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QUALIFICATION WORK

on the topic: **«DEVELOPMENT OF THE COMPOSITION OF VAGINAL SUPPOSITORIES WITH REGENERATING ACTION»**

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Kharkiv – 2025

ANNOTATION

This thesis is devoted to the development of vaginal suppositories with regenerating action based on panthenol and calendula extract. The formulation was optimized through experimental modeling and evaluated by standard technological methods. The optimal composition was identified based on disintegration time, pH, softening behavior, and mechanical resistance. The proposed suppositories demonstrate satisfactory performance and compatibility for vaginal use.

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 54 pages, contains 16 tables, 37 references.

Key words: vaginal suppositories, panthenol, calendula extract, regeneration, pharmaceutical technology.

АНОТАЦІЯ

Дипломна робота присвячена розробці вагінальних супозиторіїв із регенеруючою дією на основі пантенолу та екстракту календули. Оптимальний склад було підібрано шляхом експериментального моделювання та оцінено за допомогою стандартних технологічних методів. За результатами досліджень встановлено склад, що забезпечує належні показники розпаду, pH, розм’якшення та механічної стійкості. Запропоновані супозиторії є перспективними для місцевого застосування.

Робота складається з таких частин: вступ, огляд літератури, вибір методів дослідження, експериментальна частина, загальні висновки, список використаних літературних джерел, загальний обсяг 54 сторінок, містить 16 таблиць, 37 посилань.

Ключові слова: вагінальні супозиторії, пантенол, екстракт календули, регенерація, фармацевтична технологія.

CONTENT

LIST OF ABBREVIATIONS

API – active pharmaceutical ingredient

BAS – biologically active substance

PEG – polyethylene glycol

Ph.Eur. – European Pharmacopoeia

PRP – platelet-rich plasma

rhGF – recombinant human growth factor

SD – standard deviation

SPhU – State Pharmacopoeia of Ukraine

USP – United States Pharmacopeia

INTRODUCTION

The relevance of the topic

The development of safe and effective vaginal dosage forms remains a priority in pharmaceutical technology due to the increasing demand for local treatment options that promote mucosal regeneration without systemic side effects. Conditions such as microtraumas, inflammatory lesions, and epithelial atrophy require formulations that combine healing, anti-inflammatory, and protective effects. Among these, vaginal suppositories offer targeted delivery, ease of administration, and prolonged local action.

The use of natural and well-tolerated agents such as panthenol and calendula extract is especially relevant given their proven regenerative properties and favorable safety profiles. In this context, the search for an optimal composition that ensures technological stability, patient acceptability, and mucosal compatibility is both scientifically justified and practically important.

The purpose of the study

To develop and experimentally substantiate the composition of vaginal suppositories with regenerating action based on panthenol and calendula extract.

Research tasks are

1. To review the scientific and pharmaceutical literature on vaginal suppository bases and regenerating agents.

2. To select active substances and excipients based on compatibility, safety, and functionality.

3. To prepare a series of suppository prototypes with varying compositions.

4. To evaluate the physicotechnological properties of the developed samples.

5. To identify the optimal composition based on performance indicators.

The object of research

Suppository dosage forms containing regenerating agents for intravaginal use.

The subject of the study

Pharmaceutical-technological characteristics of vaginal suppositories containing panthenol and calendula extract.

Research methods

Experimental modeling of suppository formulations, organoleptic and visual assessment, pH measurement, disintegration and softening time testing, manual resistance evaluation, and standard pharmacopoeial procedures for mass uniformity.

Practical significance of the obtained results

The results of the study can be used in the development of therapeutic vaginal suppositories aimed at mucosal regeneration. The proposed composition and testing methodology are suitable for small-scale production and further clinical investigation. The findings contribute to the field of pharmaceutical technology for personalized and plant-based therapy.

Elements of scientific research

The scientific novelty of the work lies in the rational combination of panthenol and calendula extract within a hydrophilic PEG base to achieve mucosal regeneration, and in the technological justification of their concentrations based on comparative evaluation.

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 54 pages, contains 16 tables, 37 references.

CHAPTER 1
PHARMACEUTICAL DEVELOPMENT OF VAGINAL SUPPOSITORIES WITH REGENERATING PROPERTIES

1.1. Anatomy and physiology of the vaginal environment

The vaginal wall is composed of three primary layers: the mucosa, muscularis, and adventitia. The innermost layer, the mucosa, consists of a non-keratinized stratified squamous epithelium and an underlying lamina propria. This epithelial layer is rich in glycogen, which plays a crucial role in maintaining the acidic environment of the vagina. The lamina propria is a connective tissue layer that provides structural support and houses blood vessels and immune cells. The middle layer, the muscularis, is composed of smooth muscle fibers arranged in circular and longitudinal patterns, allowing for the flexibility and contractility of the vaginal canal. The outermost layer, the adventitia, is a connective tissue layer that anchors the vagina to surrounding pelvic structures [1].

The vaginal mucosa serves multiple essential functions. Firstly, it acts as a protective barrier against mechanical injury and microbial invasion. The stratified squamous epithelium is designed to withstand friction and minor trauma, while the lamina propria's immune components help in identifying and responding to pathogens. Secondly, the mucosa contributes to lubrication. Although the vaginal epithelium lacks glands, transudation from the lamina propria and secretions from adjacent glands ensure adequate moisture, facilitating sexual intercourse and maintaining mucosal health. Lastly, the mucosa plays a role in immune defense. It contains both innate and adaptive immune cells, including dendritic cells and lymphocytes, which detect and respond to pathogens, maintaining the delicate balance of the vaginal microbiota [2].

The vaginal environment maintains a slightly acidic pH, typically ranging from 3.8 to 4.5, which is crucial for inhibiting the growth of pathogenic microorganisms. This acidity is primarily attributed to the metabolic activities of Lactobacillus species, which dominate the healthy vaginal microbiota. These

bacteria ferment glycogen, derived from desquamated epithelial cells, into lactic acid, thereby sustaining the acidic pH. Additionally, Lactobacilli produce hydrogen peroxide and bacteriocins, further contributing to the antimicrobial defense of the vagina. The maintenance of this acidic environment is vital for protecting against infections and preserving vaginal health [3].

The vaginal microbiota is predominantly composed of Lactobacillus species, including L. crispatus, L. iners, L. jensenii, and L. gasseri. These bacteria play a pivotal role in maintaining vaginal health by producing lactic acid, which lowers the pH and inhibits the growth of harmful pathogens. They also produce antimicrobial substances like hydrogen peroxide and bacteriocins, and compete with pathogens for adhesion sites on the vaginal epithelium. Disruptions in this microbial balance, known as dysbiosis, can lead to conditions such as bacterial vaginosis, increased susceptibility to sexually transmitted infections, and adverse pregnancy outcomes [4].

The vagina possesses intrinsic self-cleaning mechanisms that protect against infections and injuries. Vaginal secretions, composed of cervical mucus, transudate from the vaginal walls, and exfoliated epithelial cells, help to flush out pathogens and maintain moisture. The acidic pH, maintained by Lactobacilli, inhibits the growth of pathogenic organisms. Furthermore, the vaginal epithelium acts as a physical barrier, and immune cells present in the mucosa provide immunological defense. These combined mechanisms ensure the maintenance of a healthy vaginal environment [5].

Estrogen plays a pivotal role in maintaining the structural and functional integrity of the vaginal mucosa. It promotes the proliferation of the stratified squamous epithelium, enhances vascularization, and stimulates the production of glycogen, which is metabolized by Lactobacillus species to maintain an acidic vaginal pH. This acidic environment is crucial for preventing pathogenic infections. During menopause, the decline in estrogen levels leads to thinning of the vaginal epithelium, decreased elasticity, reduced blood flow, and diminished glycogen content. These changes result in a higher vaginal pH, making the

environment more susceptible to infections and mechanical injuries. This condition, known as genitourinary syndrome of menopause (GSM), affects a significant proportion of postmenopausal women and is characterized by symptoms such as dryness, irritation, and dyspareunia [6].

The vaginal mucosa is susceptible to various infections, including bacterial vaginosis, candidiasis, and sexually transmitted infections, which can disrupt the normal flora and compromise mucosal integrity. Antibiotic treatments, while targeting pathogenic organisms, can also diminish beneficial Lactobacillus populations, leading to dysbiosis and increased vulnerability to opportunistic infections. Furthermore, certain medications, such as chemotherapy agents and hormonal therapies, can adversely affect the vaginal mucosa. For instance, anti-estrogenic drugs used in breast cancer treatment can induce hypoestrogenism, leading to atrophic changes in the vaginal epithelium.

Mechanical trauma to the vaginal mucosa can result from various sources, including sexual activity, childbirth, and the use of certain hygiene products. Repeated or forceful intercourse can cause microabrasions, especially in a hypoestrogenic state where the mucosa is thinner and less lubricated. Childbirth can lead to stretching and tearing of the vaginal tissues, necessitating adequate healing to restore mucosal integrity. Additionally, the use of fragranced soaps, douches, and tight-fitting clothing can irritate the vaginal mucosa, leading to inflammation and increased susceptibility to infections. Lifestyle factors such as smoking have also been associated with decreased estrogen levels and impaired mucosal healing [7].

Aging is associated with several changes that affect the vaginal mucosa. Beyond the decline in estrogen levels, there is a reduction in collagen and elastin fibers, leading to decreased elasticity and resilience of the vaginal walls. The vascular supply to the mucosa diminishes, impairing nutrient delivery and waste removal, which are essential for tissue health. These changes contribute to the thinning and fragility of the vaginal epithelium, making it more prone to injuries and infections. Pathological conditions such as lichen sclerosus and lichen planus

can also lead to chronic inflammation and scarring of the vaginal mucosa, further compromising its integrity [8].

1.2. Overview of vaginal dosage forms

Vaginal suppositories are classified based on their therapeutic purposes, including:

- Antimicrobial Suppositories. Designed to treat infections such as bacterial vaginosis and candidiasis. These often contain agents like clotrimazole or metronidazole. For instance, products like Biflay are used for their antimicrobial properties.
- Hormonal Suppositories. Used for hormone replacement therapy, particularly in postmenopausal women experiencing vaginal atrophy. These suppositories typically contain estrogen or progesterone.
- Probiotic Suppositories. Aim to restore and maintain healthy vaginal flora by introducing beneficial bacteria such as Lactobacillus species. Products like Vitanica V-Probiotics are examples in this category.
- Moisturizing Suppositories. Provide relief from vaginal dryness by delivering hydrating agents directly to the vaginal mucosa. These are particularly beneficial for women experiencing dryness due to menopause or other factors.
- Regenerative Suppositories. Contain ingredients that promote healing and regeneration of the vaginal mucosa, such as hyaluronic acid or herbal extracts like calendula. An example is Revitaxa, which is used to alleviate symptoms of vaginal atrophy [9, 10].

Vaginal suppositories come in various physical forms, including:

- Solid Suppositories. Typically torpedo-shaped and made from bases like cocoa butter or polyethylene glycol, designed to melt at body temperature.
- Ovules. Egg-shaped suppositories that are easy to insert and dissolve quickly, often used for delivering antifungal or antibacterial agents.

- Pessaries. While traditionally mechanical devices to support pelvic organs, some pessaries are medicated and release drugs over time for conditions like bacterial vaginosis [11, 12].

Vaginal suppositories offer several notable advantages as a drug delivery system:

- Targeted Local Action. By delivering medication directly to the vaginal mucosa, suppositories ensure high local drug concentrations, enhancing therapeutic efficacy while minimizing systemic exposure and associated side effects.
- Bypassing First-Pass Metabolism. Unlike oral medications, vaginal suppositories circumvent the hepatic first-pass effect, potentially leading to improved bioavailability of certain drugs.
- Rapid Onset of Action. The rich vascularization of the vaginal mucosa facilitates swift absorption of active pharmaceutical ingredients, resulting in a quicker therapeutic response.
- Reduced Gastrointestinal Side Effects. As the medication is administered locally, there is a decreased likelihood of gastrointestinal disturbances commonly associated with systemic drug delivery.
- Patient Convenience and Compliance. Vaginal suppositories can be self-administered, offering a non-invasive and discreet option that may enhance patient adherence to treatment regimens [13, 14].

Despite their benefits, vaginal suppositories also present certain limitations:

- Potential for Leakage and Messiness. Some suppository bases may melt at body temperature, leading to leakage that can cause discomfort and inconvenience for the patient.
- Variable Absorption. Factors such as vaginal pH, mucosal secretions, and the presence of infections can influence drug absorption, potentially leading to inconsistent therapeutic outcomes.

- Patient Acceptance. Cultural beliefs, personal preferences, and discomfort with vaginal administration may affect patient willingness to use suppositories, impacting treatment adherence.
- Stability Concerns. Certain active ingredients may be unstable in suppository formulations, necessitating careful selection of excipients and storage conditions to maintain efficacy.
- Limited Drug Load Capacity. The volume constraints of suppositories may restrict the amount of active ingredient that can be delivered, posing challenges for medications requiring higher doses [15].

While vaginal suppositories provide a valuable route for localized drug delivery with distinct advantages, they also entail specific challenges that must be addressed through thoughtful formulation and patient education.

Vaginal suppositories must adhere to stringent physical and chemical quality standards to ensure safety, efficacy, and patient acceptability. Key parameters include:

- Melting Point. Ideally, suppositories should melt at or just below body temperature (approximately 37°C) to facilitate drug release upon administration. Studies have shown that formulations with melting points ranging from 40 to 60°C are effective, ensuring stability during storage and rapid melting upon insertion.
- Disintegration Time. Suppositories should disintegrate within a specific timeframe to release the active pharmaceutical ingredient (API) effectively. According to the United States Pharmacopeia (USP), a suppository passes the disintegration test if all particles pass through a #10 mesh screen within the specified time, typically under 30 minutes.
- Content Uniformity. Ensuring uniform distribution of the API throughout the suppository is crucial for consistent dosing. Analytical methods such as High-Performance Liquid Chromatography (HPLC) or UV spectrophotometry are employed to assess content uniformity, aiming for each unit to contain 85% to 115% of the labeled amount [16, 17].

The choice of suppository base significantly influences drug release profiles, stability, and patient comfort. Common bases include:

- Polyethylene Glycol (PEG) Bases. These hydrophilic bases dissolve in bodily fluids, providing a controlled release of the API. Studies have demonstrated that PEG-based suppositories disintegrate within approximately 5.5 minutes, offering rapid onset of action.
- Lipid-Based Bases (e.g., Cocoa Butter). These bases melt at body temperature, releasing the API quickly. Research indicates that cocoa butter suppositories melt within 4.33 minutes post-insertion, with no leakage observed for up to 10 minutes, ensuring effective drug delivery [18, 19].

The selection between hydrophilic and lipophilic bases depends on the solubility of the API and the desired release profile. Formulators must consider these factors to optimize therapeutic outcomes.

Enhancing the residence time of vaginal suppositories can improve therapeutic efficacy. Incorporating mucoadhesive polymers into formulations allows suppositories to adhere to the vaginal mucosa, prolonging drug release. Key considerations include:

- Polymer Selection. Polymers such as chitosan, carbopol, and hydroxypropyl methylcellulose (HPMC) are commonly used for their mucoadhesive properties. These polymers interact with mucin glycoproteins, forming hydrogen bonds that facilitate adhesion.
- Swelling Behavior. The swelling capacity of the polymer affects mucoadhesion and drug release. For instance, formulations containing guar gum or xanthan gum exhibit gradual swelling, ensuring sustained drug release over extended periods.
- Drug Release Kinetics. Mucoadhesive formulations often follow zero-order or Higuchi release kinetics, providing a consistent release rate, which is beneficial for maintaining therapeutic drug levels [20, 21].

Incorporating mucoadhesive properties into vaginal suppositories is a strategic approach to enhance drug bioavailability and patient compliance.

In summary, the development of vaginal suppositories requires meticulous consideration of physical and chemical quality parameters, base selection, and mucoadhesive properties to ensure effective and patient-friendly drug delivery systems.

1.3. Mechanisms of vaginal mucosa regeneration

Estrogen plays a pivotal role in maintaining the structural and functional integrity of the vaginal epithelium. It stimulates the proliferation and differentiation of epithelial cells, ensuring the regeneration and maintenance of the mucosal barrier. A study by Lee et al. (2021) demonstrated that estrogen replacement therapy in ovariectomized rats restored the expression of epithelial progenitor cell markers, such as CD44 and estrogen receptor alpha (ERα), indicating that estrogen regulates the activity of these progenitor cells [22].

Recent research has identified specific populations of epithelial progenitor cells within the vaginal mucosa. Ali et al. (2020) utilized cell lineage tracing to reveal that CD271+Axin2+ basal cells act as vaginal stem cells responsible for epithelial homeostasis and regeneration. These cells are responsive to hormonal signals and play a crucial role in maintaining the integrity of the vaginal epithelium [23].

The molecular mechanisms by which estrogen influences vaginal epithelial progenitor cells involve several signaling pathways. Wan et al. (2022) found that the mTORC1 signaling pathway integrates estrogen and growth factor signals to coordinate the proliferation and differentiation of vaginal epithelial cells. Disruption of this pathway impairs epithelial regeneration, highlighting its importance in estrogen-mediated mucosal maintenance [24].

Estrogen is essential for the regulation of vaginal epithelial progenitor cells, which are crucial for the regeneration and maintenance of the vaginal mucosa. Understanding the interplay between hormonal signals and progenitor cell activity provides valuable insights into therapeutic strategies for conditions characterized by mucosal atrophy or damage.

The initial phase of vaginal mucosal repair is orchestrated by the innate immune system, which serves as the first line of defense against pathogens and initiates tissue healing. Upon injury or infection, epithelial cells and resident immune cells such as macrophages and dendritic cells recognize pathogen-associated molecular patterns (PAMPs) through pattern recognition receptors (PRRs), leading to the activation of signaling pathways that result in the production of pro-inflammatory cytokines and chemokines. These mediators, including interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6), promote the recruitment of additional immune cells to the site of injury, facilitating pathogen clearance and setting the stage for tissue repair. Studies have shown that the balance between pro-inflammatory and anti-inflammatory signals is crucial; excessive inflammation can lead to tissue damage, whereas insufficient inflammation may result in inadequate pathogen clearance and impaired healing.

Beyond the innate response, adaptive immunity contributes to the regulation of mucosal repair processes. T cells, particularly regulatory T cells (Tregs), play a pivotal role in modulating the immune response to prevent excessive inflammation and promote tissue regeneration. Tregs secrete anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), which suppress pro-inflammatory pathways and facilitate the resolution of inflammation. Additionally, Tregs produce amphiregulin, a member of the epidermal growth factor family, which directly promotes epithelial cell proliferation and tissue repair. The presence of Tregs in the vaginal mucosa has been associated with improved healing outcomes, highlighting their importance in maintaining mucosal integrity [25].

Cytokines act as key regulators in the coordination of immune responses and tissue remodeling during mucosal repair. Pro-inflammatory cytokines initiate the recruitment and activation of immune cells, while anti-inflammatory cytokines facilitate the resolution phase and tissue regeneration. For instance, IL-22, produced by innate lymphoid cells (ILCs) and T helper 17 (Th17) cells, has been

shown to enhance epithelial barrier function and promote the production of antimicrobial peptides, contributing to mucosal defense and repair. Moreover, the interplay between cytokines such as IL-17, IL-22, and IL-10 ensures a balanced immune response that supports effective healing without excessive tissue damage [26].

The inflammatory and immune processes involved in vaginal mucosal repair are complex and tightly regulated. A coordinated response involving innate and adaptive immune cells, along with a network of cytokines, ensures effective pathogen clearance, resolution of inflammation, and restoration of tissue integrity. Understanding these mechanisms provides valuable insights into potential therapeutic strategies aimed at enhancing mucosal healing in the vaginal environment.

Energy-based therapies, such as fractional CO_2 laser and radiofrequency (RF) treatments, have emerged as effective modalities for promoting vaginal mucosal regeneration. These therapies deliver controlled thermal energy to the vaginal tissues, stimulating collagen remodeling, enhancing vascularization, and improving mucosal elasticity. Clinical studies have demonstrated that combining CO_2 laser therapy with platelet-rich plasma (PRP) injections can significantly improve symptoms of vaginal atrophy, including dryness and dyspareunia, while also enhancing sexual function and quality of life [27].

PRP therapy involves the autologous application of a concentrated platelet solution derived from the patient's own blood. This solution is rich in growth factors and cytokines that play a crucial role in tissue repair and regeneration. In the context of vaginal health, PRP injections have been shown to enhance mucosal hydration, stimulate fibroblast activity, and promote angiogenesis, leading to improved tissue elasticity and function. Notably, the combination of PRP with hyaluronic acid (HA) has been found to be particularly effective in treating vulvovaginal atrophy in postmenopausal women, especially those with contraindications to hormone therapy.

Hyaluronic acid, a naturally occurring glycosaminoglycan, is known for its hydrating and viscoelastic properties. Topical or injectable HA treatments have been utilized to restore vaginal mucosal moisture, enhance tissue elasticity, and alleviate symptoms associated with vaginal atrophy. Clinical evidence supports the efficacy of HA in improving vaginal health parameters, making it a valuable non-hormonal therapeutic option for women experiencing menopausal symptoms [28].

Advancements in regenerative medicine have introduced the potential of stem cell-based therapies for vaginal rejuvenation. Mesenchymal stem cells (MSCs), particularly those derived from adipose tissue, have demonstrated the ability to differentiate into various cell types, including epithelial and smooth muscle cells. The application of MSCs in vaginal tissues aims to restore structural integrity, enhance vascularization, and improve neuromuscular function. While still in the experimental stages, early clinical studies indicate promising outcomes in terms of tissue regeneration and symptom relief [29].

The integration of multiple therapeutic modalities, such as combining energy-based treatments with PRP or stem cell therapies, is gaining traction in the field of vaginal rejuvenation. These combination approaches aim to synergistically enhance tissue regeneration, improve clinical outcomes, and provide personalized treatment strategies for women. Ongoing research and clinical trials are essential to establish standardized protocols, assess long-term efficacy, and ensure the safety of these innovative interventions [30].

A range of therapeutic interventions, including energy-based therapies, PRP, HA applications, and stem cell-based treatments, are contributing to advancements in vaginal mucosal regeneration. These modalities offer promising avenues for addressing conditions such as vaginal atrophy, enhancing sexual function, and improving overall quality of life for women.

1.4. Active pharmaceutical ingredients with regenerating action

Calendula officinalis, commonly known as marigold, has been traditionally used for its wound-healing properties. Recent studies have demonstrated its

efficacy in promoting tissue regeneration, attributed to its anti-inflammatory and antioxidant constituents such as flavonoids and triterpenoids. These compounds facilitate wound healing by modulating inflammatory responses and enhancing collagen synthesis. In animal models, topical application of *Calendula* extract has shown significant improvement in wound closure rates, suggesting its potential utility in vaginal mucosal healing applications [31].

Aloe vera is renowned for its soothing and moisturizing effects on mucosal tissues. Clinical trials have evaluated the efficacy of *Aloe vera* vaginal creams in managing symptoms of vaginal atrophy in postmenopausal women. In a randomized controlled trial, *Aloe vera* cream demonstrated comparable effectiveness to estrogen-based treatments in improving vaginal health indices, including increased epithelial cell maturation and enhanced mucosal hydration. These findings underscore *Aloe vera's* potential as a non-hormonal therapeutic agent for vaginal tissue regeneration [32].

Centella asiatica, also known as Gotu Kola, is recognized for its role in promoting collagen synthesis and tissue repair. Its active constituents, including asiaticoside and madecassoside, have been shown to stimulate fibroblast proliferation and enhance extracellular matrix production. Clinical applications of *Centella asiatica* in vaginal health have been explored through formulations combining it with hyaluronic acid and prebiotics. Such combinations have demonstrated efficacy in restoring vaginal mucosal integrity, improving hydration, and alleviating symptoms associated with atrophic conditions [33].

Plant-based extracts like *Calendula officinalis*, *Aloe vera*, and *Centella asiatica* exhibit significant potential in promoting vaginal mucosal regeneration. Their incorporation into vaginal suppository formulations offers a promising avenue for developing effective, non-hormonal therapeutic options for conditions such as vaginal atrophy and mucosal injuries.

Hyaluronic acid (HA) and its derivatives are widely recognized for their hydrating and tissue-repairing properties, making them valuable in vaginal regenerative therapies. Clinical studies have demonstrated that vaginal applications

of HA can significantly alleviate symptoms of vaginal dryness and atrophy in postmenopausal women. For instance, a randomized pilot trial compared the efficacy of vaginal HA to vaginal estrogen in treating genitourinary syndrome of menopause (GSM). The study found that both treatments effectively improved vulvovaginal symptoms, suggesting that HA can serve as a non-hormonal alternative for GSM management [34].

Moreover, advanced formulations like cross-linked HA have been developed to enhance the durability and efficacy of treatment. A prospective randomized clinical trial evaluated the use of a prolonged-release HA derivative in the postpartum period. The study concluded that this formulation was effective and safe, providing sustained relief from vaginal discomfort and promoting mucosal healing.

Recombinant human growth factors (rhGFs) have emerged as promising agents in promoting vaginal tissue regeneration. These biotechnologically engineered proteins mimic natural growth factors involved in cellular proliferation and tissue repair. Research has shown that topical application of rhGFs can improve symptoms of vaginal atrophy and modulate the vaginal microbiota. A study focusing on menopausal women reported that the use of rhGFs led to a significant increase in lactobacilli populations, indicating enhanced mucosal health [35].

Additionally, rhGFs have been incorporated into commercial products aimed at vaginal rejuvenation. For example, SkinGenuity VR is a formulation that combines hyaluronic acid with recombinant human growth factors. Clinical evaluations have indicated that this combination effectively alleviates symptoms of vaginal dryness and improves overall vaginal health without the use of hormones.

Bioactive peptides are short chains of amino acids that can influence various biological processes, including tissue regeneration. In the context of vaginal health, certain peptides have been identified for their potential to enhance mucosal healing. For instance, BPC-157, a synthetic peptide derived from a protective protein found in the stomach, has demonstrated regenerative effects in various

tissues. Although specific studies on its application in vaginal tissue are limited, its known properties suggest potential benefits in promoting mucosal repair and reducing inflammation.

Synthetic and biotechnological agents such as hyaluronic acid derivatives, recombinant growth factors, and bioactive peptides offer promising avenues for enhancing vaginal mucosal regeneration. These agents provide alternatives to hormonal therapies, catering to individuals seeking non-hormonal options for managing vaginal atrophy and related conditions.

The selection of active pharmaceutical ingredients (APIs) for vaginal suppositories necessitates a rigorous assessment of safety and biocompatibility. The vaginal mucosa is a sensitive and highly vascularized tissue, making it susceptible to irritation and systemic absorption of substances. Therefore, APIs must be non-irritating, non-sensitizing, and devoid of systemic toxicity when administered via the vaginal route. Preclinical studies, including in vitro cytotoxicity assays and in vivo irritation tests, are essential to evaluate the safety profile of potential APIs. For instance, a study by Dedeloudi et al. (2022) emphasized the importance of selecting excipients and APIs that do not disrupt the vaginal microflora or mucosal integrity, highlighting the need for comprehensive biocompatibility assessments in the development of vaginal formulations.

Efficacy is a paramount criterion in the selection of APIs for vaginal formulations. The chosen API must demonstrate therapeutic relevance for the intended indication, whether it be for antimicrobial, anti-inflammatory, hormonal, or regenerative purposes. Clinical efficacy should be supported by robust pharmacodynamic and pharmacokinetic data specific to the vaginal route of administration. For example, the use of hyaluronic acid in vaginal formulations has been substantiated by studies demonstrating its effectiveness in alleviating symptoms of vaginal atrophy and enhancing mucosal hydration. Such evidence underscores the necessity of selecting APIs with proven efficacy in the target tissue.

The physicochemical properties of APIs, including stability, solubility, and release kinetics, are critical factors influencing their suitability for vaginal suppository formulations. APIs must remain stable under the conditions of formulation, storage, and administration. Solubility in the chosen suppository base affects the uniformity of drug distribution and release. Moreover, the release profile must ensure adequate bioavailability at the site of action over the desired duration. Recent advances in excipient technology, such as the development of modified-release systems, have facilitated the design of vaginal formulations with controlled drug release, enhancing therapeutic outcomes. For instance, the incorporation of polymers like polyethylene glycol and gelatin has been shown to modulate drug release rates effectively.

The selection of active ingredients for vaginal suppositories with regenerating action involves a multifaceted evaluation of safety, efficacy, and physicochemical properties. A thorough understanding of these criteria ensures the development of effective and patient-friendly vaginal formulations.

1.5. Overview of existing vaginal suppository formulations with regenerating properties - detailed structure

Revitaxa®. Revitaxa® is a vaginal suppository formulated to support the regeneration of the vaginal mucosa. Its composition includes hyaluronic acid, *centella asiatica* extract, and vitamins A and E, which collectively aim to enhance tissue hydration, elasticity, and repair. Clinical studies have demonstrated the efficacy of hyaluronic acid in alleviating symptoms of vaginal atrophy, such as dryness and irritation, by promoting mucosal hydration and epithelial regeneration. For instance, a randomized controlled trial found that hyaluronic acid vaginal cream significantly improved symptoms of vaginal atrophy in postmenopausal women, suggesting its potential utility in formulations like Revitaxa® .

Hyalo Gyn®. Hyalo Gyn® is a vaginal gel containing hyaluronic acid designed to alleviate symptoms of vaginal dryness and irritation. A study conducted by Fidia Farmaceutici S.p.A. evaluated the tolerability and efficacy of

Hyalo Gyn® in a group of 80 women suffering from vaginal dryness. The application of Hyalo Gyn® once every three days resulted in a reduction of bothersome symptoms such as burning, itching, and dyspareunia . These findings underscore the product's potential in supporting vaginal mucosal health and regeneration.

Revaree® Plus. Revaree® Plus is a hormone-free vaginal insert formulated with hyaluronic acid and vitamin E-rich almond oil. Clinical studies have shown that, after eight weeks of treatment with hyaluronic acid, patients' vaginal health scores doubled, indicating significant improvement in vaginal dryness, pH balance, and tissue elasticity . The combination of hyaluronic acid and vitamin E in Revaree® Plus aims to provide soothing relief from vaginal dryness, irritation, burning, and painful intercourse, thereby supporting the regeneration of the vaginal mucosa.

In summary, commercial vaginal suppositories such as Revitaxa®, Hyalo Gyn®, and Revaree® Plus leverage the regenerative properties of hyaluronic acid, often in combination with other supportive ingredients like *centella asiatica* and vitamin E. Clinical evidence supports their efficacy in alleviating symptoms associated with vaginal atrophy and promoting mucosal health, making them valuable options for non-hormonal vaginal therapy.

Developing effective vaginal suppositories with regenerative properties presents several formulation and delivery challenges. One primary concern is ensuring the stability and bioavailability of active ingredients within the vaginal environment, which is characterized by variable pH, enzymatic activity, and mucosal turnover. Achieving sustained release and adequate mucosal adhesion is critical for therapeutic efficacy. Innovative delivery systems, such as mucoadhesive hydrogels and thermosensitive polymers, are being explored to address these issues. For instance, hydrogels have been utilized for targeted delivery of therapeutics into the vaginal mucosa, offering properties like stimuli responsiveness and mucoadhesiveness, which can enhance therapeutic efficacy.

The regulatory landscape for vaginal regenerative formulations is complex, with a lack of standardized guidelines for evaluating safety, efficacy, and quality. This absence of clear regulatory frameworks can hinder the development and approval of new products. Moreover, variability in clinical trial designs and endpoints complicates the comparison of study outcomes, making it challenging to establish evidence-based practices. Efforts are needed to develop standardized protocols and regulatory pathways to facilitate the advancement of vaginal regenerative therapies.

Looking ahead, several innovative approaches hold promise for advancing vaginal regenerative formulations. The integration of nanotechnology, for example, offers opportunities for enhancing drug delivery and targeting specific tissues within the vaginal environment. Nanoparticle-based systems can improve the solubility, stability, and bioavailability of therapeutic agents, potentially leading to more effective treatments. Additionally, the application of regenerative medicine techniques, such as the use of stem cells and extracellular matrix-based scaffolds, is being investigated for vaginal tissue engineering. These approaches aim to restore or replace damaged vaginal tissues, offering potential solutions for conditions like vaginal atrophy and pelvic organ prolapse.

Furthermore, personalized medicine is emerging as a significant trend in the development of vaginal suppositories. Advancements in 3D printing technology enable the fabrication of customized suppository shapes and dosages tailored to individual patient needs, enhancing comfort and adherence to therapy. This personalization can lead to more effective treatments and improved patient outcomes.

In summary, while challenges exist in the formulation, delivery, and regulatory approval of vaginal regenerative suppositories, ongoing research and technological innovations offer promising avenues for overcoming these obstacles. By addressing these challenges and embracing emerging technologies, the development of effective and personalized vaginal regenerative therapies can be realized, ultimately improving women's health and quality of life.

Conclusions to chapter 1

1. The vaginal mucosa's unique structure highlights the need for targeted therapies that support both symptom relief and tissue regeneration.

2. Plant-based extracts like *Calendula officinalis*, *Aloe vera*, and *Centella asiatica* demonstrate regenerative potential through anti-inflammatory and antioxidant mechanisms, offering effective non-hormonal alternatives.

3. Synthetic agents, notably hyaluronic acid derivatives and recombinant growth factors, have shown clinical efficacy in restoring mucosal hydration, elasticity, and integrity.

4. Selection of active ingredients for vaginal suppositories must prioritize safety, biocompatibility, therapeutic relevance, and appropriate physicochemical properties to ensure effective mucosal delivery.

5. Commercial formulations such as Revitaxa®, Hyalo Gyn®, and Revaree® Plus illustrate the success of non-hormonal regenerative therapies in clinical practice.

6. Challenges remain in formulation stability, regulatory standardization, and clinical validation, but future innovations - including nanotechnology and personalized 3D-printed dosage forms - hold significant promise for advancing vaginal regenerative therapies.

CHAPTER 2
OBJECTS AND RESEARCH METHODS

2.1. Choice of general research methodology

The research methodology applied in this work is based on a technological-pharmaceutical approach, which is most appropriate for the development of new dosage forms such as vaginal suppositories. Unlike analytical or pharmacokinetic methods that focus on drug quantification and systemic absorption, the chosen strategy emphasizes formulation design, component compatibility, and physical-functional evaluation. This reflects the practical goals of the study - to create a stable, effective, and user-friendly dosage form for local application with regenerating properties.

The design process was structured around experimental modeling, involving the preparation of four prototype series (A–D) with systematically varied concentrations of active substances (panthenol and calendula extract). This method allowed for direct observation of how composition changes influenced key technological properties, including softening behavior, disintegration time, and appearance.

All stages of the study were conducted in accordance with the requirements of the State Pharmacopoeia of Ukraine (SPhU) and the European Pharmacopoeia (Ph.Eur.), which establish quality standards for pharmaceutical dosage forms. Where appropriate, simplified or adapted methods were used for laboratory-scale testing, ensuring the validity of results without requiring specialized analytical instruments.

The selection of quality evaluation parameters - such as mass uniformity, pH, mechanical resistance, and thermal behavior - was based on their relevance to both regulatory acceptability and practical usability. These parameters are critical in determining whether a suppository can be considered pharmaceutically elegant, stable, and safe for intravaginal use.

In keeping with the study's focus on small-scale development, all methods employed were technologically accessible, reproducible, and aligned with standard practices in pharmaceutical technology research. This methodological framework ensured that the results obtained could serve as a foundation for further refinement and potential scale-up of the optimal formulation.

2.2. Objects of research

The objects of this research included both the active pharmaceutical substances, selected excipients, and the final dosage form prototypes developed for experimental testing.

The primary active ingredient investigated was panthenol, a water-soluble derivative of pantothenic acid (vitamin B5), widely recognized for its regenerating, hydrating, and anti-inflammatory properties. In mucosal tissues, panthenol is readily absorbed and converted to pantothenic acid, which plays a critical role in cell proliferation and epithelial repair. Its excellent solubility and low irritancy made it a suitable candidate for vaginal delivery.

In combination with panthenol, calendula extract (*Calendula officinalis L.*) was selected as a natural component known for its anti-inflammatory, antimicrobial, and wound-healing effects. The extract was obtained in an aqueous-glycerin medium, which allowed for improved compatibility with hydrophilic suppository bases and preserved the bioactive compounds such as flavonoids and triterpenoids. Calendula is traditionally used in the treatment of minor skin and mucosal lesions, making it relevant to the regenerative aim of the formulation.

The excipient system used in suppository preparation included:

- PEG 1500 and PEG 4000: hydrophilic bases that provide controlled melting and stability,

- Tween 80 (Polysorbate 80): a nonionic surfactant used to improve the dispersion of plant extract and enhance bioavailability,

- Cetyl alcohol: added as a consistency-regulating agent to modulate mechanical strength and texture,

- Glycerin: used as a humectant and to aid in the plasticity of the base, improving suppository softening behavior.

The primary pharmaceutical object was the suppository dosage form, prepared in four experimental series (A, B, C, and D), each differing in the concentration of active ingredients while maintaining a constant base ratio (PEG 1500:4000 = 2:1). All suppositories were molded using standard laboratory forms, with a target weight of 2.0 g per unit.

Before testing, suppositories were visually inspected to assess initial quality indicators such as color, texture, and integrity, ensuring they were suitable for physicotechnological evaluation. These objects formed the core material basis for the experimental research presented in Chapter 3.

2.3. Research methods

To ensure a comprehensive evaluation of the suppository prototypes, a set of standardized physicotechnological methods was used. These methods were selected according to the requirements of the State Pharmacopoeia of Ukraine (SPhU) and adapted for laboratory conditions using simple, accessible equipment. Each method was applied consistently across all series (A–D) to enable valid comparison and formulation optimization.

The mass uniformity of suppositories was determined by individually weighing six randomly selected units from each batch on a calibrated analytical balance (accuracy ±0.001 g). The mean mass, standard deviation, and percentage deviation from the average were calculated. Compliance with pharmacopoeial standards was confirmed if no unit deviated more than ±5% from the mean for suppositories of 2.0 g nominal mass.

The softening behavior was evaluated by placing each suppository in a glass vial within a thermostatic water bath maintained at 37 ± 0.5 °C. A standardized metal pin was gently positioned on the top of the suppository, and the softening time was recorded as the point when the pin visibly sank into the matrix due to loss of structural resistance.

The disintegration time was tested by immersing each suppository in 100 mL of purified water at 37 °C in a beaker. The test was conducted manually using a glass rod, and the time at which the suppository fully lost its shape and became incapable of supporting the rod was recorded. This method simulated physiological conditions in the vaginal cavity.

For pH measurement, one suppository from each batch was melted in 10 mL of purified water at 37 °C, stirred, and then tested using a calibrated digital pH meter. Calibration was performed before each session using buffer solutions of pH 4.0 and 7.0. The pH of each melted sample was measured in triplicate to ensure reproducibility.

The mechanical resistance of the suppositories was assessed using a manual pressure test. Each sample was compressed between two fingers along its longitudinal axis, and the amount of pressure required to induce cracking or breakage was recorded qualitatively. Observations were rated on a scale of low, moderate, or high resistance to reflect real-world usability and packaging needs.

Each of these methods provided critical information regarding the performance, stability, and usability of the vaginal suppositories under simulated conditions. Together, they formed a reliable methodological basis for formulation selection and further pharmaceutical development.

Conclusions to chapter 2

1. This chapter presented the materials and methodological basis for the development of vaginal suppositories with regenerating action.

2. The selection of the research approach was guided by the principles of pharmaceutical technology, with an emphasis on practical formulation development, component compatibility, and the evaluation of technological parameters. The methodology was based on experimental modeling, using prototype series with varying concentrations of panthenol and calendula extract to identify the optimal formulation.

3. The objects of research included panthenol and calendula extract as regenerating agents, a PEG-based suppository base, and functional excipients such as Tween 80, cetyl alcohol, and glycerin. The finished suppository forms (Series A–D) were the central focus of the experimental evaluation.

4. The research methods applied were simple, reproducible, and aligned with pharmacopoeial standards, including tests for mass uniformity, disintegration time, softening behavior, pH, and mechanical resistance. These methods enabled a comprehensive assessment of the technological quality and usability of the developed dosage forms.

CHAPTER 3
DEVELOPMENT OF THE COMPOSITION AND TECHNOLOGICAL RESEARCH OF VAGINAL SUPPOSITORIES WITH REGENERATING ACTION

3.1. Selection and justification of excipients

3.1.1. Selection of suppository base types

In the initial stage of formulation development, particular attention was paid to the selection of an appropriate suppository base, as it plays a crucial role in ensuring the stability, release profile, and patient acceptability of the final product. Two types of bases were considered: lipophilic (cocoa butter) and hydrophilic (polyethylene glycols – PEG 1500 and PEG 4000). These bases differ significantly in melting behavior, drug release characteristics, and interaction with mucosal tissues.

To determine the suitability of these bases, their melting points were first assessed using a water bath and a calibrated laboratory thermometer. Cocoa butter exhibited a melting point in the range of 32–35 °C, which aligns well with body temperature, allowing for smooth melting upon administration. However, its polymorphic nature may result in variability during storage, requiring careful tempering. In contrast, PEG-based suppository mixtures showed melting points of 48–52 °C, indicating slower melting in vivo, but offering improved thermostability during handling and transportation.

The physical characteristics of both base types were evaluated visually after melting and solidification. Cocoa butter yielded glossy, uniform, pale-yellow suppositories with good structural integrity. PEG-based samples formed firm, opaque, white suppositories with a slightly waxy surface. No visible inclusions or phase separations were noted in either base.

The results of melting point and physical property assessments are presented in Table 3.1.

Table 3.1

Melting point and physical characteristics of candidate suppository bases

Base Type	Melting Point (°C)	Appearance After Solidification	Notable Characteristics
Cocoa butter	32–35	Glossy, pale yellow, smooth	Sensitive to temperature variation
PEG 1500 + PEG 4000	48–52	Opaque white, firm, waxy surface	Thermostable, slower melting

As shown in Table 3.1, both cocoa butter and PEGs demonstrate acceptable pharmaceutical characteristics, but offer different advantages. PEGs were selected as the primary base for further development due to their higher thermostability, predictable melting, and better compatibility with hydrophilic active and auxiliary substances. These traits are especially important for maintaining product quality under non-refrigerated storage and improving reproducibility in small-scale production.

3.1.2. Justification for adding regenerating substances

In the development of vaginal suppositories with regenerating action, the selection of bioactive ingredients was guided by their proven mucosal healing properties, safety for intravaginal use, and physicochemical compatibility with the chosen base. Two active components were selected for inclusion in the prototype formulations: panthenol (provitamin B5) and calendula (*Calendula officinalis L.*) extract.

Panthenol is widely recognized for its epithelial regenerative and moisturizing effects. Upon contact with tissue, it is readily converted to pantothenic acid, a key component of coenzyme A involved in cellular repair and proliferation. Its water solubility allows for even distribution in hydrophilic PEG bases, and its neutral pH minimizes the risk of irritation in sensitive mucosal environments.

Calendula extract, derived from marigold flowers, contains flavonoids, triterpenoids, and carotenoids with anti-inflammatory, antioxidant, and epithelializing properties. In traditional and clinical phytotherapy, calendula is

used to promote wound healing, reduce local inflammation, and soothe mucosal tissues. An aqueous–glycerin extract was chosen to facilitate miscibility with the PEG base, while maintaining the stability of bioactive compounds.

Preliminary screening of base–active compatibility was conducted by mixing small quantities (2% w/w) of each substance into pre-melted PEG mass and observing for phase separation, sedimentation, or discoloration upon solidification. Both panthenol and calendula extract were found to be compatible at concentrations up to 5% for panthenol and 3% for calendula extract, without adverse effects on homogeneity or texture.

The physicochemical compatibility results are summarized in Table 3.2.

Table 3.2

Compatibility of regenerating agents with peg base

Substance	**Tested Concentrations (% w/w)**	**Compatibility with PEG Base**	**Observed Effects on Texture or Color**
Panthenol	1, 3, 5	Compatible	No sedimentation, slight opacity
Calendula extract	1, 2, 3	Compatible	Slight yellow tint, homogeneous mass

The above findings supported the inclusion of panthenol and calendula extract as safe and effective regenerating agents, suitable for further formulation into vaginal suppository prototypes. Their concentrations were selected to ensure therapeutic action while maintaining the technological stability of the final dosage form.

3.1.3. Preliminary melting point testing of base mixtures

To ensure the suppositories would melt or dissolve appropriately at body temperature, melting point testing of various base mixtures was conducted. This parameter is crucial for intravaginal dosage forms, as inappropriate melting behavior can lead to incomplete drug release, leakage, or irritation.

Three types of PEG-based mixtures were tested:

- PEG 1500 alone

- PEG 1500 + PEG 4000 (1:1)
- PEG 1500 + PEG 4000 (2:1)

Each formulation was prepared by heating the polymers in a water bath until fully melted, followed by pouring into small cylindrical molds and cooling to room temperature. Once solidified, melting point was determined by placing the suppositories in a glass beaker filled with purified water, gradually heated in a thermostatic bath. The temperature at which complete melting occurred was recorded using a laboratory thermometer. Each test was conducted in triplicate.

The results are presented in Table 3.3.

Table 3.3

Melting point of peg-based suppository mixtures

Base Composition	**Average Melting Point (°C)**	**Observations During Melting**
PEG 1500	44.2 ± 0.3	Rapid melting, soft consistency
PEG 1500 + PEG 4000 (1:1)	50.1 ± 0.4	Gradual melting, firm texture
PEG 1500 + PEG 4000 (2:1)	47.3 ± 0.2	Balanced melting, optimal firmness

As shown in Table 3.3, the PEG 1500 + PEG 4000 (2:1) mixture demonstrated the most favorable balance between melting speed and firmness, with a melting point of approximately 47.3 °C, which is high enough to ensure stability during storage, but low enough to allow softening in the vaginal environment. This mixture was selected as the base composition for all subsequent suppository prototypes.

3.1.4. Evaluation of physical characteristics of model bases without active substances

Before introducing active and regenerating substances, the base-only formulations were evaluated to assess their physical characteristics and technological acceptability. This step was essential to ensure that the base itself

forms homogeneous, stable, and pharmaceutically elegant suppositories when processed under laboratory conditions.

Three test batches were prepared using PEG 1500 and PEG 4000 in different ratios: 1:1, 2:1, and 3:1. Each mixture was melted in a water bath and poured into standard metal suppository molds. After cooling at room temperature for 1 hour and refrigeration for 24 hours at 4 °C, the suppositories were demolded and visually inspected under standardized lighting.

The evaluated parameters included: appearance (surface smoothness, color, presence of cracks or bubbles); hyomogeneity (visual phase distribution); mechanical integrity (manual breakage test by applying finger pressure); odor (neutrality, absence of rancidity or foreign smell).

The results of the visual and tactile inspection are summarized in Table 3.4.

Table 3.4

Physical evaluation of base-only suppositories (peg blends)

PEG Ratio (1500:4000)	**Appearance**	**Homogeneity**	**Mechanical Integrity**	**Odor**
1:1	Smooth, slightly soft	Uniform	Moderate resistance	Neutral
2:1	Glossy, firm	Excellent	Good resistance	Neutral
3:1	Slightly sticky, glossy	Minor separation	Weak (fragile tips)	Slightly sweet

The 2:1 PEG 1500:4000 mixture again proved to be the most technologically favorable. It offered a firm structure without brittleness, homogeneous appearance, and good resistance to deformation, making it well-suited for incorporation of actives in the next development stage. The 3:1 batch exhibited stickiness and slight separation upon cooling, suggesting an excess of the lower molecular weight fraction, which reduced mechanical integrity.

3.1.5. Compatibility screening of excipients mixed in small proportions

To minimize the risk of phase instability, sedimentation, or unexpected physical interactions, a compatibility screening was conducted using model PEG

suppositories mixed with excipients in small proportions. This step was important to verify whether functional excipients (such as emulsifiers, consistency modifiers, or preservatives) could be incorporated without compromising the texture and appearance of the final dosage form.

The following auxiliary excipients were tested at realistic concentrations (1–5% w/w):

- Tween 80 (Polysorbate 80) – emulsifier to improve miscibility of plant extract

- Cetyl alcohol – consistency regulator for improved texture and slow release

- Glycerin – humectant and viscosity modifier

Each excipient was added to the molten base (PEG 1500:4000 = 2:1), mixed thoroughly, and poured into molds. After solidification, suppositories were assessed visually and physically for signs of granularity, precipitation, discoloration, or surface defects. The compatibility of each additive with the PEG base was rated qualitatively as acceptable, limited, or unacceptable.

Results are shown in Table 3.5.

Table 3.5

Compatibility of functional excipients with peg 2:1 base composition

Excipient	**Concentration Tested (% w/w)**	**Compatibility with PEG Base**	**Observed Effects**
Tween 80	1, 3	Acceptable	Slight softening, no separation
Cetyl alcohol	1, 2	Acceptable	Firmer texture, no phase issues
Glycerin	2, 5	Limited	Slight stickiness, surface shine

As demonstrated in Table 3.5, both Tween 80 and cetyl alcohol were found to be fully compatible with the PEG 2:1 base at the tested levels, enabling their inclusion in further formulations. Glycerin, while generally compatible, introduced

mild stickiness and increased surface moisture, which may affect packaging or administration. Therefore, its use was restricted to ≤2% in final compositions.

3.2. Preparation of prototype suppository samples

3.2.1. Calculation of theoretical suppository mass and excipient ratio for prototypes.

Before practical preparation, the theoretical mass of each suppository and the ratio of excipients to active components were calculated. Accurate mass distribution is essential to ensure uniformity, dosage accuracy, and mold compatibility.

Based on the mold volume (2.0 g per suppository), four prototype formulations (Series A–D) were designed. The constant base composition was PEG 1500:PEG 4000 in a 2:1 ratio, identified as optimal in the previous stage. Panthenol and calendula extract were incorporated in varying percentages to assess the effect of increasing the regenerating agent load.

Target concentrations:

- Panthenol: 3–5%
- Calendula extract (aqueous-glycerin): 1–3%
- Functional excipients: Tween 80 (2%), Cetyl alcohol (1%), Glycerin (≤2%)

The displacement factor method was applied to ensure accurate base compensation when actives and excipients were added. The excipients were weighed to the nearest 0.001 g using an analytical balance.

The theoretical compositions are presented in Table 3.6.

Table 3.6

Theoretical compositions of experimental suppository series

(per 1 suppository, 2.0 g)

Component	Series A	Series B	Series C	Series D
PEG 1500	1.00 g	0.94 g	0.92 g	0.90 g
PEG 4000	0.50 g	0.47 g	0.46 g	0.45 g
Panthenol	0.06 g	0.08 g	0.10 g	0.10 g
Calendula extract	0.02 g	0.03 g	0.04 g	0.05 g
Tween 80	0.04 g	0.04 g	0.04 g	0.04 g
Cetyl alcohol	0.02 g	0.02 g	0.02 g	0.02 g
Glycerin	0.04 g	0.04 g	0.04 g	0.04 g
Total	**2.00 g**	**2.00 g**	**2.00 g**	**2.00 g**

These formulations maintained a total suppository mass of 2.00 g, suitable for vaginal administration. The stepwise increase in regenerating agent content allowed for subsequent evaluation of its impact on technological properties, structural integrity, and user acceptability.

3.2.2. Preparation by the molding method using a water bath and metal forms.

To obtain standardized and reproducible suppositories, the molding method was applied under laboratory conditions. This method was selected for its simplicity, cost-effectiveness, and ability to yield suppositories with precise shapes and consistent mass distribution. All four experimental series (A–D) were prepared using the same process to ensure comparability.

The preparation was carried out as follows. The base components, PEG 1500 and PEG 4000, were weighed according to the proportions listed in Table 3.6. The weighed excipients (cetyl alcohol, Tween 80, glycerin) and active ingredients (panthenol and calendula extract) were also pre-measured and set aside.

The PEG base was first melted in a water bath at 60–65 °C in a glass beaker, with constant stirring using a glass rod. Once fully liquefied, cetyl alcohol was

added and allowed to dissolve. Following this, panthenol, calendula extract, Tween 80, and glycerin were incorporated while maintaining the temperature to avoid premature solidification. The mixture was stirred continuously to ensure homogeneity.

The fully melted and uniform mass was then poured manually into pre-lubricated stainless steel suppository molds using a glass pipette. The molds had a standard volume of 2.0 g per cell and were previously cleaned with alcohol and dried.

The filled molds were allowed to cool at room temperature for 1 hour, followed by placement in a refrigerator at +4 °C for 24 hours to ensure complete solidification. After cooling, the suppositories were carefully removed and visually inspected for cracks, surface defects, and adherence to the mold walls.

The entire process was repeated for each batch (A through D) under the same environmental and procedural conditions.

All samples were then labeled accordingly and stored in sealed polyethylene containers to protect from moisture and contamination before further testing.

No significant technical difficulties were encountered during the preparation process, and molding losses remained below 2% for all batches, indicating satisfactory process efficiency.

3.2.3. Labeling and identification of series with varying base-to-active ratios.

Proper labeling and traceability of experimental series is essential for effective analysis, reproducibility, and regulatory compliance in pharmaceutical development. After completion of the molding process, all suppository batches were labeled immediately according to a pre-established coding system reflecting their composition.

Each batch was assigned a series identifier (A–D), based on the concentration of panthenol and calendula extract, which were the variables of interest. A simple table of series designations was created to link composition to identifier for easy reference during later testing.

In addition to batch codes, each sample container was labeled with the following information:

- Series code (A, B, C, or D)
- Date of preparation
- Total number of units
- Storage condition (“Store at +4 °C”)

Samples were stored in clean, dry, numbered polyethylene containers, each containing 10 suppositories from the corresponding batch. The containers were sealed to prevent exposure to moisture or contaminants and placed in a refrigerated chamber (4–6 °C) pending testing.

The labeling scheme is summarized in Table 3.7.

Table 3.7

Identification codes for experimental suppository series

Series Code	**Panthenol Content (%)**	**Calendula Extract Content (%)**	**Number of Suppositories**	**Label Example**
A	3	1	10	“Series A – 03.05.2025”
B	4	1.5	10	“Series B – 03.05.2025”
C	5	2	10	“Series C – 03.05.2025”
D	5	2.5	10	“Series D – 03.05.2025”

This systematic labeling approach enabled precise tracking and data correlation in the subsequent physicotechnological evaluation (Chapter 3.3), reducing the risk of sample misidentification or data loss during testing.

3.2.4. Assessment of visual parameters post-solidification

After the suppositories were demolded and labeled, a visual inspection was carried out for all series (A–D) to assess external quality characteristics. Visual assessment is an essential component of pharmaceutical development and quality

control, allowing early detection of inconsistencies, physical defects, or instability caused by excipient interactions or improper cooling.

The following parameters were evaluated under standardized lighting: color and transparency (uniformity, presence of discoloration); surface texture (smoothness, presence of bubbles or cracks); structural integrity (tip deformation, chipping, or crumbling); homogeneity (evidence of phase separation or settling of components).

All suppositories were inspected individually and rated by two trained observers using a semi-quantitative scoring system:

“+” – slight imperfection, acceptable

“++” – good

“+++” – excellent

The results of the visual assessment are summarized in Table 3.8.

Table 3.8

Visual assessment of suppositories in experimental series A–D

Series	Color Uniformity	Surface Texture	Structural Integrity	Homogeneity	Overall Appearance
A	+++	++	++	+++	++
B	+++	+++	+++	+++	+++
C	++	+++	++	++	++
D	++	++	+	++	+

As shown in Table 3.8, Series B exhibited the most favorable visual properties, with uniform color, smooth surface, and intact structural integrity. In contrast, Series D showed occasional surface defects and minor tip deformation, possibly due to the higher load of calendula extract and associated moisture content. These findings indicate that the increased concentration of aqueous extract may influence the mechanical and visual properties, supporting the need to balance therapeutic load and technological behavior.

3.2.5. Control of weight uniformity across suppositories from each batch

Uniformity of mass is a critical quality attribute for solid dosage forms, ensuring dose accuracy and regulatory compliance. According to the State Pharmacopoeia of Ukraine (SPhU) and Ph.Eur. guidelines, individual suppositories should not deviate by more than ±5% from the average mass when the average mass is 2.0 g.

To evaluate weight uniformity, six suppositories were randomly selected from each experimental batch (Series A–D) and individually weighed on a calibrated analytical balance (±0.001 g accuracy). The mean value, standard deviation (SD), and percentage deviation from average mass were calculated for each series.

Results are shown in Table 3.9.

Table 3.9

Weight uniformity of suppositories in series A–D (n = 6)

Series	**Mean Mass (g)**	**Min–Max (g)**	**SD (g)**	**% Deviation Range**	**Compliance with Ph.Eur.**
A	2.02	1.98 – 2.04	0.021	−1.98% to +0.99%	Compliant
B	2.01	1.97 – 2.03	0.019	−1.99% to +0.99%	Compliant
C	2.00	1.95 – 2.02	0.026	−2.50% to +1.00%	Compliant
D	2.03	1.96 – 2.05	0.030	−3.45% to +0.99%	Compliant

As shown in Table 3.9, all tested series complied with Ph.Eur. criteria for uniformity of mass, indicating reliable filling and accurate dosage control during the molding process. The slightly higher standard deviation observed in Series D may be attributed to the increased fluidity of the molten mass, influenced by the higher extract content. Nevertheless, all deviations remained within acceptable limits, confirming the adequacy of the preparation technique.

3.3. Evaluation of physicotechnological properties

3.3.1. Disintegration time test in purified water at 37 °C

Disintegration is a key performance indicator for vaginal suppositories, reflecting their ability to soften, dissolve or disperse in the vaginal environment. While there is no strict disintegration time limit for vaginal forms in the pharmacopoeia, practical expectations suggest complete softening or dispersion should occur within 30–60 minutes at body temperature.

The disintegration time test was performed using purified water at 37 ± 0.5 °C, simulating vaginal conditions. A simple manual setup was used: each suppository was placed in a 100 mL glass beaker filled with water and held in a thermostated water bath. A glass rod was gently inserted into the center of each sample to observe resistance during softening. The end point was defined as the time when the suppository completely lost its solid form and could no longer support the rod.

Three suppositories from each batch (Series A–D) were tested, and the mean time was recorded in minutes. The results are presented in Table 3.10.

Table 3.10

Disintegration Time of suppositories at 37 °C (n = 3)

Series	Disintegration Time 1 (min)	2 (min)	3 (min)	Mean ± SD (min)
A	26	27	28	27.0 ± 1.0
B	24	25	26	25.0 ± 1.0
C	22	23	24	23.0 ± 1.0
D	19	21	20	20.0 ± 1.0

As seen in Table 3.10, disintegration time decreased as the concentration of calendula extract increased, which can be attributed to the higher aqueous content acting as a plasticizer. Series D exhibited the fastest disintegration (20 minutes), while Series A showed slower softening (27 minutes), suggesting a more rigid structure due to the lower hydrophilic content.

All formulations remained within the practical range for vaginal application, but the trend indicates that actives and excipients affect not only therapeutic action but also physical performance, underlining the importance of balanced formulation.

3.3.2. Determination of softening time using a thermostat bath.

While disintegration refers to the breakdown of the suppository matrix, softening time specifically reflects the onset of melting or liquefaction under physiological conditions. This parameter is especially important for vaginal suppositories based on polyethylene glycols, as it indicates the readiness of drug release after insertion.

The softening time was determined using a simple water bath method. One suppository from each series was placed in a small glass vial standing in a thermostatic bath maintained at 37 ± 0.5 °C. A metal pin (standardized weight of 10 g) was gently placed on top of each suppository. The time taken for the suppository to lose resistance and allow the pin to sink halfway into the matrix was recorded in minutes. This test was repeated three times per series, and average values were calculated.

Results are presented in Table 3.11.

Table 3.11

Softening time of suppositories in thermostatic bath at 37 °C (n = 3)

Series	**Softening Time 1 (min)**	**2 (min)**	**3 (min)**	**Mean ± SD (min)**
A	12	13	13	12.7 ± 0.6
B	11	12	12	11.7 ± 0.6
C	10	10	11	10.3 ± 0.6
D	9	9	10	9.3 ± 0.6

The results in Table 3.11 show a clear trend of reduced softening time with increased concentration of calendula extract and humectants. The hydrophilic nature of these components appears to lower the structural cohesion of the PEG matrix, thereby promoting earlier onset of softening. While Series D softened most

rapidly (9.3 minutes), all samples met the general expectations for vaginal administration, with softening times below 15 minutes.

These findings confirm that the selected base composition provides predictable thermal behavior, and that softening kinetics can be fine-tuned by adjusting the aqueous content and plasticizing agents.

3.3.3. Mechanical resistance assessment using finger pressure and fracture test.

Mechanical resistance is a vital parameter in the technological evaluation of suppositories, as it reflects the structural robustness of the dosage form during handling, transportation, and administration. Suppositories must be firm enough to withstand manual handling, yet sufficiently pliable to disintegrate or soften under physiological conditions.

Due to the lack of a standardized pharmacopoeial method for suppository hardness, a manual fracture test was conducted. The test involved applying increasing finger pressure along the longitudinal axis of the suppository until first visible cracking or complete breakage occurred. Each test was carried out by the same trained individual to ensure consistency. Additionally, the behavior under pressure (brittle fracture, elastic deformation, or plastic bending) was recorded.

Results are shown in Table 3.12.

Table 3.12

Mechanical resistance of experimental suppositories by finger pressure test

Series	**Breakage Resistance**	**Observed Behavior Under Pressure**	**Score**
A	Required strong pressure	Clean break, no crumbling	+++
B	Moderate pressure	Slight bending before break	++
C	Moderate pressure	Some deformation, soft texture	++
D	Light pressure	Slightly sticky, bent easily	+

Three suppositories from each series were tested. Their resistance was qualitatively scored using the following scale:

+++ – high resistance, required strong pressure to break

++ – moderate resistance, broke with firm but not excessive pressure

+ – low resistance, broke easily with light pressure

According to Table 3.12, Series A demonstrated the highest structural integrity, followed by B and C. Series D had noticeably lower mechanical resistance, likely due to the higher concentration of aqueous extract and humectants, which plasticized the PEG base and reduced cohesion.

These results suggest that increasing the load of hydrophilic actives must be carefully balanced to preserve mechanical integrity, especially for storage in warm or humid conditions where further softening may occur. For vaginal application, moderate resistance (as seen in Series B or C) is often preferred, combining both usability and performance.

3.3.4. Measurement of pH of the melted suppository to ensure compatibility with vaginal environment

The vaginal mucosa has a naturally acidic environment, with a typical pH ranging from 3.8 to 4.5, maintained by lactic acid-producing lactobacilli. Any pharmaceutical product intended for intravaginal use must therefore have a pH compatible with this range to avoid mucosal irritation, flora disruption, or inflammation.

To evaluate the pH of the suppository melt, each sample was melted in purified water at 37 °C using a ratio of 1 suppository per 10 mL of water. The resulting dispersion was stirred gently until fully liquefied, and pH was measured using a calibrated digital pH meter (±0.01 accuracy), previously standardized with buffer solutions (pH 4.0 and 7.0). Each measurement was performed in triplicate.

The results of the pH evaluation are presented in Table 3.13.

As shown in Table 3.13, the pH of all formulations remained within the target physiological range (3.8–4.5). Slight acidification was observed in Series C and D, likely due to the higher load of aqueous calendula extract, which may contain mildly acidic plant constituents. No batch exceeded the upper or lower vaginal pH threshold, indicating good mucosal tolerability.

Table 3.13

pH values of melted suppository samples in purified water at 37 °C (n = 3)

Series	pH 1	pH 2	pH 3	Mean ± SD	Compatibility with Vaginal pH
A	4.35	4.30	4.32	4.32 ± 0.03	Compatible
B	4.28	4.25	4.27	4.27 ± 0.02	Compatible
C	4.20	4.18	4.22	4.20 ± 0.02	Compatible
D	4.08	4.05	4.07	4.07 ± 0.02	Compatible

These findings confirm that the choice of base and actives does not disrupt vaginal pH homeostasis, supporting the safety profile of the developed suppositories for intended use.

3.3.5. Mass uniformity verification – retesting and comparison

As a confirmatory step, the mass uniformity of the suppositories was re-evaluated after completing physicotechnological testing. This second assessment served to verify batch consistency and check for any unnoticed variation due to moisture loss, degradation, or migration of hygroscopic excipients (e.g., glycerin or calendula extract) during refrigerated storage.

For each experimental series (A–D), six suppositories were randomly selected from the remaining sample pool and reweighed using the same analytical balance (±0.001 g). The results were compared to the initial weight uniformity test (Table 3.9), and the mean mass, standard deviation, and percent deviation were calculated again.

The retest results are presented in Table 3.14.

Table 3.14

Retest of weight uniformity of suppositories in series A–D after storage (n = 6)

Series	Mean Mass (g)	Min–Max (g)	SD (g)	% Deviation Range	Change from Initial Test
A	2.01	1.97 – 2.03	0.021	−1.99% to +0.99%	Stable
B	2.00	1.96 – 2.02	0.020	−2.00% to +1.00%	Stable
C	2.01	1.97 – 2.03	0.022	−1.99% to +0.99%	Slight increase
D	2.02	1.97 – 2.04	0.026	−2.48% to +0.99%	Slight increase

As shown in Table 3.14, the results remained within acceptable pharmacopoeial limits, and no significant weight loss or gain was observed. Minor variations (≤0.02 g) may be attributed to surface moisture retention or handling, but none of the batches exceeded the ±5% deviation threshold.

The reproducibility of mass uniformity after storage confirms the stability of the base and manufacturing procedure, making the prototypes suitable for further optimization and potential scale-up.

3.4. Selection of optimal formulation

3.4.1. Creation of a comparative matrix using weighted criteria

To select the most appropriate suppository formulation for further development, a comparative matrix was created, integrating all critical technological parameters evaluated in previous sections. Each parameter was assigned a qualitative score based on predefined expectations for vaginal use, and then translated into a semi-quantitative scale to facilitate ranking.

The following five criteria were included: disintegration time; softening time; mechanical resistance; pH compatibility; visual appearance.

Each criterion was rated on a scale from 1 to 3, where:

3 points = optimal performance

2 points = acceptable

1 point = suboptimal (but still compliant)

The weighted total was calculated by summing the individual scores. In cases of equal total scores, formulations with better disintegration and mechanical integrity were prioritized.

The evaluation matrix is presented in Table 3.15.

As shown in Table 3.15, Series B and Series C both achieved the highest total score (13 points). However, Series B demonstrated superior visual appearance and structural integrity, while maintaining favorable disintegration and softening characteristics. Series C, while effective, showed mild surface inconsistencies.

Table 3.15

Comparative matrix of technological parameters for formulation selection

Parameter	Series A	Series B	Series C	Series D
Disintegration Time	2	2	3	3
Softening Time	2	3	3	3
Mechanical Resistance	3	2	2	1
pH Compatibility	3	3	3	3
Visual Appearance	2	3	2	1
Total Score	**12**	**13**	**13**	**11**

Based on the comparative analysis, Series B was selected as the optimal prototype, combining mechanical robustness, acceptable disintegration, pH compatibility, and visual appeal. It represents a balanced formulation suitable for further refinement or scale-up in future development phases.

3.4.2. Scoring system for batch evaluation and explanation of selection criteria

The selection of the optimal suppository formulation was based on a semi-quantitative scoring system designed to reflect both technological performance and patient-relevant usability. Each batch was evaluated across five key parameters, as outlined in the previous comparative matrix (Table 3.15), and a point system from 1 to 3 was used to normalize results for comparison.

The scoring logic was grounded in the following rationale:

Disintegration time. Ideally between 20–30 minutes. Batches that disintegrated within this range received 3 points. Slower disintegration (26–30 minutes) was acceptable (2 points). Over 30 minutes would be considered suboptimal.

Softening time. A softening time of 9–12 minutes was considered ideal (3 points), offering rapid action without compromising structure. Times between 12–15 minutes were acceptable (2 points).

Mechanical resistance. Suppositories with high manual strength were scored higher (3 points) as they are more resistant to deformation during handling. Excessively soft forms received only 1 point.

pH compatibility. All series fell within the acceptable range of vaginal pH (3.8–4.5); therefore, all received the maximum score (3 points).

Visual appearance. Smooth, uniform, and elegant suppositories were rated as optimal (3 points), while slight defects or tackiness led to deductions.

Each criterion reflects a balance between pharmaceutical standards and user acceptability, such as ease of insertion, comfort, and perception of quality. While therapeutic effectiveness ultimately depends on bioavailability and active release, these technological parameters are crucial in early formulation screening.

The equal weighting of each parameter (maximum 15 points total) ensured an unbiased assessment across multiple quality domains. However, when total scores were identical (as in Series B and C), mechanical resistance and surface quality were prioritized, given their role in patient handling and formulation stability.

This method provided a structured, reproducible, and transparent framework for decision-making in formulation development, allowing the selection of Series B as the lead prototype for future preclinical studies or stability testing.

3.4.3. Ranking of all tested batches and justification for Series B selection

Following the comparative evaluation based on standardized scoring criteria, all tested suppository batches (Series A–D) were ranked according to their total performance scores and critical attributes affecting therapeutic usability and manufacturability.

The rankings were as follows:

- Series B – Score: 13/15
- Series C – Score: 13/15
- Series A – Score: 12/15
- Series D – Score: 11/15

While Series B and C showed identical total scores, further differentiation was based on two key parameters:

- Mechanical resistance, essential for handling and packaging stability
- Visual uniformity, important for patient acceptability and dosing confidence

Series B maintained better mechanical integrity than Series C, with moderate but reliable resistance to deformation. It also had the most aesthetically uniform appearance, without surface roughness or tip deformation. These advantages suggest greater resilience during production, shipping, and use. Additionally, its disintegration and softening times fell within the ideal range, allowing both prompt onset of action and structural coherence.

In contrast, Series C, while effective, exhibited occasional inconsistencies in surface texture and slightly softer structure, which may raise concerns for shelf stability or patient comfort under non-ideal storage conditions.

Therefore, based on comprehensive analysis, Series B was chosen as the optimal formulation due to its:

- Balanced disintegration and softening behavior
- Acceptable pH and mass uniformity
- Favorable mechanical strength
- Pharmaceutical elegance and reproducibility

This formulation was identified as the most suitable candidate for further optimization, long-term stability testing, and potential clinical application.

3.4.4. Validation of reproducibility by re-preparing Series B and retesting key parameters

To ensure the reliability of Series B as the lead prototype, a reproducibility validation test was conducted. This step is crucial in early formulation development to confirm that the selected composition consistently yields suppositories with comparable physicotechnological characteristics when produced under the same conditions.

Using the exact formulation defined for Series B (as detailed in Table 3.6), a new batch of 10 suppositories was prepared following the previously described molding method. All materials, equipment, environmental conditions, and handling techniques were kept constant to replicate the original process accurately.

Three critical parameters were selected for verification: mass uniformity; disintegration time; softening time.

The results of the reproducibility check are presented in Table 3.16, alongside the original Series B values for comparison.

Table 3.16

Reproducibility check: key parameters for original and reproduced series B

Parameter	Original Series B	Reproduced Batch B	Relative Difference
Mean Mass (g)	2.01 ± 0.019	2.00 ± 0.018	−0.50%
Disintegration (min)	25.0 ± 1.0	24.7 ± 0.6	−1.20%
Softening Time (min)	11.7 ± 0.6	11.3 ± 0.6	−3.42%

As seen in Table 3.16, the re-prepared batch of Series B showed minimal deviations (<3.5%) across all evaluated parameters. Such consistency confirms that the formulation is robust and reproducible, even when re-manufactured under small-scale laboratory conditions.

These findings support the technological stability of the selected formulation and validate its suitability for further development, including stability testing, packaging assessment, and potential scale-up for preclinical or clinical phases.

3.4.5. Final formulation justification and summary of selection outcome

Based on the comprehensive experimental data generated throughout Chapter 3, the final selection of Series B as the optimal vaginal suppository formulation is fully justified from both a technological and practical standpoint.

This composition, containing 4% panthenol and 1.5% calendula extract in a PEG 1500:4000 (2:1) base, supplemented with 2% Tween 80, 1% cetyl alcohol, and 2% glycerin, exhibited the most favorable profile across all critical parameters:

- Balanced disintegration (25 minutes) and softening time (11.3 minutes), ensuring both timely drug release and structural stability

- Excellent mechanical resistance for manual handling and transportation

- Visual uniformity and elegant appearance, important for user confidence and product appeal

- pH compatibility with vaginal mucosa, ensuring tolerability and minimizing irritation risk

- Reproducibility, as confirmed by successful retesting with minimal deviation from the original data

These features make Series B a technologically sound and patient-acceptable dosage form, with the potential to deliver effective mucosal regeneration through the synergistic action of panthenol and calendula extract. The excipient profile supports both physical performance and bioactive compatibility.

This formulation provides a stable platform for future phases of pharmaceutical development, including long-term stability studies, scale-up process optimization, and biopharmaceutical evaluation.

Conclusions to chapter 3

1. The experimental studies presented in this chapter enabled the successful development and technological evaluation of vaginal suppository prototypes with regenerating activity.

2. The selection of excipients was based on the requirements for mucosal safety, thermal behavior, and structural stability. A hydrophilic base composed of PEG 1500 and PEG 4000 in a 2:1 ratio was identified as optimal based on its melting profile, visual uniformity, and compatibility with active ingredients.

3. Formulations containing panthenol and calendula extract were developed in four series, varying in active concentration. All prototypes met pharmacopoeial requirements for mass uniformity, pH compatibility, and acceptable disintegration and softening behavior.

4. Among them, Series B demonstrated the most favorable balance of physicotechnological properties, including satisfactory mechanical strength, homogeneous appearance, and reproducible performance. This formulation was selected as the optimal composition for further pharmaceutical development.

5. The findings confirm that suppositories based on the selected composition provide technological feasibility, mucosal compatibility, and reproducibility, laying a solid foundation for subsequent research phases.

CONCLUSIONS

1. The conducted research resulted in the development and technological substantiation of a vaginal suppository formulation with regenerating action, combining panthenol and calendula extract as active ingredients. The literature review confirmed the high relevance of non-hormonal, locally acting regenerating therapies, especially those based on plant-derived and synthetic bioactive agents. Ingredients such as *Calendula officinalis* and panthenol demonstrate strong potential for promoting epithelial healing, supported by both traditional use and scientific evidence.

2. Through experimental modeling, four prototype compositions were created and comprehensively evaluated by standardized physicotechnological methods. The results demonstrated that the base composition (PEG 1500:4000 = 2:1), when combined with 4% panthenol and 1.5% calendula extract, provided optimal balance between disintegration, softening time, mechanical strength, pH compatibility, and visual characteristics.

3. The selected formulation (Series B) showed high reproducibility and compliance with pharmacopoeial quality requirements, confirming its suitability for vaginal administration. The methodological approach, based on simple and validated technological tests, allowed for reliable assessment of product quality at the small-scale development stage.

4. Despite promising results, further studies are recommended to assess long-term stability, biopharmaceutical properties, and in vivo performance. The formulation may serve as a foundation for future clinical application and contribute to the expanding field of mucosal regenerative therapy.

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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

_____
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Olena RUBAN

"02" September 2024

ASSIGNMENT
FOR QUALIFICATION WORK
OF AN APPLICANT FOR HIGHER EDUCATION

Nohaila MSAILIH

1. Topic of qualification work: «Development of the composition of vaginal suppositories with regenerating action», supervisor of qualification work: Dmytro Soldatov, PhD, assoc. prof.,

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

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

3. Outgoing data for qualification work: to develop and experimentally substantiate the composition of vaginal suppositories with regenerating action based on panthenol and calendula extract

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 – 16_____

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 _____ Nohaila MSAILIH

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				
Мсаіліх Нохаіла	Розробка складу вагінальних супозиторіїв із регенеруючою дією	Development of the composition of vaginal suppositories with regenerating action	доц. Солдатов Д.П.	доц. Ковальов В.В.

Ректор

Верно. Секретар

ФА2.8-03-317

ВИСНОВОК

експертної комісії про проведену експертизу
щодо академічного плагіату у кваліфікаційній роботі

здобувача вищої освіти

«05» травня 2025 р. № 331121134

Проаналізувавши кваліфікаційну роботу здобувача вищої освіти Мсаіліх Нохаіла, групи Фм20(4,10д)англ-04, спеціальності 226 Фармація, промислова фармація, освітньої програми «Фармація» навчання на тему: «Розробка складу вагінальних супозиторіїв із регенеруючою дією / Development of the composition of vaginal suppositories with regenerating action», 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

Nohaila MSAILIH

on the topic: **«Development of the composition of vaginal suppositories with regenerating action»**

Relevance of the topic. The development of vaginal suppositories with regenerating action is highly relevant, addressing the growing demand for local treatments that promote mucosal healing and tissue repair. The use of natural ingredients like panthenol and calendula extract aligns with current trends in patient-centered, non-hormonal therapy.

Practical value of conclusions, recommendations and their validity. The work provides valuable insights into the formulation of vaginal suppositories, including the selection of active ingredients, excipients, and optimal processing methods. The findings are directly applicable to small-scale production and further clinical studies, supporting the development of effective regenerative therapies.

Assessment of work. The thesis demonstrates a systematic approach to formulation development, including comprehensive preformulation studies and evaluation of physicotechnological properties. The data is presented clearly, reflecting a solid understanding of the topic and strong experimental skills.

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

Nohaila MSAILIH

on the topic: **«Development of the composition of vaginal suppositories with regenerating action»**

Relevance of the topic. The development of vaginal suppositories with regenerating action is highly relevant, addressing the need for local treatments that support mucosal healing and tissue repair. This approach is aligned with current trends in non-hormonal, patient-centered therapy.

Theoretical level of work. The work demonstrates a solid theoretical foundation, including a thorough review of active ingredients like panthenol and calendula extract, known for their regenerative and anti-inflammatory properties. The analysis effectively covers the mechanisms of mucosal healing and suppository formulation.

Author's suggestions on the research topic. The study presents practical approaches to improving suppository formulation, including the selection of excipients and optimization of base composition. The author's choices effectively address the challenges of consistency, bioavailability, and patient comfort.

Practical value of conclusions, recommendations and their validity. The findings provide clear guidelines for developing stable, high-quality suppositories for mucosal regeneration, supporting both small-scale production and potential industrial application.

Disadvantages of work. Minor typographical errors were noted, but they do not significantly affect the overall quality or scientific validity of the work.

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 вагінальних супозиторіїв із регенеруючою дією»

здобувачки вищої освіти випускного курсу Фм20(4,10д.)англ-04 групи НФаУ 2025 року випуску _____Нохаіла МСАІЛІХ_____
(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_Нохаіла МСАІЛІХ__
(ім'я, прізвище)
на тему:__«Розробка складу вагінальних супозиторіїв із регенеруючою дією»

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 Нохаіла МСАІЛІХ до захисту кваліфікаційної роботи
за галуззю знань 22 Охорона здоров'я
спеціальністю 226 Фармація, промислова фармація
освітньо-професійною програмою Фармація
на тему: «Розробка складу вагінальних супозиторіїв із регенеруючою дією».

Кваліфікаційна робота і рецензія додаються.

Декан факультету _____ / Микола ГОЛІК /

Висновок керівника кваліфікаційної роботи

Здобувачка вищої освіти Нохаіла МСАІЛІХ 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 Нохаіла МСАІЛІХ 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 /