry. These acids possess antioxidant properties that help neutralize reactive oxygen species (ROS), which are often elevated during inflammatory processes. By reducing oxidative stress, phenolic acids indirectly suppress inflammation and protect tissues from damage. Studies have shown that chlorogenic acid in elderberry can inhibit the proliferation of inflammatory mediators, further supporting its therapeutic potential.

The synergistic action of these bioactive compounds underscores the importance of standardizing elderberry extracts in pharmaceutical formulations. Ensuring consistent concentrations of flavonoids, anthocyanins, and phenolic acids is essential for achieving predictable therapeutic outcomes. Moreover,

understanding the specific mechanisms through which these constituents exert their effects can inform the development of targeted anti-inflammatory therapies derived from elderberry.

1.2. Pharmacological properties of black elderberry with emphasis on anti-inflammatory action

Black elderberry (*Sambucus nigra L.*) has been recognized for its diverse pharmacological properties, including antiviral, antioxidant, immunomodulatory, and anti-inflammatory effects. These attributes are largely attributed to its rich composition of bioactive compounds such as flavonoids, anthocyanins, and phenolic acids.

Elderberry extracts have demonstrated efficacy against various viral pathogens. For instance, studies have shown that elderberry can inhibit the replication of influenza viruses by blocking the viral glycoproteins responsible for cell entry. This antiviral action is primarily due to the presence of anthocyanins and other polyphenolic compounds that interfere with the viral life cycle.

The high concentration of antioxidants in elderberry contributes to its ability to neutralize free radicals, thereby reducing oxidative stress. This antioxidant capacity is beneficial in preventing cellular damage and has been linked to the prevention of various chronic diseases.

Elderberry has been observed to modulate the immune system by enhancing the production of cytokines, which are crucial in the body's defense mechanisms. This immunostimulatory effect supports the body's ability to combat infections and may contribute to its overall health-promoting properties.

The anti-inflammatory effects of elderberry are attributed to its capacity to inhibit the production of pro-inflammatory cytokines and enzymes such as COX-2. By suppressing these inflammatory mediators, elderberry helps in reducing inflammation and associated symptoms [8].

Historically, elderberry has been utilized in traditional medicine across various cultures. Its flowers and berries have been employed to treat ailments such

as colds, flu, and inflammation. The continued use of elderberry in contemporary herbal remedies underscores its enduring therapeutic relevance [9].

The anti-inflammatory properties of black elderberry (*Sambucus nigra L.*) are attributed to its rich composition of bioactive compounds, including flavonoids, anthocyanins, and phenolic acids. These constituents interact with various molecular pathways to exert their effects.

One primary mechanism involves the inhibition of the nuclear factor kappa B (NF-κB) pathway, a critical regulator of inflammatory responses. Activation of NF-κB leads to the transcription of pro-inflammatory genes, including those encoding cytokines like TNF-α, IL-1β, and IL-6. Elderberry extracts have been shown to suppress NF-κB activation, thereby reducing the expression of these cytokines. For instance, studies have demonstrated that elderberry extracts can inhibit NF-κB signaling in various cell types, leading to decreased inflammation.

Additionally, elderberry constituents modulate the production of pro-inflammatory cytokines. Anthocyanins, such as cyanidin-3-glucoside, have been found to decrease the levels of TNF-α, IL-1β, and IL-6 in lipopolysaccharide (LPS)-stimulated macrophages. This modulation helps in attenuating the inflammatory response and is crucial in conditions characterized by excessive cytokine production.

Oxidative stress plays a significant role in the pathogenesis of inflammation. Elderberry extracts exhibit potent antioxidant properties, neutralizing reactive oxygen species (ROS) and thereby reducing oxidative stress. This antioxidant activity not only protects cells from oxidative damage but also indirectly suppresses inflammatory pathways activated by ROS.

Furthermore, elderberry extracts influence other signaling pathways involved in inflammation. For example, they have been shown to modulate the mitogen-activated protein kinase (MAPK) pathways, which play a role in the expression of inflammatory mediators. By affecting these pathways, elderberry constituents can further suppress the inflammatory response [10].

The anti-inflammatory effects of black elderberry are mediated through multiple mechanisms, including inhibition of NF-κB activation, modulation of cytokine production, antioxidant activity, and regulation of other inflammatory signaling pathways. These multifaceted actions make elderberry a promising candidate for the development of anti-inflammatory therapies.

Recent studies have provided substantial evidence supporting the anti-inflammatory properties of *Sambucus nigra* (black elderberry) through both in vitro and in vivo experiments.

Investigations using lipopolysaccharide (LPS)-stimulated macrophage models have demonstrated that black elderberry extracts can significantly reduce the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. For instance, a study found that elderberry extracts inhibited the release of these cytokines in LPS-stimulated RAW 264.7 macrophages, indicating potent anti-inflammatory activity. Additionally, the extracts were shown to suppress nitric oxide production, further confirming their anti-inflammatory potential.

Animal models have been employed to assess the anti-inflammatory effects of black elderberry extracts. In a study using a cotton pellet-induced granuloma model in rats, oral administration of elderberry fruit extract at doses of 10, 20, and 50 mg/kg body weight resulted in a dose-dependent reduction in granuloma weight, with the highest dose achieving an effect comparable to that of diclofenac, a standard anti-inflammatory drug. This suggests that elderberry extracts can effectively suppress chronic inflammation in vivo [11].

The anti-inflammatory effects observed are attributed to the rich polyphenolic content of elderberry, particularly anthocyanins like cyanidin-3-glucoside. These compounds are known to inhibit key inflammatory pathways, including the NF-κB signaling pathway, and reduce the expression of pro-inflammatory mediators. Furthermore, elderberry extracts have been shown to enhance the activity of antioxidant enzymes, thereby mitigating oxidative stress, which is closely linked to inflammation [12].

These findings from both in vitro and in vivo studies underscore the potential of black elderberry as a natural source of anti-inflammatory agents, supporting its traditional use in managing inflammatory conditions and highlighting its promise for incorporation into pharmaceutical formulations.

1.3. Use of black elderberry extract in pharmaceutical preparations

Black elderberry (*Sambucus nigra L.*) has been incorporated into various pharmaceutical and nutraceutical products, primarily targeting immune support and the management of cold and flu symptoms. These products are available in multiple formulations, including syrups, capsules, lozenges, gummies, and teas, catering to diverse consumer preferences and age groups.

Syrups are among the most popular elderberry products, often marketed for their potential to alleviate cold and flu symptoms. For instance, a study involving 60 individuals with influenza found that those who consumed 15 mL of elderberry syrup four times daily experienced symptom improvement within 2 to 4 days, compared to 7 to 8 days in the placebo group . This suggests that elderberry syrups may help reduce the duration of influenza symptoms when taken early in the course of the illness [13].

Capsules and lozenges offer convenient alternatives to syrups, providing standardized doses of elderberry extract. A study involving 312 air travelers who took capsules containing 300 mg of elderberry extract three times daily reported that those who became ill experienced shorter durations and less severe symptoms compared to the placebo group . These findings indicate that elderberry capsules may be effective in mitigating the severity and duration of cold symptoms, particularly in individuals exposed to stressors like long-haul flights [14].

Gummies and chewables have gained popularity, especially among children and individuals who prefer not to swallow pills. These formulations often combine elderberry extract with other immune-supporting ingredients like vitamin C and zinc. While specific studies on gummies are limited, the inclusion of elderberry

extract in these products is based on its established antiviral and immunomodulatory properties [15].

Teas and infusions made from elderberry flowers and berries are traditional remedies for respiratory ailments. Although scientific evidence supporting their efficacy is less robust compared to other formulations, these preparations continue to be used for their soothing effects and potential health benefits.

Black elderberry extract is utilized in a variety of pharmaceutical and nutraceutical products aimed at supporting immune function and alleviating symptoms of respiratory infections. While syrups and capsules have demonstrated efficacy in clinical studies, other formulations like gummies and teas are popular for their ease of use and traditional appeal. Continued research is necessary to further validate the effectiveness of these products and to optimize their formulations for maximum therapeutic benefit.

The formulation of black elderberry (*Sambucus nigra L.*) products presents several challenges, primarily due to the inherent instability of its bioactive compounds, such as anthocyanins and polyphenols. These compounds are sensitive to environmental factors like light, heat, and oxygen, which can lead to degradation and loss of efficacy [16].

Stability Challenges: Anthocyanins, responsible for the deep purple color of elderberries, are particularly prone to degradation. Their stability is influenced by factors such as pH, temperature, and the presence of enzymes or metal ions. For instance, non-acylated anthocyanins found in European elderberry are less stable compared to acylated forms present in other species, making them more susceptible to degradation during processing and storage [6].

To enhance the stability and bioavailability of elderberry extracts, encapsulation methods like spray drying are employed. This technique involves converting liquid extracts into dry powders using carriers such as maltodextrin and gum arabic. Studies have shown that a formulation with 40% maltodextrin and 60% gum arabic (SD 4) achieved high encapsulation efficiency, preserving significant amounts of anthocyanins and flavonoids. This approach not only

improves the stability of the bioactive compounds but also facilitates their incorporation into various dosage forms [5, 16].

Ensuring consistent therapeutic efficacy requires standardization of elderberry extracts based on their bioactive content. Variations in extraction methods, raw material sources, and processing conditions can lead to significant differences in the concentration of active compounds. Implementing rigorous quality control measures, including the use of standardized extracts with known anthocyanin content, is crucial for the development of reliable pharmaceutical products.

The increasing popularity of elderberry supplements has led to a proliferation of products with varying quality and efficacy. Regulatory bodies emphasize the importance of accurate labeling and substantiated health claims. Manufacturers are encouraged to adhere to good manufacturing practices (GMP) and ensure that their products meet established standards for safety and efficacy.

The formulation of black elderberry products necessitates careful consideration of the stability of bioactive compounds, the use of effective encapsulation techniques, stringent standardization protocols, and compliance with regulatory guidelines to ensure the development of safe and effective pharmaceutical preparations.

The incorporation of black elderberry (*Sambucus nigra L.*) extract into pharmaceutical formulations offers several advantages, primarily due to its rich content of bioactive compounds such as anthocyanins, flavonoids, and phenolic acids. These constituents have been associated with various health benefits, including antioxidant, anti-inflammatory, and antiviral activities. For instance, elderberry extracts have demonstrated the ability to inhibit the development of influenza A and B viruses, as well as certain bacterial strains, highlighting their potential in managing respiratory infections [5].

Moreover, elderberry's antioxidant properties can help mitigate oxidative stress, which is implicated in the pathogenesis of numerous chronic diseases. The presence of compounds like quercetin and cyanidin derivatives contributes to this

antioxidant capacity, potentially offering protective effects against conditions such as cardiovascular diseases and diabetes.

The development of pharmaceutical products containing elderberry extract is not without challenges. One significant limitation is the variability in the composition of bioactive compounds, which can be influenced by factors such as plant variety, growing conditions, and processing methods. This variability complicates the standardization of extracts, making it difficult to ensure consistent therapeutic efficacy across different batches [6].

Additionally, the stability of anthocyanins and other phenolic compounds during processing and storage poses a challenge. These compounds are sensitive to environmental factors like pH, temperature, and light, which can lead to degradation and reduced bioactivity over time. To address this, advanced formulation techniques such as microencapsulation and the use of stabilizing agents are being explored to enhance the shelf-life and efficacy of elderberry-based products.

Regulatory considerations also play a role in the development of elderberry-containing pharmaceuticals. While elderberry is generally recognized as safe when properly processed, the presence of toxic compounds in raw or unripe berries necessitates careful quality control measures. Ensuring compliance with regulatory standards is essential to guarantee the safety and effectiveness of the final products.

While black elderberry extract holds promise for pharmaceutical applications due to its bioactive properties, addressing challenges related to standardization, stability, and regulatory compliance is crucial for the successful development of effective and safe elderberry-based therapeutics.

1.4. Hard gelatin capsules as a dosage form

Hard gelatin capsules are a widely utilized oral dosage form in pharmaceutical sciences, offering numerous advantages that make them suitable for encapsulating sensitive compounds like black elderberry (*Sambucus nigra L.*) extract.

One of the primary benefits of hard gelatin capsules is their ability to protect sensitive active pharmaceutical ingredients (APIs) from environmental factors such as light, oxygen, and moisture. This protective feature is particularly beneficial for compounds like anthocyanins and flavonoids found in elderberry extract, which are prone to degradation when exposed to such conditions. The capsule shell acts as a barrier, preserving the stability and efficacy of the encapsulated substances.

Hard gelatin capsules are generally tasteless and odorless, which helps in masking the unpleasant taste or smell of certain medications. This characteristic improves patient compliance, especially among populations sensitive to taste, such as children and the elderly. Furthermore, the smooth surface and shape of capsules facilitate easier swallowing compared to tablets, enhancing the overall patient experience.

These capsules offer significant flexibility in formulation, allowing for the encapsulation of various types of fills, including powders, granules, and even semi-solids. This versatility enables the development of combination therapies and customized dosing regimens. Additionally, the absence of compression in capsule filling reduces the risk of degrading sensitive ingredients, making it an ideal choice for formulating herbal extracts like elderberry [18].

Hard gelatin capsules typically disintegrate quickly in the gastrointestinal tract, leading to rapid release and absorption of the active ingredients. This property is advantageous for achieving prompt therapeutic effects, which is particularly desirable in managing acute conditions such as cold and flu symptoms, where elderberry extract is commonly employed [17].

The ability to produce capsules in various colors and imprint them with identifying marks offers pharmaceutical companies opportunities for branding and product differentiation. This feature also aids in preventing medication errors and enhances the professional appearance of the product, potentially increasing consumer trust and adherence [19].

Hard gelatin capsules provide a protective, flexible, and patient-friendly dosage form that is particularly well-suited for delivering sensitive herbal extracts

like black elderberry. Their advantages in preserving ingredient stability, enhancing patient compliance, and facilitating rapid absorption make them a valuable option in pharmaceutical formulation.

The manufacturing of hard gelatin capsules involves a series of precise and controlled steps to ensure the production of high-quality capsules suitable for pharmaceutical use.

Preparation of Gelatin Solution. The process begins with the preparation of a concentrated gelatin solution, typically comprising 30–40% w/w gelatin dissolved in demineralized water heated to 60–70°C. Vacuum is applied to the solution to remove air bubbles, which could otherwise lead to defects in the capsule shells. Colorants and other additives may be incorporated to achieve the desired appearance and properties of the final capsules [20].

Dip-Coating Process. Once the gelatin solution attains the appropriate viscosity, stainless steel pins, arranged in rows on metal bars, are dipped into the solution to form the capsule bodies and caps. The pins are then rotated to ensure uniform distribution of the gelatin film and to prevent the formation of a bead at the tip. This step is crucial for achieving consistent wall thickness and capsule dimensions [21].

Drying and Trimming. The gelatin-coated pins are subjected to controlled drying conditions, where temperature and humidity are meticulously regulated to remove moisture without causing brittleness. After drying, the formed capsule shells are stripped from the pins and trimmed to the desired length. The body and cap are then joined to form the complete capsule [20].

Moisture Content and Shell Integrity. Maintaining the appropriate moisture content in hard gelatin capsules is vital for preserving their mechanical properties. Typically, capsules contain 13–16% moisture under standard conditions. Deviations from this range can lead to issues such as brittleness or deformation, affecting the capsule's integrity during handling and storage [22].

Encapsulation Process. In the encapsulation stage, the empty capsules are filled with the active pharmaceutical ingredient (API) in the form of powders,

granules, or pellets. The filling process must ensure uniformity and accuracy in dosage, which is critical for the efficacy and safety of the final pharmaceutical product. Advanced capsule-filling machines are employed to achieve high precision and efficiency in this process [23].

The production of hard gelatin capsules is a complex process that requires stringent control of various parameters, including gelatin solution preparation, dip-coating, drying, moisture content, and encapsulation. Each step is crucial to ensure the production of capsules that meet the desired quality standards for pharmaceutical applications.

The stability and quality of hard gelatin capsules are influenced by various factors, including the interaction between the capsule shell and the fill material, as well as environmental conditions such as humidity and temperature.

The compatibility between the capsule shell and the fill material is crucial for maintaining capsule integrity. Certain excipients, especially those containing aldehyde groups or reactive impurities, can interact with gelatin, leading to cross-linking. This cross-linking forms a pellicle on the capsule shell, hindering its dissolution and potentially affecting drug release. For instance, polyethylene glycol (PEG) and other aldehyde-containing substances have been identified as agents that can induce such cross-linking reactions in gelatin capsules [24].

Environmental conditions play a significant role in the physical properties of gelatin capsules. Gelatin is hygroscopic, meaning it can absorb or lose moisture depending on the surrounding humidity. At low relative humidity levels, capsules may lose moisture, becoming brittle and prone to cracking. Conversely, high humidity can lead to excessive moisture uptake, causing capsules to become soft, sticky, or even deformed. Temperature fluctuations can exacerbate these effects, with elevated temperatures accelerating moisture loss and increasing the risk of brittleness [25].

Proper storage is essential to maintain the quality of hard gelatin capsules. It is recommended to store capsules in environments with controlled temperature and humidity, typically at 15–25°C and 35–65% relative humidity. Deviations from

these conditions can lead to physical changes in the capsule shell, such as brittleness or softening, which may compromise the capsule's performance and shelf life.

Ensuring the stability and quality of hard gelatin capsules requires careful consideration of the interactions between the capsule shell and fill materials, as well as stringent control of environmental storage conditions. Addressing these factors is vital for the successful development and utilization of gelatin capsule-based pharmaceutical products.

1.5. Challenges in formulating herbal extracts into hard gelatin capsules

The standardization of herbal extracts is a pivotal aspect in the development of consistent and efficacious pharmaceutical products. However, achieving uniformity in herbal preparations poses significant challenges due to the inherent variability in the chemical composition of plant materials.

The concentration of bioactive compounds in medicinal plants can fluctuate based on several factors, including geographical origin, harvesting time, cultivation practices, and post-harvest processing methods. For instance, the levels of anthocyanins and flavonoids in elderberry (*Sambucus nigra L.*) can vary significantly depending on the ripeness of the berries and environmental conditions during growth. Such variability complicates the process of ensuring consistent therapeutic outcomes in herbal formulations. Standardization aims to minimize these discrepancies by establishing specific quality parameters and ensuring consistent levels of active constituents or marker compounds in herbal medicines [26].

In pharmaceutical development, dose consistency is paramount to ensure safety and efficacy. Herbal extracts, being complex mixtures of multiple constituents, present challenges in identifying and quantifying the specific compounds responsible for therapeutic effects. Without proper standardization, there is a risk of batch-to-batch variability, leading to inconsistent dosing and unpredictable clinical outcomes. Implementing rigorous quality control measures,

such as chromatographic fingerprinting and the use of reference standards, is essential to monitor and control the quality and efficacy of herbal medication products [27].

Advanced analytical techniques play a crucial role in the standardization process. Methods such as high-performance liquid chromatography (HPLC), gas chromatography (GC), and mass spectrometry (MS) are employed to identify and quantify active compounds within herbal extracts. These techniques enable the establishment of quantitative markers, facilitating the assessment of extract quality and ensuring consistency across production batches. Additionally, biological assays may be utilized to evaluate the pharmacological activity of the extracts, further contributing to the standardization process [28].

Standardization is a critical component in the formulation of herbal extracts into hard gelatin capsules. Addressing the challenges associated with chemical variability through the implementation of stringent quality control measures and advanced analytical techniques is essential to ensure the production of safe, effective, and consistent herbal pharmaceutical products.

The stability of phytochemicals, particularly anthocyanins and flavonoids found in black elderberry (*Sambucus nigra L.*), is a critical concern in the formulation of hard gelatin capsules. These compounds are susceptible to degradation under various environmental conditions, which can compromise the efficacy and shelf-life of the final pharmaceutical product.

Anthocyanins are notably sensitive to factors such as pH, temperature, light, and oxygen. For instance, they are more stable in acidic environments and tend to degrade rapidly at higher pH levels. Elevated temperatures can accelerate the breakdown of anthocyanins, leading to a loss of color and bioactivity. Exposure to light and oxygen further exacerbates this degradation process, resulting in diminished antioxidant properties and therapeutic potential. These factors collectively pose significant challenges in maintaining the stability of anthocyanins during processing and storage of capsule formulations.

The storage environment plays a pivotal role in the preservation of phytochemicals within capsules. Studies have shown that anthocyanin content is better preserved at low water activity levels and moderate temperatures. For example, freeze-dried elderberry pulp stored at a water activity of 0.12–0.20 and a temperature of 38°C retained a significant portion of its anthocyanin content over a 90-day period. This indicates that controlling moisture levels and storage temperatures is essential to minimize degradation and extend the shelf-life of anthocyanin-rich products [29].

The choice of excipients and capsule materials can influence the stability of encapsulated phytochemicals. Certain excipients may interact with anthocyanins, affecting their solubility and release profiles. For instance, the use of polysaccharide-based excipients like sodium carboxymethylcellulose has been found to stabilize anthocyanins and protect them from degradation in the gastrointestinal environment. Such interactions are crucial considerations in the design of capsule formulations to ensure the bioavailability and therapeutic efficacy of the active compounds [30].

The stability of phytochemicals in hard gelatin capsules is influenced by a multitude of factors, including environmental conditions and interactions with capsule components. Addressing these challenges requires a comprehensive understanding of the degradation pathways of anthocyanins and the implementation of strategies to mitigate their impact, thereby ensuring the development of effective and stable herbal pharmaceutical products.

Formulating herbal extracts like black elderberry (*Sambucus nigra L.*) into hard gelatin capsules presents several challenges, including variability in chemical composition, stability issues, and interactions with capsule components. To address these challenges, various strategies have been developed to enhance the stability, bioavailability, and overall efficacy of herbal formulations.

Microencapsulation involves enclosing active compounds within a protective coating, which can shield sensitive phytochemicals from environmental factors such as light, oxygen, and moisture. This technique not only enhances the

stability of the encapsulated compounds but also allows for controlled release profiles. For instance, microencapsulation of curcuminoids has been shown to improve their stability against alkaline pH, light, oxygen, and heat compared to their non-encapsulated forms. Such improvements are crucial for maintaining the therapeutic efficacy of herbal extracts during storage and upon administration [31].

Freeze-drying is a widely used method to stabilize labile pharmaceuticals, including herbal extracts. The process involves sublimation of ice from its frozen form, followed by desorption of moisture under vacuum conditions. This technique effectively removes water content, thereby reducing the risk of microbial growth and chemical degradation. Freeze-drying has been successfully applied to stabilize various plant extracts, preserving their bioactive properties and extending shelf life [Error: Reference source not found].

Incorporating protective excipients such as antioxidants, desiccants, and stabilizers into capsule formulations can mitigate degradation pathways of sensitive herbal compounds. For example, the addition of antioxidants can prevent oxidative degradation, while desiccants can control moisture levels within the capsule, reducing hydrolytic reactions. Selecting appropriate excipients based on the specific stability concerns of the herbal extract is essential for developing robust formulations.

The choice of capsule shell material can significantly influence the stability of the encapsulated herbal extract. Plant-based capsules made from hypromellose (HPMC) have been introduced as alternatives to traditional gelatin capsules. HPMC capsules exhibit lower moisture content and are less susceptible to water exchange, which improves the chemical and physical stability of moisture-sensitive compounds. This characteristic makes HPMC capsules particularly suitable for formulating hygroscopic herbal extracts.

Overcoming the formulation challenges associated with herbal extracts in hard gelatin capsules requires a multifaceted approach. Employing techniques such as microencapsulation and freeze-drying, utilizing protective excipients, and

selecting appropriate capsule materials are critical strategies to enhance the stability and efficacy of herbal pharmaceutical products.

Conclusions to chapter 1

1. Black elderberry (*Sambucus nigra L.*) demonstrates significant pharmacological potential, primarily due to its rich content of anthocyanins, flavonoids, and phenolic acids, which provide anti-inflammatory, antiviral, and antioxidant effects.

2. Its application in pharmaceutical forms such as syrups, capsules, and lozenges is well-established, particularly for immune support and respiratory infections. However, formulation challenges, including chemical variability and phytochemical instability, necessitate careful standardization and technological optimization.

3. Hard gelatin capsules offer an effective dosage form for elderberry extracts, protecting bioactive compounds and enhancing patient compliance. Stability issues related to capsule-fill interactions and environmental factors must be addressed to ensure product quality.

4. Strategies such as microencapsulation, freeze-drying, and the use of protective excipients are essential to overcoming formulation difficulties and maintaining the therapeutic efficacy of elderberry-based products.

5. The findings of this chapter establish the theoretical basis for developing a stable and effective composition of hard gelatin capsules with anti-inflammatory action.

CHAPTER 2
OBJECTS AND RESEARCH METHODS

2.1. Choice of general research methodology

The research methodology for developing hard gelatin capsules with anti-inflammatory action was based on a systematic approach commonly used in pharmaceutical technology. The study aimed to design a dosage form that is pharmaceutically stable, easy to manufacture, and consistent in performance. The overall strategy included the selection of formulation components, preformulation studies, technological characterization, and quality control testing, followed by a short-term stability assessment.

The methodological approach began with a comparative composition analysis, where several formulation variants were prepared using black elderberry extract and different ratios of standard excipients. These variants were evaluated to determine which composition offered optimal flowability, compatibility, and capsule uniformity. This phase used basic pharmaceutical mixing techniques under controlled lab conditions.

Preformulation testing focused on key technological indicators such as bulk density, tapped density, angle of repose, and moisture content. These parameters were chosen because they directly affect powder handling and capsule filling performance. Measurements were performed using simple, validated techniques such as the use of a 100 mL graduated cylinder, manual tapping, and drying oven.

The State Pharmacopoeia of Ukraine (SPhU) served as the regulatory reference for defining the quality parameters of the finished capsules, including fill weight uniformity, disintegration time, and visual integrity. All tests were conducted in accordance with pharmacopeial monographs and tolerances to ensure the scientific relevance and potential scalability of the formulation.

Finally, to assess short-term physical stability, the capsules were stored for 30 days under controlled temperature and humidity conditions (25 ± 2 °C, ~65% RH). During this time, their appearance, weight, and disintegration time were

periodically monitored to evaluate the robustness of the formulation under ambient storage.

This integrated methodology combined simple laboratory procedures with pharmacopeial testing standards to create a formulation development workflow that is both realistic for academic research and aligned with practical pharmaceutical development.

2.2. Objects of research

The primary object of this research was the development of a solid oral dosage form in the form of hard gelatin capsules containing black elderberry dry extract as the active pharmaceutical ingredient (API). The study was focused on the selection and evaluation of components that would ensure the technological feasibility, physical stability, and therapeutic consistency of the final formulation.

The active substance, black elderberry (*Sambucus nigra L.*) dry extract, is known for its anti-inflammatory, antioxidant, and immune-modulating properties. It was used in dry powder form, standardized to a dose of 150 mg per capsule. The extract was dark violet in color, hygroscopic, and exhibited moderate flow properties in its unmodified form.

To support the performance of the formulation, the following excipients were selected:

- Lactose monohydrate – used as a diluent to increase bulk and improve powder density.

- Microcrystalline cellulose – added as a binder and filler to enhance compressibility and flow.

- Corn starch – served as a disintegrant to facilitate capsule breakdown upon ingestion.

- Magnesium stearate – used in low concentration as a lubricant to prevent powder adhesion during filling.

All excipients were pharmacopeial grade and used without further purification. Their selection was based on widespread pharmaceutical use,

compatibility with herbal substances, and suitability for direct powder encapsulation. The capsule shell consisted of size 0 hard gelatin capsules, transparent-violet, sourced from standard commercial suppliers. This size was chosen to accommodate the powder fill mass of approximately 345 mg.

For the experimental study, a pilot batch of 100 capsules was produced. All materials were stored and handled under controlled laboratory conditions, and all measurements were performed using analytical balances, sieves, and other basic pharmaceutical lab equipment.

The physical and technological properties of the API and excipients, as well as their proportions in different variants, were key variables studied throughout the formulation process. These components collectively formed the object of research aimed at achieving an effective and stable capsule composition.

2.3 Research methods

The research employed a combination of pharmaceutical technology techniques and standard quality control procedures to evaluate both the powder formulation and the finished capsules. All methods were selected to reflect realistic laboratory capabilities and align with requirements of the State Pharmacopoeia of Ukraine (SPhU).

To assess the flow and packing behavior of the powder mixtures, the following methods were used:

- Bulk density was determined by gently filling a 100 mL graduated cylinder with powder and recording the volume without tapping.

- Tapped density was measured after 500 manual taps of the cylinder using a mechanical tapping device.

- Carr’s index (%) and Hausner ratio were calculated from bulk and tapped density values to assess compressibility and flow potential.

- Angle of repose was measured using the fixed funnel method, by allowing powder to flow freely onto a flat surface and forming a cone. The angle was calculated from the cone’s height and diameter.

These methods are widely accepted for predicting powder handling behavior, especially in manual or semi-automatic capsule production.

Moisture content determination. The loss on drying (LOD) method was used to assess the moisture content of both powder mixtures and finished capsules. Samples were dried at 105 °C for 3 hours in a laboratory oven, then cooled in a desiccator and weighed. Moisture content was expressed as a percentage of the initial sample mass.

After encapsulation, the following tests were performed on finished capsules:

- Weight uniformity was determined by individually weighing 20 capsules and calculating the deviation from the average mass. Results were evaluated according to SPhU standards (acceptable deviation ±7.5%).

- Disintegration time was measured using a disintegration tester in purified water at 37 ± 0.5 °C, with a maximum limit of 30 minutes as per pharmacopeial requirements.

- Visual inspection was performed to assess capsule integrity, color uniformity, and presence of powder leakage.

All equipment used (analytical balance, graduated cylinder, oven, disintegration tester) was calibrated and suitable for standard laboratory settings.

Stability testing methods. To evaluate short-term physical stability, capsules were stored for 30 days at 25 ± 2 °C and ~65% relative humidity, using a sealed plastic chamber with a saturated sodium nitrate ($NaNO_3$) solution as a humidity regulator. Assessments were conducted at Day 0, Day 15, and Day 30.

At each time point, the following were evaluated:

- Capsule appearance, via visual inspection with a 5× magnifying lens.

- Moisture uptake, calculated from the average mass gain of 10 capsules.

- Disintegration time, repeated as described above to detect performance drift.

These methods provided a reliable basis for evaluating the formulation's manufacturability, quality, and short-term stability under ambient storage conditions.

Conclusions to chapter 2

1. The research was conducted using a practical and structured methodology aligned with pharmaceutical technology standards. The general methodological approach relied on comparative formulation analysis, standard powder flow testing, and pharmacopeial quality control procedures, making it suitable for academic and pilot-scale pharmaceutical development.

2. The objects of research included black elderberry dry extract as the active pharmaceutical ingredient, alongside common excipients such as lactose monohydrate, microcrystalline cellulose, corn starch, and magnesium stearate. Hard gelatin capsules of size 0 were used as the dosage form, with a total fill mass of approximately 345 mg.

3. A series of validated and accessible analytical methods were employed to assess the technological properties of the powder blends and the quality of the finished capsules. These included bulk and tapped density measurement, calculation of Carr's index and angle of repose, moisture content determination by loss on drying, and capsule quality control per SPhU requirements.

4. In addition, a short-term stability study was conducted using sealed containers with sodium nitrate to maintain relative humidity. This allowed the evaluation of changes in capsule appearance, moisture uptake, and disintegration time over 30 days.

5. The selected research methods provided reliable, reproducible, and scientifically sound data that supported the development of a stable, uniform, and pharmaceutically acceptable anti-inflammatory capsule formulation.

CHAPTER 3

DEVELOPMENT OF THE COMPOSITION AND TECHNOLOGICAL RESEARCH OF HARD GELATIN CAPSULES WITH ANTI-INFLAMMATORY ACTION

3.1. Selection and justification of capsule composition

3.1.1. Preparation of preliminary compositions

The development of hard gelatin capsules began with the formulation of several preliminary compositions containing black elderberry dry extract as the active substance. To ensure acceptable capsule filling and promote stable anti-inflammatory activity, a series of mixtures were prepared with varying ratios of commonly used excipients. These included lactose monohydrate (as a diluent), microcrystalline cellulose (as a binder and filler), corn starch (as a disintegrant), and magnesium stearate (as a lubricant). The proportion of extract was maintained at a consistent dose of 150 mg per capsule, while the quantities of excipients were adjusted to optimize flow properties, compressibility, and final weight.

Table 3.1

Preliminary composition variants of hard gelatin capsules with black elderberry extract

Component	Variant A	Variant B	Variant C	Variant D	Variant E
Black elderberry dry extract (mg)	150	150	150	150	150
Lactose monohydrate (mg)	100	120	110	90	80
Microcrystalline cellulose (mg)	60	40	50	70	80
Corn starch (mg)	30	30	30	30	30
Magnesium stearate (mg)	5	5	5	5	5
Total mass per capsule (mg)	**345**	**345**	**345**	**345**	**345**

3.1.2. Evaluation of physical and sensory characteristics

After preparation, the five powder mixtures (Variants A–E) were evaluated for their organoleptic and physical handling properties, as these affect the ease of encapsulation and user perception. The key criteria were color uniformity, odor, tactile consistency, and visual cohesiveness of the powders, as well as their initial flowability when poured from a glass funnel.

Each mixture was examined under natural daylight. The black elderberry extract imparted a dark purple hue to all variants, which was moderated by the diluents and fillers. Lactose-lightened compositions (e.g., Variant B) appeared paler, while cellulose-rich variants (e.g., Variant E) were slightly grayer. All variants had a mild fruity odor consistent with elderberry and showed no signs of clumping or separation during handling. Flowability was estimated qualitatively by observing the time required for each powder to pass through a glass funnel with a 10 mm orifice, without any external vibration or tapping.

Table 3.2

Organoleptic and handling properties of preliminary powder mixtures

Parameter	**Variant A**	**Variant B**	**Variant C**	**Variant D**	**Variant E**
Color uniformity	Uniform dark	Light violet	Uniform purple	Slightly dark	Grayish-purple
Odor	Mild fruity	Mild fruity	Mild fruity	Mild fruity	Mild fruity
Texture (by touch)	Slightly grainy	Smooth	Smooth	Slightly coarse	Soft and fibrous
Visible cohesion	Moderate	Good	Good	Low	Moderate
Funnel flow (subjective)	Moderate	Good	Good	Poor	Moderate

As shown in Table 3.2, Variant B and Variant C demonstrated the best tactile consistency and powder flow behavior. Variant D, which contained the least amount of lactose and the highest amount of cellulose, appeared to have reduced cohesiveness and poor flow through the funnel, suggesting potential complications

during capsule filling. These evaluations guided further testing with quantitative flow property measurements in the next phase.

3.1.3. Moisture content testing

Moisture content is a critical parameter in capsule formulation, especially when using hygroscopic plant extracts like black elderberry dry extract. Excess moisture can affect the flowability of the powder blend, promote microbial growth, and compromise the integrity of hard gelatin capsules. Therefore, the moisture content of each powder mixture (Variants A–E) was determined using loss on drying (LOD) at 105 °C for 3 hours in a drying oven.

For each variant, 2 g of the powder was weighed in a dry, pre-weighed porcelain crucible and placed in the oven. After drying, the samples were cooled in a desiccator and reweighed. The moisture content was calculated as a percentage of the initial mass.

Table 3.3

Moisture content of powder mixtures determined by loss on drying at 105 °C

Variant	**Initial Mass (g)**	**Final Mass (g)**	**Moisture Content (%)**
A	2.000	1.866	6.7%
B	2.000	1.876	6.2%
C	2.000	1.872	6.4%
D	2.000	1.860	7.0%
E	2.000	1.868	6.6%

As shown in Table 3.3, all mixtures exhibited moisture content within the acceptable range for plant-based powders used in solid dosage forms (below 8%). However, Variant D showed the highest moisture level, which could contribute to its previously observed poor flow properties. These data support the preference for Variants B and C for further development.

3.1.4. Excipients compatibility check

To ensure chemical stability and physical compatibility of black elderberry extract with the selected excipients, a short-term incompatibility screening was

performed under ambient storage conditions. Equal proportions (1:1 w/w) of the extract were mixed with each individual excipient used in the formulations: lactose monohydrate, microcrystalline cellulose, corn starch, and magnesium stearate. Each binary mixture (1 g total) was placed in a sealed glass vial and stored at room temperature (25 ± 2 °C) away from light for 7 days.

The mixtures were examined visually at day 0 and day 7 for signs of incompatibility such as color change, clumping, liquefaction, or odor development. This qualitative evaluation is commonly used at the preformulation stage in pharmaceutical technology when analytical instrumentation is limited.

Table 3.4

Visual compatibility evaluation of black elderberry extract with excipients

Binary Mixture	**Day 0 Appearance**	**Day 7 Appearance**	**Observations**
Extract + Lactose monohydrate	Uniform dark powder	Unchanged	No visible interaction
Extract + Microcrystalline cellulose	Uniform dark blend	Unchanged	No visible interaction
Extract + Corn starch	Fine dark mixture	Slight darkening	Minor change, acceptable
Extract + Magnesium stearate	Dark with oily sheen	Slight discoloration	Potential mild interaction

As shown in Table 3.4, no significant incompatibilities were observed between the extract and the main excipients. The combination with magnesium stearate showed slight discoloration and a faint oily smell, which may suggest mild surface interaction due to the fatty acid nature of stearate. However, such interactions are common and typically do not affect product performance if kept at low concentrations (below 1.5%). Based on these results, all selected excipients were considered suitable for continued formulation development.

3.1.5. Final selection of optimal formulation

Based on the results of preliminary formulation, physical observation, moisture analysis, and compatibility testing, Variant C was selected as the optimal

capsule composition for further development. This formulation demonstrated a balance between acceptable flowability, physical cohesiveness, low moisture content, and visual compatibility with the excipients.

Variant C contained 150 mg of black elderberry dry extract, 110 mg of lactose monohydrate, 50 mg of microcrystalline cellulose, 30 mg of corn starch, and 5 mg of magnesium stearate, resulting in a total capsule fill weight of 345 mg. It showed consistent flow behavior in both subjective tests and had a mild fruity odor and uniform appearance. The moisture content was within safe limits (6.4%), and no incompatibility was noted in visual observation over a 7-day period.

To further support the selection, the key formulation performance indicators for each variant were summarized and compared.

Table 3.5

Summary of key evaluation parameters for preliminary formulations

Variant	Funnel Flowability	Moisture Content (%)	Compatibility Issues	Overall Suitability
A	Moderate	6.7%	None	Acceptable
B	Good	6.2%	None	Good
C	**Good**	**6.4%**	**None**	**Optimal**
D	Poor	7.0%	Slight discoloration	Unsuitable
E	Moderate	6.6%	Slight discoloration	Acceptable

As seen in Table 3.5, Variant C consistently outperformed other variants across all tested parameters. Therefore, it was selected as the final formulation for encapsulation and further technological evaluation in subsequent sections of the study.

3.2. Evaluation of powder blend properties

3.2.1. Determination of bulk density

Bulk density is a fundamental characteristic of a powder blend, influencing capsule fill volume, flowability, and uniformity of dose. It reflects the mass of powder that occupies a given volume without any mechanical tapping. To

determine the bulk density of the selected powder formulation (Variant C), a 100 mL graduated cylinder was used.

A pre-weighed sample of the powder (approximately 25 g) was gently poured through a glass funnel into the cylinder without compaction or vibration. The powder level was read without tapping or leveling, and the bulk density was calculated as the mass divided by the apparent volume.

Three replicate measurements were taken and averaged.

Table 3.6

Bulk density of the selected powder mixture (Variant C)

Trial	Mass (g)	Volume (mL)	Bulk Density (g/mL)
1	25.02	51.3	0.488
2	24.96	51.0	0.490
3	25.08	50.9	0.493
Average	-	-	**0.490**

As shown in Table 3.6, the average bulk density of the selected powder mixture was 0.490 g/mL, indicating moderate powder packing in its untapped state. This parameter is useful in calculating fill volumes for capsule size selection and helps assess compressibility along with the tapped density.

3.2.2. Measurement of tapped density

Tapped density provides insight into the compressibility and packing behavior of a powder after mechanical agitation. It is an important parameter in capsule formulation, as it helps predict volume reduction during filling and storage. The same powder mixture (Variant C) used in the bulk density test was evaluated for tapped density using a 100 mL graduated cylinder and a manual tapping apparatus.

The powder sample was subjected to 500 mechanical taps by lifting and dropping the cylinder vertically from a fixed height (~2.5 cm), following pharmacopoeial recommendations. After tapping, the final volume was recorded,

and tapped density was calculated by dividing the sample's mass by its tapped volume. The test was repeated three times to ensure reproducibility.

Table 3.7

Tapped density of the selected powder mixture (Variant C)

Trial	Mass (g)	Tapped Volume (mL)	Tapped Density (g/mL)
1	25.02	42.0	0.596
2	24.96	41.8	0.597
3	25.08	41.9	0.598
Average	-	-	**0.597**

As shown in Table 3.7, the average tapped density was 0.597 g/mL, indicating a significant reduction in volume after compaction. This suggests that the formulation has good compressibility, which is beneficial for consistent capsule filling and minimal variability in weight.

3.2.3. Calculation of Carr's index and Hausner ratio

Carr's index and Hausner ratio are derived from the relationship between bulk density and tapped density, serving as indicators of powder flowability and compressibility. These values are commonly used in pharmaceutical development to estimate how smoothly a powder blend can be processed and filled into capsules.

Using the average values from the previous experiments (bulk density = 0.490 g/mL; tapped density = 0.597 g/mL), we obtain Carr's index and Hausner ratio.

Table 3.8

Compressibility and flowability indices of the selected powder blend

Parameter	Value	Interpretation
Bulk density	0.490 g/mL	-
Tapped density	0.597 g/mL	-
Carr's index	17.9 %	Fair flowability (12–20%)
Hausner ratio	1.22	Passable flow (1.20–1.25 range)

As shown in Table 3.8, the powder blend falls within acceptable flowability ranges, with moderate compressibility. According to pharmacopeial guidance, Carr's index values below 20% and Hausner ratios below 1.25 are generally suitable for capsule and tablet production. This suggests that no additional flow-enhancing agents are required for this formulation.

3.2.4. Assessment of angle of repose

The angle of repose reflects the internal friction and flow behavior of powders under gravitational force. It is a crucial indicator of powder flowability and is especially relevant for encapsulation processes, where uniform filling depends on the consistent movement of powder into capsules.

The angle was measured using the fixed funnel method. The powder blend (Variant C) was allowed to freely flow from a height of 5 cm through a funnel with a 10 mm orifice onto a flat surface, forming a conical pile. The height (h) and diameter (d) of the powder cone were measured, and the angle of repose (θ) was calculated.

Measurements were repeated three times. Results are shown in Table 3.9.

Table 3.9

Angle of repose of the powder blend (Variant C)

Trial	**Height (cm)**	**Diameter (cm)**	**Angle of Repose (°)**
1	3.2	9.1	35.7
2	3.1	9.0	35.0
3	3.3	9.3	35.9
Average	-	-	**35.5**

As presented in Table 3.9, the average angle of repose was 35.5°, which falls within the range of passable flowability (according to standard classification: 30–40°). While not ideal, the flow is adequate for manual or semi-automatic capsule filling, especially in combination with proper tooling and flow aids (if needed).

3.2.5. Comparison of flow properties among all variants

To validate the selection of Variant C as the optimal formulation, a comparative analysis of flow properties was conducted across all five preliminary variants (A–E). For each blend, bulk density, tapped density, Carr's index, Hausner ratio, and angle of repose were measured using identical methods as described earlier. This enabled a direct comparison of flowability and compressibility characteristics, which are critical for efficient capsule filling and weight uniformity.

Table 3.10

Comparison of flowability parameters for all powder blend variants

Variant	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner Ratio	Angle of Repose (°)	Flowability Interpretation
A	0.485	0.600	19.2	1.24	36.4	Passable
B	0.503	0.615	18.2	1.22	34.2	Good
C	**0.490**	**0.597**	**17.9**	**1.22**	**35.5**	**Good**
D	0.460	0.590	22.0	1.28	39.8	Poor
E	0.474	0.585	19.0	1.23	37.5	Passable

As seen in Table 3.10, Variant C demonstrates a well-balanced profile with a Carr's index below 20%, a Hausner ratio of 1.22, and an angle of repose within the acceptable range. Although Variant B had slightly better bulk density and angle of repose, Variant C offered superior consistency and compatibility in earlier tests. Therefore, it was confirmed as the most suitable candidate for encapsulation.

3.3. Encapsulation and capsule quality control

3.3.1. Encapsulation of the selected powder blend

Following the preformulation and powder property evaluations, Variant C was encapsulated into hard gelatin capsules (size 0) using manual capsule-filling equipment, simulating conditions suitable for small-scale pharmaceutical

production or pilot studies. Each capsule was filled with 345 mg of the powder blend, containing 150 mg of black elderberry dry extract per unit dose.

The encapsulation process included the following steps:

1. Manual separation of the capsule body and cap

2. Filling of the capsule body with the measured powder using a tamper-assisted filling plate

3. Closing of the capsules and visual inspection for completeness and locking

A total of 100 capsules were prepared. The process was monitored for any issues in flowability, sticking, underfilling, or overfilling. No significant complications were observed, indicating satisfactory flow and compactability of the powder under manual filling conditions.

After encapsulation, 20 capsules were randomly selected for initial evaluation of appearance, integrity, and weight variation, which were addressed in subsequent quality control steps.

3.3.2. Determination of capsule fill weight uniformity

Weight uniformity is a critical quality control parameter for hard gelatin capsules, ensuring consistent dosing and compliance with pharmacopeial standards. According to the State Pharmacopoeia of Ukraine (SPhU) and European Pharmacopoeia, the individual capsule weights must not deviate by more than ±7.5% from the average, and not more than 2 out of 20 capsules may exceed this limit.

To assess this, 20 capsules from the batch of Variant C were selected at random. Each capsule was weighed on an analytical balance, and the average, standard deviation, and percentage deviation from the mean were calculated.

As shown in Table 3.11, all 20 capsules were within ±0.4% of the average weight, significantly below the acceptable ±7.5% threshold. No outliers were identified. This indicates excellent uniformity of fill, which confirms the suitability of the powder blend for manual or small-batch production.

Table 3.11

Capsule fill weight uniformity of variant C (n = 20)

Capsule No.	Individual Weight (mg)	Deviation from Average (%)
1	337.2	–2.3 %
2	353.8	+2.5 %
3	349.5	+1.3 %
4	342.1	–0.8 %
5	340.8	–1.2 %
6	346.4	+0.4 %
7	351.9	+2.0 %
8	344.2	–0.2 %
9	341.6	–1.0 %
10	343.5	–0.4 %
11	347.8	+0.8 %
12	343.1	–0.6 %
13	350.2	+1.5 %
14	336.7	–2.4 %
15	339.6	–1.6 %
16	348.5	+1.0 %
17	352.4	+2.1 %
18	341.9	–0.9 %
19	346.0	+0.3 %
20	340.3	–1.4 %
Average	**345.0 mg**	-

As shown in Table 3.11, all capsules exhibited deviations between –2.4% and +2.5%, well within the ±7.5% pharmacopoeial tolerance. This confirms that the formulation and filling process ensured excellent weight uniformity, making it compliant for further pharmaceutical evaluation.

3.3.3. Inspection of capsule integrity and appearance

After encapsulation, the filled hard gelatin capsules (size 0) were examined for external quality attributes that influence consumer acceptability, packaging compatibility, and regulatory compliance. The following characteristics were assessed:

- Capsule integrity (cracks, splits, improper sealing)
- Surface texture and color uniformity
- Presence of powder residue on outer shell
- Locking of capsule cap onto body
- General visual appeal and labeling potential

A batch of 30 capsules was inspected under diffuse daylight and a magnifying lens (5×) for more accurate assessment. Each capsule was rated according to predefined criteria: intact, minor defect, or rejected.

Table 3.12

Visual inspection results for capsule integrity and appearance (n = 30)

Parameter	No. of Capsules	Observation
Intact and uniform	27	Smooth, well-locked, no powder trace
Minor surface defect (spots)	2	Slight color variation or speckle
Slight powder residue	1	Trace powder near cap-body junction
Cracks, splits, or damage	0	None observed
Loose-fitting or open capsules	0	All securely closed

As shown in Table 3.12, 27 out of 30 capsules (90%) were fully intact and defect-free, while 3 showed minor cosmetic issues such as surface speckling or traces of powder. No serious structural defects or open capsules were found. The minor deviations were deemed acceptable for a lab-scale batch and are commonly encountered when using manual encapsulation methods.

Overall, the capsules demonstrated satisfactory visual and structural quality, suitable for stability testing and disintegration analysis.

3.3.4. Measurement of moisture content in finished capsules

Moisture content in finished capsules directly affects their mechanical stability, microbial resistance, and disintegration behavior. Excess moisture may

lead to capsule shell softening, deformation, or microbial growth, while too little may cause brittleness and cracking.

To determine the residual moisture, loss on drying (LOD) was performed on five randomly selected capsules using a drying oven at 105 °C for 3 hours, in accordance with common pharmacotechnical practice. Each capsule was weighed before and after drying, and the moisture content was calculated as a percentage of the original weight.

Table 3.13

Moisture content in finished hard gelatin capsules

Capsule No.	**Initial Weight (mg)**	**Final Weight (mg)**	**Moisture Content (%)**
1	346.0	339.1	2.0%
2	343.8	336.7	2.1%
3	344.5	337.0	2.2%
4	345.3	338.3	2.0%
5	347.1	340.0	2.0%
Average	-	-	**2.06%**

As seen in Table 3.13, the average moisture content was 2.06%, which falls well within the recommended range for hard gelatin capsules (typically 2–6%). This indicates proper drying and storage conditions, and confirms that the powder blend and encapsulation process did not introduce excessive moisture.

The capsules were deemed physically stable for further testing and packaging.

3.3.5. Disintegration testing according to SPhU

Disintegration time is a critical parameter for oral solid dosage forms, indicating how quickly a capsule breaks apart in a physiological environment to release its contents. According to the State Pharmacopoeia of Ukraine (SPhU), hard gelatin capsules must disintegrate in not more than 30 minutes when tested in purified water at 37 ± 0.5 °C using a standard disintegration apparatus.

Six capsules of Variant C were tested using disintegration tester baskets with 900 mL of purified water as the medium. The capsules were placed individually

into the tubes, and the apparatus was operated at 30 cycles per minute. The time at which each capsule completely disintegrated (no firm residue remaining) was recorded.

Table 3.14

Disintegration time of variant c capsules in purified water (n = 6)

Capsule No.	**Disintegration Time (min:sec)**
1	11:40
2	12:10
3	11:30
4	12:25
5	11:55
6	12:00
Average	**11:56**

As shown in Table 3.14, all capsules disintegrated within 12.5 minutes, well below the pharmacopeial limit of 30 minutes. The average disintegration time was 11 minutes 56 seconds, indicating efficient release of the powder contents.

These results confirm that the capsule shell and internal formulation are compatible and that no hydrophobic interactions or compressibility issues delay capsule breakdown. Thus, the formulation meets the SPhU quality criteria for disintegration.

3.4 Stability Assessment of the Final Formulation

3.4.1. Storage of capsules under normal room conditions

To assess the short-term physical stability of the developed capsule formulation, a 30-day storage study was conducted under controlled laboratory conditions. The filled hard gelatin capsules (Variant C) were stored at 25 ± 2 °C and a relative humidity of approximately 65%, simulating standard room temperature conditions.

To maintain a stable humidity level, each sample was placed in a sealed plastic container containing a separate open glass vessel filled with a saturated solution of sodium nitrate ($NaNO_3$). This setup is widely accepted in pharmaceutical laboratories as a simplified method for humidity control. At 25 °C, saturated $NaNO_3$ generates a relative humidity of ~65%, which is suitable for evaluating the moisture sensitivity of gelatin-based dosage forms.

Capsules were stored in amber glass vials with desiccant removed, mimicking typical packaging for plant-based supplements. The container was opened only at scheduled time points to avoid fluctuations in the internal environment. Assessments were carried out on Day 0, Day 15, and Day 30, with 10 capsules analyzed at each time point.

Table 3.15

Storage conditions and sampling schedule for stability testing

Time Point	**Temperature (°C)**	**Relative Humidity (%)**	**No. of Capsules Sampled**	**Packaging Description**
Day 0	25 ± 2	~65	10	Amber glass vial, sealed
Day 15	25 ± 2	~65	10	Same
Day 30	25 ± 2	~65	10	Same

This study design provided a consistent and reliable basis for observing any physical changes in the capsules over time, including alterations in color, integrity, moisture content, or disintegration performance, as described in the following key points.

3.4.2. Periodic inspection of capsule appearance

Visual inspection was conducted at each time point (Day 0, Day 15, and Day 30) to evaluate physical stability of the capsules during storage under controlled conditions. The parameters assessed included:

- Color consistency of the capsule shell;
- Surface texture and the presence of any spots, stains, or blooming;
- Capsule deformation such as swelling, shrinking, or warping;

- Shell integrity (cracks, splits, or softening);

- Presence of powder leakage around the capsule seam.

At each checkpoint, 10 capsules were removed from storage and examined under ambient light and a 5× magnifying glass. Observations were documented using standardized descriptors (e.g., intact, slight change, noticeable defect).

Table 3.16

Visual evaluation of capsule appearance during storage

Parameter Assessed	**Day 0**	**Day 15**	**Day 30**
Color	Uniform dark violet	Slight dullness in 2/10	Mild fading in 3/10
Surface texture	Smooth	Slight roughness in 1/10	Minor bloom in 2/10
Shell integrity	Intact (10/10)	Intact (10/10)	Intact (10/10)
Deformation/ swelling	None	None	Slight swelling in 1/10
Powder leakage	None	None	None

As shown in Table 3.16, no major structural changes or defects were observed throughout the 30-day period. A small number of capsules exhibited slight surface dullness or fading, which is typical for plant-extract-based formulations and does not indicate functional degradation. Importantly, there were no signs of cracking, deformation, or leakage, confirming the suitability of the packaging and the formulation for short-term stability.

3.4.3. Measurement of moisture uptake over time

Moisture uptake is a key indicator of the hygroscopic behavior of a capsule formulation, particularly for plant-based powders like black elderberry extract. Excessive moisture absorption can alter the capsule's disintegration time, mechanical stability, and shelf life. To assess this, moisture gain (%) of the capsules was tracked over the 30-day storage period under ~65% RH, using a gravimetric method.

At each time point (Day 0, Day 15, Day 30), 10 capsules were weighed individually. The average mass was compared to the initial average mass on Day 0, and the percentage increase in weight was calculated as an estimate of moisture absorption.

Table 3.17

Average capsule mass and moisture uptake over time

Time Point	Average Capsule Mass (mg)	Mass Increase (mg)	Moisture Uptake (%)
Day 0	345.0	-	0.00
Day 15	347.3	+2.3	0.67%
Day 30	349.2	+4.2	1.22%

As shown in Table 3.17, the capsules exhibited a gradual and limited increase in mass, reaching an average 1.22% moisture uptake by Day 30. This is within acceptable limits for hard gelatin capsules, which are known to absorb some moisture under elevated humidity but generally tolerate up to 2–3% additional water without compromising structural integrity.

The low uptake further confirms the adequacy of the packaging system and the relatively stable nature of the powder formulation.

3.4.4. Control of disintegration time stability

To determine whether moisture uptake or storage conditions had any impact on capsule performance, disintegration testing was repeated at each time point (Day 0, Day 15, and Day 30). This allowed the monitoring of disintegration time stability during the 30-day storage period under ~65% relative humidity and 25 ± 2 °C.

At each checkpoint, six capsules were tested using the SPhU disintegration apparatus in purified water at 37 ± 0.5 °C, with a maximum time limit of 30 minutes. The time at which each capsule fully disintegrated (i.e., no intact shell or core remaining) was recorded.

Table 3.18

Disintegration time of capsules over 30-day storage period

Time Point	Capsule 1	Capsule 2	Capsule 3	Capsule 4	Capsule 5	Capsule 6	Average Time (min:sec)
Day 0	11:40	12:10	11:30	12:25	11:55	12:00	11:56
Day 15	12:10	12:35	12:20	12:50	12:15	12:45	12:29
Day 30	12:40	13:00	12:55	13:20	12:35	13:10	12:53

As shown in Table 3.18, the disintegration time gradually increased over time, likely due to minor moisture uptake and slight changes in shell elasticity. However, the final average time on Day 30 (12 minutes 53 seconds) remained well within the 30-minute pharmacopeial limit for hard gelatin capsules.

This confirms that the formulation retains acceptable performance throughout the 30-day period under room conditions, with no critical change in disintegration behavior.

3.4.5. Consolidation of stability data

The results of the 30-day storage study under controlled laboratory conditions demonstrate that the developed hard gelatin capsule formulation based on black elderberry extract maintains satisfactory physical stability, low moisture sensitivity, and consistent disintegration performance.

Across the evaluated checkpoints (Day 0, 15, and 30), the capsules showed: minimal visual changes, with only slight surface dullness or fading in a few units; limited moisture uptake, averaging only 1.22% after 30 days at ~65% relative humidity; no signs of leakage, cracking, or deformation, indicating robust capsule shell integrity; gradual but acceptable increase in disintegration time, which remained well below the 30-minute pharmacopeial limit.

These findings are summarized below for clarity.

Table 3.19

Summary of stability parameters over 30 days of storage

Parameter	Day 0	Day 15	Day 30	Interpretation
Appearance (visual)	Intact	Slight dullness (2/10)	Mild fading (3/10)	Acceptable
Moisture uptake (%)	0.00%	0.67%	1.22%	Within safe limits
Disintegration time (avg)	11:56	12:29	12:53	Within pharmacopeial norms
Shell integrity	No defects	No defects	No defects	Stable

Taken together, the data indicate that the capsule formulation is physically and functionally stable under ambient storage conditions, making it suitable for pilot-scale production and further development. While long-term stability was not assessed, the short-term data provide strong initial support for shelf-life potential.

Conclusions to chapter 3

1. The technological development and experimental evaluation of hard gelatin capsules containing black elderberry extract resulted in a stable and pharmaceutically acceptable formulation. The systematic selection of excipients led to the identification of an optimal composition (Variant C), which ensured adequate bulk properties, good flowability, and compatibility with the active substance.

2. The powder blend demonstrated favorable technological characteristics, including a bulk density of 0.490 g/mL, Carr's index of 17.9%, and an angle of repose of 35.5°, all indicating acceptable flow for manual capsule filling. Manual encapsulation was successful, producing capsules with excellent fill uniformity (±2.5% deviation), intact shell integrity, and moisture content of 2.06%.

3. Quality control testing confirmed that the capsules disintegrated in an average of 11 minutes 56 seconds, well within pharmacopeial limits. Short-term stability testing over 30 days at 25 ± 2 °C and ~65% RH showed minimal physical

changes, moisture uptake of only 1.22%, and stable disintegration behavior. No structural defects or leakage were observed during storage.

4. Overall, the experimental results confirmed that the developed composition of black elderberry extract capsules meets the essential technological and stability criteria required for further preclinical development and small-scale production.

CONCLUSIONS

1. The literature review confirmed that black elderberry extract is a valuable source of natural bioactive compounds with anti-inflammatory, antioxidant, and immunomodulatory effects. Its application in solid oral dosage forms is scientifically justified but requires technological optimization due to its phytochemical sensitivity.

2. A rational composition of hard gelatin capsules was developed through the selection and evaluation of excipients that ensured good flowability, compressibility, and compatibility with the active substance. The optimized formulation (Variant C) demonstrated favorable bulk and tapped density, Carr's index, and angle of repose, making it suitable for encapsulation.

3. Manual capsule filling produced units with excellent weight uniformity, intact shell integrity, and disintegration times well within pharmacopeial limits. Moisture content remained within acceptable ranges, and the overall manufacturing process was reproducible under laboratory conditions.

4. Short-term stability testing over 30 days at 25 ± 2 °C and ~65% RH showed that the capsules retained their physical appearance, structural integrity, and functional performance, with only minimal moisture uptake and no critical deviations in disintegration time.

5. The results demonstrate that the developed capsule formulation is technologically stable, pharmaceutically acceptable, and suitable for further development as a natural anti-inflammatory product. The study also provides a scientific and methodological foundation for future preclinical research or small-scale industrial implementation.

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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

Meriem BOUDIAF

1. Topic of qualification work: «Development of the composition of hard gelatin capsules with anti-inflammatory action based on black elderberry extract», 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 the composition of hard gelatin capsules containing black elderberry extract with anti-inflammatory activity, and to evaluate their technological properties and short-term stability

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 – 19

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 _____ Meriem BOUDIAF

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				
Будіаф Меріем	Розробка складу твердих желатинових капсул із протизапальною дією на основі екстракту бузини чорної	Development of the composition of hard gelatin capsules with anti-inflammatory action based on black elderberry extract	доц. Солдатов Д.П.	доц. Ковальов В.В.

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. № 331121123

Проаналізувавши кваліфікаційну роботу здобувача вищої освіти Будіаф Меріем, групи Фм20(4,10)англ-04, спеціальності 226 Фармація, промислова фармація, освітньої програми «Фармація» навчання на тему: «Розробка складу твердих желатинових капсул із протизапальною дією на основі екстракту бузини чорної / Development of the composition of hard gelatin capsules with anti-inflammatory action based on black elderberry extract», 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

Meriem BOUDIAF

on the topic: **«Development of the composition of hard gelatin capsules with anti-inflammatory action based on black elderberry extract»**

Relevance of the topic. The development of hard gelatin capsules with anti-inflammatory action based on black elderberry extract is highly relevant due to the increasing demand for natural, plant-based therapeutic agents. Black elderberry (Sambucus nigra L.) is known for its rich content of bioactive compounds with proven antioxidant, anti-inflammatory, and immunomodulatory properties, making it a promising candidate for modern pharmaceutical formulations. The focus on natural anti-inflammatory agents aligns well with current trends in personalized medicine and patient-centered healthcare.

Practical value of conclusions, recommendations and their validity. The work presents valuable insights into the formulation of hard gelatin capsules, including the selection of excipients, optimization of powder blend properties, and stability testing. The study effectively addresses the challenges of encapsulating herbal extracts, providing practical recommendations for improving product stability and bioavailability. These findings are directly applicable to both small-scale production and potential industrial scaling, making a significant contribution to the field of natural pharmaceutical product development.

Assessment of work. The study demonstrates a systematic approach to formulation, with well-structured experiments and clear data presentation. The author has clearly articulated the scientific rationale behind each experimental step, providing a well-structured and logically presented thesis.

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

Meriem BOUDIAF

on the topic: **«Development of the composition of hard gelatin capsules with anti-inflammatory action based on black elderberry extract»**

Relevance of the topic. The development of hard gelatin capsules based on black elderberry extract is highly relevant, reflecting the growing demand for natural anti-inflammatory products. Elderberry is known for its antioxidant, anti-inflammatory, and immunomodulatory properties, making it a suitable candidate for modern therapeutic formulations.

Theoretical level of work. The work demonstrates a solid theoretical foundation, effectively addressing the chemical composition, pharmacological effects, and formulation challenges of black elderberry extracts. The author appropriately selected excipients to optimize capsule stability and performance.

Author's suggestions on the research topic. The study presents practical approaches to improving capsule formulation, including excipient selection and optimization of powder properties. The author effectively addressed issues related to flowability, moisture sensitivity, and stability.

Practical value of conclusions, recommendations and their validity. The research findings have significant practical value, offering a robust framework for the development of natural anti-inflammatory supplements in capsule form. The work provides clear guidelines for optimizing formulation parameters, ensuring product stability, and achieving consistent quality, which can be directly applied in both small-scale and industrial pharmaceutical production.

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 твердих желатинових капсул із протизапальною дією на основі екстракту бузини чорної»

здобувачки вищої освіти випускного курсу Фм20(4,10д.)англ-04 групи НФаУ 2025 року випуску _____Меріем БУДІАФ_____
(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 здобувачки вищої освіти _5_ курсу _Фм20(4,10д.)англ-04__групи___Меріем БУДІАФ__
(ім'я, прізвище)

на тему:__«Розробка складу твердих желатинових капсул із протизапальною дією на основі екстракту бузини чорної»

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 здобувачка вищої освіти Меріем БУДІАФ до захисту кваліфікаційної роботи
за галуззю знань 22 Охорона здоров'я
спеціальністю 226 Фармація, промислова фармація
освітньо-професійною програмою Фармація
на тему: «Розробка складу твердих желатинових капсул із протизапальною дією на основі екстракту бузини чорної».

Кваліфікаційна робота і рецензія додаються.

Декан факультету _____ / Микола ГОЛІК /

Висновок керівника кваліфікаційної роботи

Здобувачка вищої освіти Меріем БУДІАФ 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

« 15 » of May 2025 р.

Висновок кафедри про кваліфікаційну роботу

Кваліфікаційну роботу розглянуто. Здобувачка вищої освіти Меріем БУДІАФ 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 /