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QUALIFICATION WORK

on the topic: «**JUSTIFICATION OF THE COMPOSITION AND TECHNOLOGY OF BUCCAL FILMS WITH KALANCHOE JUICE»**

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ANNOTATION

The results of the analysis of scientific literature data on the development of the composition and technology of buccal films with Kalanchoe juice are presented in the work. The technological methods of including juice in the composition of buccal films are studied. The composition and technology of buccal films prescribed for aphthous stomatitis, and gingivitis are substantiated in this research.

The work consists of the parts: introduction, literature review, choice of research methods, experimental part, conclusions, list of reference sources, total volume of work 40 pages, contains 4 tables, 6 figures, 32 literature sources.

Key words: buccal films, Kalanchoe juice, composition, Kalanchoe pinnate, technology.

АНОТАЦІЯ

У роботі наведено результати аналізу даних наукової літератури щодо розробки складу та технології букальних плівок із соком каланхое. Вивчено технологічні прийоми включення соку до складу букальних плівок. У роботі обґрунтовано склад і технологію виготовлення букальних плівок, призначені для лікування афтозного стоматиту і гінгівіту.

Робота складається з таких частин: вступ, огляд літератури, вибір методів дослідження, експериментальна частина, загальні висновки, список використаних джерел літератури, загальний обсяг роботи 40 сторінок, містить 4 таблиці, 6 рисунків, 32 джерела літератури.

Ключові слова: букальні плівки, сік каланхое, склад, каланхое перисте, технологія.

CONTENT

LIST OF ABBREVIATIONS

API	–	active pharmaceutical ingredients
CMC	–	Carboxymethyl cellulose sodium
GIT	–	gastrointestinal tract
HEC	–	Hydroxyethyl cellulose
HPC	–	Hydroxypropyl cellulose
HPMC	–	Hydroxypropyl methylcellulose
IUPAC	–	International Union of Pure and Applied Chemistry
mg	–	milligram
PVP	–	poly(vinyl pyrrolidone)
sec	–	seconds
SPU	–	State Pharmacopeia of Ukraine

INTRODUCTION

The relevance of the topic. One of the urgent problems of modern dentistry is inflammatory periodontal disease both in children and adults, against the background of untimely consultation with a doctor. In recent several decades, there has been a negative trend in the spread of periodontal disease among people of working age. In the treatment of inflammatory periodontal diseases, synthetic drugs are used, which can have a large number of side effects. Therefore, one of the search areas for new medicines is the analysis of plants containing biologically active substances that can affect various links in the pathogenesis in periodontal tissues inflammation and may be used in the treatment of gingivitis and aphthous stomatitis.

Diseases of periodontal tissues rank second after caries among dental pathologies and constitute an important modern problem. Periodontal tissue diseases appear under the influence of both local and general causes in nature. The smoking is a risk factor that causes diseases specific to smokers, and also contributes to the occurrence and progression of dental diseases, such as periodontal tissues [11–13].

The phytopreparation prescribed for gingivitis and aphthous stomatitis treatment is Kalanchoe juice from the plant *Kalanchoe pinnata* (genus *Kalanchoe*), which has anti-inflammatory effect, may helps clean wounds of necrotic tissues, and stimulate their healing. Kalanchoe juice is applied to the oral mucosa three – four times a day in the applications form, which is uncomfortable when used. In recent years, there has been growing attention in the scientific investigation of this plant. Therefore, there is a certain interest in the creation of new pharmaceuticals with Kalanchoe juice in new medicinal forms.

Buccal films are the perspective drug delivery system due to their ability to deliver drugs directly to the place of the action in the oral cavity, and they are capable of facilitating local delivery. Mucoadhesive buccal films are the patient preferred dosage form, owing to their superior flexibility which enhances comfort.

The purpose and research tasks. This research was aimed to demonstrate the possibility of the composition and technology development of buccal films with Kalanchoe juice prescribed for aphthous stomatitis and gingivitis.

The research tasks that we solved to achieve the purpose are following:

– to summarize and analyze the data of literature sources about medicines for the treatment of inflammations of the oral cavity mucosa and gums, about application and active chemical compounds of *Kalanchoe pinnata*;

– to consider buccal films as a pharmaceutical form and technologies for their formulation;

– based on the results of pharmaco-technological research to choose suitable excipients for buccal films with Kalanchoe juice;

– to substantiate the composition and technology of buccal films with Kalanchoe juice;

– to analyze the results of the main quality indicators of developed buccal films with Kalanchoe juice.

The object of the research is green part of the stems and fresh leaves of the Kalanchoe pinnata, Kalanchoe juice, buccal films based on Kalanchoe juice.

The subject of presented research is the rational composition and technology of buccal films with Kalanchoe juice.

Research methods. Pharmacopoeial methods for determining physico-chemical and technological parameters of the Kalanchoe juice and obtained films were used. Experimental data that were obtained during studies of buccal films with Kalanchoe juice were processed with the methods of the mathematical statistics.

The approbation of qualifying work results and scientific publications – author's participation in the scientific-practical Internet conference with international participation «Pharmaceutical technologies, standardization and quality assurance of medicines» on May 22, 2025 (Kharkiv) with publishing abstract [32] and in the XXXI International scientific and practical conference of young scientists and students «Current issues of creating new medicines» on 23–25 April, 2025 (Kharkiv) with oral report.

Structure and scope of qualification work. Qualification work consists from introduction, three chapters, conclusions, list of the references (32 sources) and annex. The content of work is presented on 40 pages of basic text and contains 4 tables and 6 pictures.

CHAPTER 1
CURRENT STATE OF THE PROBLEM OF CREATING MEDICINES FOR THE TREATMENT OF INFLAMMATIONS OF THE ORAL CAVITY MUCOSA AND GUMS (REVIEW OF LITERATURE)

1.1. Medicines used in the treatment of oral mucosal diseases

The oral mucosa, gums and the surrounding tissues are the entrance to the body, where oral lesions can be seen, and also symptoms of various systemic diseases can be observed. The etiology of the lesions occurring in the oral mucosa and gums may be immunological, infection, trauma causes or idiopathic.

Medicines application onto the mucosa of the oral cavity has long been a problem of pharmacology. However, some forms of medicines have desired biopharmaceutical properties on the oral mucosa, with which dentists deal.

Common oral mucosal disorders include aphthous stomatitis, gingivitis, candidiasis. Recurrent aphthous stomatitis is characterized by persistent painful oral ulcers lasting days to months. Gingivitis means inflammation of the gums, or gingiva. It is a form of gum disease that causes irritation, redness and swelling of your gums. Gingivitis commonly occurs because bacteria, or a film of plaque, accumulates on the teeth [17].

A wound in the oral cavity is the deterioration of the integrity of tissue by a physical damage. Wound healing is a complex process and consists of three phases: inflammation, proliferation and maturation.

Hemostasis and inflammatory infiltration occur in an inflammatory phase. The blood vessels are damaged at the site of the injury of tissues and platelets start hemostasis in a wound region by a cellular plaque forming. Microfibrils and collagen are exposed to the circulation in the subendothelium. This activates thrombocytes and causes adhesion of platelets in the wound area. Metabolites of arachidonic acid, various growth factors and proteases released from platelets adhered to the subendothelium activate the inflammatory process formation. Inflammation, increased vascular permeability and activation of the complement system result in

migration of various immunological cells, primarily neutrophils, to the wound area. Immunological cells secrete cytokines and proteolytic enzymes, while they also play a protective role against foreign organisms. Then the number of immunological cells begins to decrease at the end of this phase. Fibroblasts and endothelial cells appear at the region of the wound and initiate the proliferative phase [19].

Granulation formation, fibroplasia, contraction, angiogenesis, and epithelization occur in the proliferative phase. New blood vessels are formed from the epithelial cells to provide oxygen and nutrients for the proliferating cells in angiogenesis. The epithelial cells proliferate and spread to the site of wound during epithelization. Fibroblasts proliferate also at the wound area and transform into myofibroblasts.

Collagen and fibronectin are secreted, and involved in the new connective tissue to form extracellular transient matrix. Collagen is an important compound that contains large amounts of hydroxyproline. Besides that, the scar tissue contraction occurs by the myofibroblasts contraction. Keratinocytes appear and initiate re-epithelization in the early period of wound healing. Formed granulation tissue begins to replace a missing tissue.

In the maturation phase, scar tissue forms. Thus, wound healing is completed. Then the remodeling phase begins when keratinocytes differentiate into dermis. The important feature of this phase is accumulation of collagen in an wound which starts after formation of a cellular matrix. Collagen synthesis is initiated with a contribution of proteoglycans and glycosaminoglycan. As a result of the collagen fibrils cross-linking that are in a filaments form (fine yarns), their thickness increases.

Factors that slow wound healing include viral, bacterial, and fungal infections; diabetes mellitus; old age; adverse environmental factors. Factors that promote wound healing include medicines used, proper nutrition.

Medicines for the treatment of oral mucosal diseases are corticosteroids.

Corticosteroids are important drug groups due to their strong anti-inflammatory and immunosuppressive effects. Local, topical (cream, gel and lotion

forms), nasal, inhalation, systemic (orally or intravenously) routes administration, intraarticular injections of corticosteroid are available. For example, beclomethasone dipropionate, flunisolide, budesonide, mometasone furoate and fluticasone propionate are corticosteroids that can be administered by inhalation. Topical corticosteroids, such as triamcinolone acetonide, clobetasol propionate and fluocinonide, are widely used in the treatment of inflammatory diseases [17, 18].

Dexpanthenol is epithelizing agent that administered orally (lozenges), parenteral and topically (ointments, lotions). When topically applied it is absorbed rapidly. Dexpanthenol is an alcohol form of pantothenic acid, which is a factor of a vitamin B complex. After absorption, the pantothelium transforms into enriched acid in the liver. Pantothenic acid is an essential molecule for the formation and renewal of mucous membranes and skin. Dexpanthenol facilitates epithelization by supporting proliferation of fibroblasts [31].

Mouthwashes are important pharmaceutical forms in dental clinical practice. The aim of antimicrobial mouthwashe is to reduce the number of microorganisms in an oral cavity.

Benzydamine hydrochloride and chlorhexidine gluconate are the commonly used API in mouthwashes in the treatment of periodontitis, gingivitis, candida infections, in the symptomatic treatment of ulceration. Benzydamine hydrochloride is a non-steroidal anti-inflammatory agent wich provides local anesthesia and has a stabilizing effect on membranes. But chlorhexidine may cause color changes on teeth and the tongue, these effects disappear after cessation [23].

Listerine is a lipid-based phenol compound and frequently used today, the mechanism of action of which results from bacterial cells walls destruction, and destruction of bacterial biofilm.

Triclosan is added to toothpastes and mouthwashes. Sodium lauryl sulphate mouthwash and paste forms available, but it is not preferred due to harmful effects.

Zinc salts are used due to their antibacterial properties. Zinc ions reduce bacterial absorption and plaque build-up on teeth [18].

There are nystatin-containing preparations available in suspension form among antifungal mouthwashes. After determination of *Candida albicans*, mouthwashes should be used in accordance with the doctor's recommendation.

Mouthwashes containing benzocaine, pastilles with benzocaine and cetylpyridinium chloride, lidocaine hydrochloride 2% gel, lidocaine 1% cream or spray are other topical agents in reducing pain.

Mouthwashes with tetracycline reduce the duration of oral ulcers. Mouthwashes are effective in prevention of secondary infections and concomitantly inhibit collagenase activity and processes leading to inflammation, cell destruction. Doxycycline in muco-adhesive gel has been reported to be more effective.

Amlexanox 5% paste or 2 mg tablets cause reduction in the number of aphthous ulcers and pain severity when they are used in the prodromal period [19].

There are different herbal agents. The active ingredients of *Centella asiatica* extract (*Gotu cola*), one of the herbal agents, include triterpenic saponins (madecassic acid, amino acid, flavone). The re-epithelialization effect in the wound region is thought to originate from triperpenoid saponins in extracts content. The ointment form, gels, creams and powders with *Centella asiatica* extract are produced.

Chamomile contains various phytochemicals that provide therapeutic benefits, mainly flavonoids, coumarins, and essential oils. It is used topically in oral inflammation, mucous membranes, wound healing, and for gums with bacterial infections.

Aloe vera plant positively affect wound healing. *Aloe vera* contains potentially active compounds including enzymes, vitamins, minerals, sugars, lignin, salicylic acid, saponin, and amino acids. It binds to growth the factor receptors in fibroblasts and increases their proliferation and activity. Aloe gel alters the amount and composition of collagen, it strengthens a scar tissue and accelerates a wound contraction. After topical application, aloe gel causes an increase in the hyaluronic acid and dermatan sulfate synthesis in the granulation tissue during the healing process of wounds. The beneficial effects of *Aloe vera* have been reported in the

treatment mucositis and aphthous stomatitis. *Aloe vera* is not superior to corticosteroids, but it may be used as a supportive agent.

Triticum vulgare extract supports re-epithelization by stimulating mRNA and DNA synthesis in lymphocytes and fibroblasts. It enhances wound healing by fibroblast and chemotaxis maturation with synthesis glycosaminoglycans and collagen fibers.

Clove oil (Eugenol) is frequently used in dentistry and has local anesthetic, antiseptic (which inhibits bacterial replication), analgesic, antifungal, antiviral and antiinflammatory properties [31].

1.2. The use of Kalanchoe pinnata juice in medical practice

Kalanchoe pinnata (*K. pinnata,* homotypic synonym *Bryophyllum pinnatum*) (Lamarck) Persoon (*Crassulaceae*) is a perennial succulent plant native to Madagascar. The *K. pinnata* is an erect herb, growing up to 1-1,9 meters tall, with juicy and fleshy stems that are green or may be reddish in color. The leaves are ovate to lanceolate, alternate, and arranged spirally on stems (Fig. 1.1). They are thick and succulent, with the crenate margin, and have small plantlets growing on margins that may reproduce vegetatively. The flowers are bell-shaped, small, and greenish-white in color, arranged in pendulous clusters at stems tips.

The plant produces numerous small, dark brown, and shiny seeds. The root system of plant is shallow and fibrous, with lateral roots that help anchor the plant to a soil. Stems are hollow, and leaves are held in a rosette-like arrangement at the stems top.

The *K. pinnata* morphological characters make it the easily identifiable and unique plant. It is a popular ornamental plant; its medicinal properties have been used in traditional medicine for centuries. The medicinal plant is valued for its ability to grow in the variety of environments, making it adaptable to the wide habitats range [5].

Fig. 1.1. *K. pinnata* leaves [29]

It is used for healing wounds in a traditional medicine. Extracts of *K. pinnata* are reported to exhibit antimicrobial and virucide activity. Further, they were found to kill malaria plasmodium and leishmanias. It exhibits immunomodulatory, anti-inflammatory, antihistamine, antimutagenesis, and hepatoprotective effect; and inhibits thyroid peroxidase. It has been reported about positive effect of *K. pinnata* extracts towards experimental gastric ulcer in mice. Antifungal activity of Kalanchoe extracts is mentioned. Study of the *in vitro* antimicrobial action of *K. pinnata* leaf demonstrated that the water concentrates of the leaf had effectively restrain the zones of microorganism.

Kalanchoe pinnata contains a number of biologically active compounds that contribute to pharmacological properties of its extracts: flavonoid glycosides, bufadienolides and lectins.

Flavonoid glycosides in *K. pinnata* are two phenolic glucosides, 4′-O-*β*-D-glucopyranosyl-cis-p-coumaric acid and syringic acid *β*-D-glucopyranosyl ester; nine flavonoids including kaempferol, acacetin, and diosmetin glycosides; and flavonol glycosides such as myricetin (3-O-*α*-L-arabinopyranosyl-(1 → 2)-*α*-L-rhamnopyranoside) and quercetin (3-O-*α*-L-arabinopyranosyl-(1 → 2)-*α*-L-rhamnopyranoside 7-O-*β*-D-glucopyranoside).

Bufadienolides in *K. pinnata* are bryophyllin A, bersaldegenin-3-acetate, bersaldegenin-1-acetate, and bersaldegenin-1,3,5-orthoacetate [15, 21].

Blood-agglutinating lectins with Mr 44–47 kDa contain ~1.5% carbohydrate.

The *K. pinnata* leaf extract was evaluated by scientists for its wound healing activity with using excision wound model in animals. There was progressive

reduction in the wound area in rats on the 11th day wounding [8]. The histological analysis showed that *K. pinnata* extract exhibited significant wound healing potential that may be attributed to the steroid glycosides presence.

The different polyphenols, flavonoids, triterpenoids and other chemical compounds of the plant are speculated to account for the antinociceptive (suppress activity in the neurons, which respond specifically to nociceptive pain), and anti-inflammatory properties.

Some external applications of the *K. pinnata* leaf extract are found to be effective for severe burns, painful boils, insect bites, chronic ulcers, deep wounds, severe infections, earache, toothache and headache. Aqueous extract has proved to be potential antitumour and anti-inflammatory agent. It has proved to be effective against epithelial desquamation and blood vessel congestion. Leaves of *Kalanchoe pinnata* are used for wounds, ulcers, swellings, plegmon [22].

Juice of *Kalanchoe pinnata* is obtained from fresh leaves and the green part of the stems. The juice is produced in 100 ml bottles or 10 ml ampoules [1]. The juice of the leaves is applied in the form of lotions for ulcerative wounds. It is also used for various types of inflammation of the oral mucosa and gums in dentistry.

Kalanchoe juice is applied to the mucous membranes in the oral cavity by the application 3−4 times a day. The juice is heated in a water bath to a temperature of +37 °C before use in dental practice.

We can conclude from the information mentioned above, that such pharmaceutical form is inconvenient. Therefore, we considered buccal films for use in the oral cavity for further research.

1.3. Characteristics and technologies of buccal films

Buccal flexible films in the form of thin, solid, mucoadhesive patches that can be used as the dressings separating aphthous lesions from the oral cavity environment. They can reduce the pain perception and shorten the treatment period [6, 7].

Mucoadhesive buccal films are preferred over the mucoadhesive tablets because they are flexible and thin that induces comfort and ease during routine activities such as drinking, eating, and speaking.

The buccal delivery films or films based on thermoresponsive hydrogel can be composed by natural or synthetic polymers. The API released from the matrix into the oral cavity owing to the erosion and its diffusion controlled in the dosage form [9, 14].

Various factors determine the optimum formulation of buccal mucoadhesive films, such as biodegradation, mucoadhesive properties of polymers, biocompatibility, water permeation, API release, and physiomechanical properties. The choice of polymers allows the modulation of films properties designed for oral cavity. Polymers that are used as mucoadhesive are hydrophilic polymers that swell and allow chain interactions with mucin molecules of the buccal mucosa. Examples of swellable polymers are hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), sodium carboxymethyl cellulose (CMC), hydroxyethyl cellulose (HEC), chitosan and poly(vinyl pyrrolidone) (PVP) [10].

This review focused on buccal films for target API delivery to the treatment of mucosa disease.

Buccal drug delivery refers to an administration of API to the buccal mucosa, located within the mouth on the inside of the cheek. Buccal films are capable of facilitating both systemic and local drug delivery. This route avoids enzymatic drug degradation, first-pass metabolism, and it provides effective therapy to patient groups with swallowing difficulties or unable to swallow. Buccal tablets have the greatest presence within the commercial pharmaceutical marketplace of limited dosage forms in this area. But when compared to buccal tablets, mucoadhesive buccal films are believed to be the favoured dosage form amongst patients, owing to films superior flexibility that enhances patients' comfort, in addition to customizable sizes. Buccal films can be comprised of multiple layers and predominantly indicated for prolonged medicine release within the oral cavity.

The therapeutic potential of the buccal route of administration is great. But the lack of translation from published work into the commercial pharmaceutical marketplace. The scarcity of buccal formulations is thought to be due to the lack of physiologically and compendial relevant evaluative methodologies to properly characterise buccal dosage forms *in vitro.* Today, the development of such methods continues on thorough understanding of the physiological environment where buccally administered form reside. The various factors can influence physiological characteristics. Human saliva has innumerable characteristics that can not be fully understood. Such characteristics are not always considered in an *in vitro* dissolution analysis of buccal films. The human biological membranes complexity such as the buccal mucosa are poorly represented within *in vitro* permeation and mucoadhesion evaluations, in addition. The heterogeneity between the very young and the old-aged patients, who are affected by multi-morbidities and different disease status, renders it a difficulty *in vitro* methodology for the evaluation of buccal delivery systems. But must be taken into account the availability of alternative pharmaceutical forms such as syrups, solutions, may also be contributory to the scarcity of commercial realisation of the buccal film technology [14, 25, 30].

Buccal films represent therapeutic advantages in special patient populations (paediatric and geriatric age groups), due to instances of swallowing difficulties and the prevalence of dysphagia. Swallowing difficulties in the paediatric population are also a consequence of the developmental process, resulting in the using dose aids, for example, oral syringe. Some scientists demonstrated that children aged 6–11 years old were able to swallow a small oral tablet. They also demonstrated that most children aged between 4 and 8 years old swallowed tablet upon attempting to do so and successfully. But such results are based on individual children's populations and are subject to variability. This makes the definition of the age from where children may definitively swallow tablet problematic.

Difficulty in swallowing tablets may be a prominent issue in geriatric patients who are more than 65 years old. This highlights a requirement for alternative routes of administration, for example, the buccal route. Dysphagia has been referred to as

the geriatric syndrome in this population, that can also induce the dry mouth. The development of buccal films for geriatric age group patients is necessity.

The buccal mucosa surface area plays a role in buccal API delivery. It influences the area available for films to be applied to and consequently for medicine absorption. It has been determined a total surface area of the adult oral mucosa to be 214.5 cm^2 on average, and in a group of 5-year-old children's oral mucosal surface area to be 117.5 cm^2. In addition, scientists also estimated the film of saliva covering the buccal mucosa to be 70–100 μm thick. The results are based on volumes of saliva after and before swallowing. The superficial epithelial cells are the main barrier to API permeation across the oral mucosa, when compared to that of a submucosal space. It is believed that the buccal epithelium is 4–4000 times more permeable than a human skin. It has been shown that lipophilic, small molecules are able to permeate as paracellularly, while hydrophilic small molecules permeate as transcellularly. The enzymatic action of a mucus layer coating an epithelium and tight junctions present within a buccal epithelium represent barrier to large macromolecules such as peptides or proteins. For medicines molecules to be able to travel through an oral mucosa, APIs must diffuse through the lipophilic cell membrane initially, and then pass through the hydrophilic interior of oral epithelial cells. So, the lipophilic compound exhibits the superior permeability coefficient than the hydrophilic compound, but aqueous solubility of the lipophilic compounds is inferior. But it has been determined that the amount of a lipophilic API that is absorbed due to high hydrophobicity can not be as high as expected. Systemic absorption of the buccally administered API is facilitated by a distribution of medicine molecules throughout the body *via* the jugular vein into a systemic circulation thus avoiding the hepatic first pass metabolism.

The composition of human saliva is important to drug delivery systems as its components can influence API dissolution and then absorption. Saliva is comprised of water approximately 99,0 %, in addition to mucins, enzymes, electrolytes, inorganic ions, and other small molecules. The human saliva pH is known to be variable. It is an indicator of poor health when the salivary pH falls outside the

typical physiologically range. Attention should be paid to the pH of saliva, as variations in pH may induce API ionisation, when developing buccal films. The salivary buffer capacity ensures the maintenance of pH, and also plays a important role in oral health through reduction of bacterial growth and aiding in dental remineralization. Human saliva is buffered by such key systems: the phosphate system, the protein system, the bicarbonate system, and the urea system [16, 20].

The API dissolution and absorption from buccal films is facilitated by a continuous saliva flow over the surface of dosage form. The dry mouth could reduce ultimately the amount of medicine that ends up in a systemic circulation. The gustatory, olfactory and mechanical stimulation of saliva may occur, affecting characteristics of saliva such as buffer capacity, the pH, and the obviously salivary flow rate. The stimulation saliva state is the important physiological characteristic, and it may influence buccal medicine delivery.

The salivary osmolarity is believed to play a role in hydration status. The osmolarity of saliva refers to the electrolytes concentration of per litre of saliva. The surface tension of saliva may affect the dosage forms dissolution rate in the oral cavity. The wettability of drug particles is reduced with a high interfacial tension and consequently the drug dissolution rate is reduced [25–27].

When compared to a medium of lower viscosity of saliva the increased viscosity of saliva can increase the boundary layer thickness and decrease a diffusion coefficient of API molecules. So, the rate of drug dissolution is decreased also [28, 30].

The use of salivary stimulants can increase the salivary flow rate, the salivary pH, decrease the salivary ionic concentration, and the viscosity of saliva.

Several manufacturing techniques have been employed for the mucoadhesive buccal films, including hot melt extrusion, solvent casting, inkjet printing and 3D printing. These manufacturing techniques offer some advantages. Stability of buccal films after obtaining is very crucial. Packaging represents a critical barrier to moisture, oxygen and light, provides mechanical protection for mucoadhesive films. Aluminium foils that offer moisture and light protection and lidding foil that may

offer tamper-proof packaging are common in the case of buccal films. Packaging of films in this manner offers handling, ease, and economic advantages. Commercialised buccal films that have been produced by the PharmFilm® technology, are hermetically packaged within sealed child-resistant foil wrappers in order to stop film from sticking to packaging. The packaging also gives produced films high portability with increasing patients convenience [24, 25].

Solvent casting is the most widely used process for obtaining buccal films, due to the simplicity of the processes and low cost. The solvent casting include dissolving water soluble ingredients (polymers) to form viscous homogenous solution and then subsequently dissolving the medicine and other excipients. Films are cut in specified dimensions as to contain the dose of the API once the solution is dried [14].

Conclusions to chapter 1

1. Lesions in the oral mucosa can arise from a number of disorders, including a sign of trauma, local or systemic diseases, and also due to infection. The aim of the healing is to apply the symptomatic treatment that mainly improve the patient's comfort while solving the underlying problem. These are achieved primarily by prescribing medicines in the appropriate manner mentioned in the review.

2. *Kalanchoe pinnata* has been used in medicine for the treatment of numerous ailments such as wounds and respiratory infections. This review summarizes pharmacological activities of K. pinnata including anti-inflammatory and anti-microbial effects.

3. The review highlights the development features of mucoadhesive buccal films, given their significant therapeutic opportunities.

CHAPTER 2
THE JUSTIFICATION OF THE RESEARCH GENERAL CONCEPT. OBJECTS AND METHODS OF RESEARCH

2.1. Methodological approaches to the buccal films formulation with Kalanchoe juice

The buccal route can be considered a suitable local and systemic delivery to prevent and treat aphthous stomatitis, and gingivitis, ensuring a quick API action with reduced side effects given the complexity of an oral cavity system, divided in epithelium (avascular and thick) and also underlying tissue (vascular). Buccal films have emerged as a valuable drug delivery technology for this purpose. Aside from their small thickness and size, these delivery systems are characterized by a painless application, potential for removal in case of negative therapeutic side effects. Buccal films present a protective barrier effect, which increase patient compliance. The main goal of this research was to incorporate an Kalanchoe juice in buccal films to explore their potential use to treat inflammatory periodontal disease.

Research of buccal films with Kalanchoe juice carried out with different mucoadhesive polymers. The chemical characteristics that provided films mucoadhesive functionality, polymers use alongside other constituents of film formulation, their commercial availability, and details of polymers effect on in vitro medicine release properties have been evaluated.

2.2. Characteristics of Kalanchoe juice and excipients

K. pinnata juice has a characteristic faint pleasant odor and a sour, slightly astringent taste, which is due to the presence of volatile oils and other phytochemicals. Kalanchoe juice is a transparent or yellowish liquid with an orange tint.

Kalanchoe juice was obtained by a known method that allows preserving the active substances with a long shelf life due to the lack of offers now at the pharmaceutical market of Ukraine. Fresh plant shoots were used. Kalanchoe shoots

were collected initially during the growing season. Then we kept shoots at a temperature of 4±2 °C in a dark place for 7 days. The washed biostimulated Kalanchoe green mass was ground in the grinder, then centrifuged at 600 rpm for 15.0±0.5 min. The liquid phase of green mass was collected in glass containers and placed in a refrigerator for one day at a temperature of 4±2 °C. The precipitate that formed in glass containers was separated by filtration. Ethanol as preservative in an amount of 3 % was added to the filtrate and kept in the cold at a temperature of 2±1 °C for maturation for one day until a precipitate formed. The liquid was filtered and the resulting Kalanchoe juice was poured into bottles.

The pH of Kalanchoe juice was 5.0.

Kalanchoe juice contains usually a small amount of tannins (0.032%), polysaccharides (about 40 %), and compounds with P-vitamin activity (0.05%). Tannins and catechins have been determined in Kalanchoe juice. Catechins are polyphenolic compounds from the group of flavonoids (Fig. 2.1, 2.2.). Catechins are strong antioxidants.

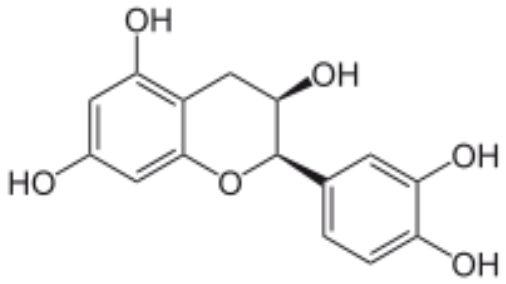

Fig. 2.1. Structural formula of epicatechin

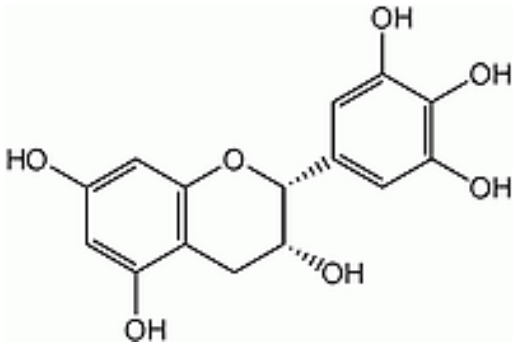

Fig. 2.2. Structural formula of epigallocatechin

The main phenolic compound (60–63 % of all phenolic components) is an diglycosylflavonoid identified as quercetin 3-O-α-L-arabinopyranosyl (1→2)-α-L-rhamnopyranoside (Fig. 2.3) or quercetin arabinopyranosyl rhamnopyranoside among the phenolic components in aqueous extracts of K. pinnata leaves that have been described in scientific literature. The glycosylation pattern of the flavonoid is quite unusual despite the presence of quercetin — one of the most common flavonol aglycones. Flavonols 3-O-glycosylation by the arabinosyl fragment occurs less frequently than by the rhamnosyl or glucosyl fragments. This difference is due to the presence of the corresponding glycosylation enzymes at these sites (arabinosyl, rhamnosyl and glucosyl). This phenolic compound (quercetin 3-O-α-L-arabinopyranosyl (1→2)-α-L-rhamnopyranoside) is rarely found in nature.

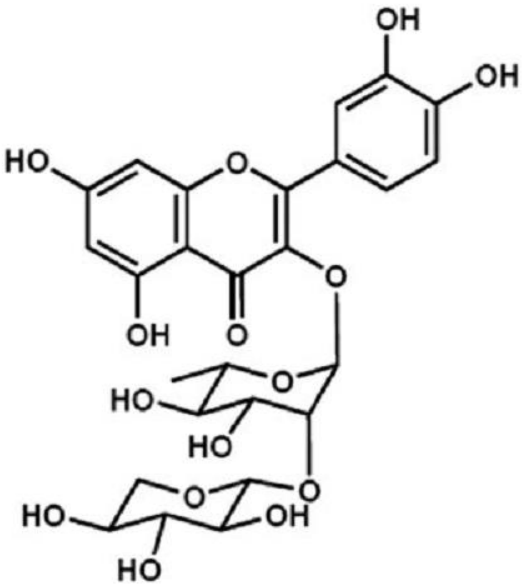

Fig. 2.3. Structural formula of quercetin 3-O-α-L-arabinopyranosyl (1→2)-α-L-rhamnopyranoside

Excipients included in the list of excipients permitted for medicines and approved by Order of the Ministry of Health of Ukraine No. 339 dated June 19, 2007 were used during experimental research on the composition development of the buccal films with Kalanchoe juice.

Purified water is colorless, odorless liquid that satisfies the endotoxins test described in SPU. It is produced usually from potable water. Purified water is a grade

of pharmaceutical water that is free of calcium, carbon dioxide, sulfates, chloride, ammonia, and heavy metals.

HPMC K100LV is a low–molecular weight hydroxypropyl methylcellulose polymer. In water at 20°C HPMC yields a viscosity of 80–120 cPs at a 2 % addition rate. HPMC K100LV is a low-viscosity (LV) type of HPMC with moderate hydroxypropyl substitution. When HPMC K100LV is added at 2 % to water, solutions impart high lubricity, and shear-thinning making them easy to spread. Solutions of the scipient has excellent pH stability and allows precise rheology control in the solution with low viscosity in alkaline and acid environments. HPMC K100LV features are also thermal gelation properties. Solutions containing this excipient will gel at 70–90 °C, producing a soft gel.

Carbopol 940 is an crosslinked polyacrylic acid polymer extensively utilized for its superior thickening and gelling properties at low concentrations. Carbopol 940 polymer is a white powder, soluble in water: 3-4 g/L (20 °C) with gel forming.

Polyvinylpyrrolidone K-17 powder is used in adhesive sticks and in pick-up adhesives that can be broken and remade several times. Excipient can be used as a protective colloid and thickening agent in adhesive dispersions. PVP K-17 known for its properties such as the ability to form strong films.

Glycerol (propan-1,2,3-triol) is a thick, sweet, colourless liquid. Glycerol is a simple triol compound. Molecules of glcerol are highly polar due to the presence of three polar hydroxyl (-OH) groups. These hydroxyl groups readily form hydrogen bonds with polar water molecules when mixed. As water is a polar molecule, which indicates that the electric charges in its molecules are oriented in different directions, this makes water an excellent solvent for polar molecules like glycerol. In water, glycerol is soluble at concerning 1.2656 g/mL. Glycerol dissolves slowly as it takes time for water molecules to disrupt the extensive hydrogen bonding between glycerol molecules themselves. Density of glycerol is 1.261 g/cm^3. As such, initially it forms a dense layer below the layer of water. However when stirred it is seen to dissolve completely.

2.3. Methods of research

Research methods of films described in the literature [14] were used by us.

2.3.1. Mass uniformity of films

The weight of Kalanchoe buccal films was evaluated in an analytical balance (Radwag, Poland) to assess the mass uniformity. Films portions from different batches (n = 5) were individually weighed and a mean weight and standard deviations were calculated.

2.3.2. Folding endurance of films

Buccal film samples (4 cm^2) were repeatedly folded (180°) until break or observe signs of tare. The 300 folds limit was set. The number of times the films samples were folded was accounted as folding endurance value (n = 5).

2.3.3. Thickness of films

Thickness was measured using a electronic digital calibrated micrometer. The measurements were performed for different buccal film samples from different batches (n = 5).

2.3.4. Moisture content and swelling capacity of films

The swelling capacity and moisture content of buccal films were evaluated. Film samples (4 cm^2) from various batches were weighted and placed in an infrared moisture balance with an infrared lamp heated at 105 °C.

The moisture percentage was calculated automatically through the differential of the film sample weight before and after heating by the device.

Then the indirect swelling capacity was determined as the water mass increase. New buccal film samples were hydrated for 2 min and 30 s with 20 mL phosphate buffer with pH 7.4 and gently collected with a filter paper to remove the excess of water. The moisture of hydrated buccal film samples was measured as as described above.

2.3.5. Mechanical properties of films

Mechanical properties of Kalanchoe buccal films, namely percent of elongation (%) (Eq. (2.1), resistance to extension (N), and Young's modulus (Eq. (2.2) were evaluated using a texture analyzer. In this test films samples were cut in

4 × 1 cm portions and were vertically held by the using a tensile grip probe with a separation of 20 mm. Then films samples were stretched by moving a probe at the constant speed of 0.1 mm/s until the rupture. The calibrations of the force and height were performed with the 5 kg weight and Mini Tensile Grips, respectively.

$$\%EL = \frac{L_f - L_0}{L_0} \times 100, \quad (2.1)$$

where *%EL* — percent of elongation, %;

L_f — distance at the rupture instant, m;

L_0 — initial grip distance, m.

$$Y = \frac{F \cdot l}{A \cdot x} \times 100, \quad (2.2)$$

where Y — Young's modulus, MPa;

F — force at corresponding strain, N;

l — length of sample, m;

A —cross-sectional area of the film, m^2;

x — corresponding strain, m.

2.3.6. Disintegration time of films

The disintegration time of buccal films was evaluated by a film sample dipping (4 cm^2) into a petri dish containing 20 mL of artificial saliva (pH 6.9) pre-heated at 37 °C and with constant stirring. Artificial saliva was a buffer solution (pH 6.9) 0.964 g/L KCl, containing 0.126 g/L NaCl, 0.655 g/L KH_2PO_4, 0.189 g/L KSCN, and 0.200 g/L urea. Different buccal film portions from different batches were evaluated. The results are presented in minutes and the time stopped when the complete disintegration occurred.

2.3.7. Statistical analysis

All measurements were performed with $n = 5$ and the results were expressed as mean ± standard deviation (SD).

Conclusions to chapter 2

1. Methodological approaches to the development of the Kalanchoe buccal films are suggested.

2. The technology method of Kalanchoe juice obtaining and excipients characteristics that were used for the development of the buccal films are contained in this chapter.

3. The basic methods of physico-chemical and technological research for the formulation and evaluation of Kalanchoe buccal films are presented.

CHAPTER 3
EXPERIMENTAL PART.
RESEARCH FOR DEVELOPMENT OF PREPARATION COMPOSITION IN FORM OF BUCCAL FILMS WITH KALANCHOE JUICE

3.1. Choice of excipients and development of buccal films composition

The formulation development was aimed at creating buccal films with Kalanchoe juice that could provide the prolonged API release, a faster onset of action, and improved bioavailability. The films prepared have been characterized and the dosage form was evaluated *in vitro*.

The initial obtaining of buccal films production was implemented using different polymers at different concentrations (Carbopol 940, HPMC K100LV and combination HPMC K100LV with Polyvinylpyrrolidone K-17). The concentration of glycerol as plasticizer was also adjusted. The qualitative parameters were used for the evaluation, namely, presence of excessive glycerol residue and surface roughness. After first studies, glycerol was fixed to 3.0 % (*w/v*), polymers solution 1.5–2.5 % (*w/v*) and 90 ml Kalanchoe juice were used. Water was added up to 100 ml. The composition of selected polymers, plasticizer and Kalanchoe juice used in polymeric solutions for film formulations are summarized in Table 3.1.

The Kalanchoe buccal films mixture was mixed for 1 hour, and then 50 g of mixture were transferred into petri dishes (8.5 cm in diameter) and incubated at temperature 4 °C for 24 hours to remove the air bubbles. Then for solvent casting, petri dishes were placed in the dryer at 40 °C for 48 hours. After that, the obtained Kalanchoe buccal films were cut into 4 cm^2 portions (2 × 2 cm) and conserved for further analysis in a desiccator.

The physical and chemical properties of buccal films can significantly impact the dosage accuracy, the handling features, bioactive compounds release behavior, the patient comfort and, most important, buccal films effectiveness. To ensure that Kalanchoe buccal films are suitable for their purpose, it is essential to study their

thickness and weight, flexibility, ability to endure movements inside the buccal cavity, their capacity to effectively deliver the API.

Table 3.1

Composition of selected polymers, plasticizer and Kalanchoe juice used in polymeric solutions for film formulations

Sample number	Carbopol 940, % w/v	HPMC K100LV, % w/v	PVP K-17, % w/v	Glycerol, % w/v	Kalanchoe juice, ml
F1	1.5	–	–	3.0	90.0
F2	2.0	–	–	3.0	90.0
F3	2.5	–	–	3.0	90.0
F4	–	1.5	–	3.0	90.0
F5	–	2.0	–	3.0	90.0
F6	–	2.5	–	3.0	90.0
F7	–	2.5	0.5	3.0	90.0
F8	–	2.5	1.0	3.0	90.0
F9	–	2.5	1.5	3.0	90.0

3.2. Research of the quality of obtained buccal films

Determination physical characteristics of buccal films with Kalanchoe juice

The moisture content and swelling capacity of Kalanchoe buccal films (the hydration ability) and the disintegration time are also factors that need to be evaluated. Table 3.2 summarizes the results for the Kalanchoe buccal films developed.

The Kalanchoe buccal films' weight determines an uniform distribution of the API, which directly affects its therapeutic impact and effectiveness. Thickness, handling features, mechanical qualities, and API release behavior are properties greatly influenced by weight, along with the conformability and flexibility.

According to Table 3.2, the HPMC K100LV buccal films were ($p < 0.05$) lighter (59.5 *vs* 95.2 mg) and thinner (0.25 *vs* 0.39 mm) than Carbopol 940 ones. Normally, buccal films for oral application may present thickness between 50 and 1000 μm [14, 28, 30].

Table 3.2

Weight, moisture content, swelling capacity, thickness, and disintegration time of buccal films with Kalanchoe juice

Sample number	Weight, mg	Moisture content, %	Swelling capacity, %	Thickness, mm	Disintegration time, min
F1	76.6 ± 9.1	9.51 ± 1.24	56.45 ± 2.89	0.29 ± 0.05	110 ± 1.08
F2	84.8 ± 11.4	8.93 ± 1.71	58.15 ± 2.48	0.34 ± 0.04	114 ± 1.64
F3	95.2 ± 11.2	8.58 ± 2.47	60.57 ± 2.43	0.39 ± 0.05	119 ± 1.29
F4	44.9 ± 4.0	9.22 ± 1.94	45.28 ± 3.14	0.18 ± 0.03	122 ± 1.22
F5	52.1 ± 5.3	9.53 ± 1.56	47.95 ± 2.89	0.21 ± 0.04	126 ± 1.53
F6	59.5 ± 6.9	9.18 ± 1.87	52.48 ± 2.36	0.25 ± 0.06	128 ± 1.28
F7	71.6 ± 6.3	9.76 ± 1.91	50.21 ± 3.44	0.33 ± 0.04	133 ± 1.23
F8	89.8 ± 7.8	10.53 ± 2.16	53.49 ± 3.23	0.38 ± 0.08	136 ± 1.65
F9	101.8 ± 6.4	9.23 ± 1.46	55.35 ± 2.28	0.41 ± 0.06	140 ± 1.05

Concerning mass, the incorporation of Polyvinylpyrrolidone K-17 led to a mass increase when compared to the films with one polymer, despite the films are still lighter (200 mg). Mass depends on the amount of plasticizer, polymers, and API incorporated in the formulation, as well as buccal films dimensions selected to conduct this evaluation.

Folding endurance reflects the durability and mechanical strength of buccal films. None of buccal films formulated in this study broken when manually folded (180°), after reaching the set limit of 300 folds. So, it is expected that the buccal films with Kalanchoe juice will be able to withstand of buccal cavity movements

after administration, being also predictable without damage their processing and packaging.

Hydration ability should be carefully evaluated since this ability may greatly impact the buccal films performance, from the mechanical properties to the release profile. The difference was observed between the 2.5 % Carbopol 940 films and 2.5 % HPMC+1.5 % PVP films with Kalanchoe juice in swelling capacity (60.57 % vs 55.35 %). The 2.5 % HPMC K100LV ones presented a significantly higher. Despite no significant differences ($p > 0.05$) were observed between the Carbopol 940 films and the HPMC K100LV buccal films in what concerns to moisture content. Moisture is the crucial parameter of buccal films because in low moisture amounts may result in brittleness or reduced flexibility, while in high quantities molecules of water can interpose the polymer chains and lead to sticky films which adhere to packaging or fingers of patients, enabling the microbial growth. Nevertheless, the moisture content is adequate since PVP and HPMC (a cellulose derivate) were used as polymers and naturally absorb water.

The swelling capacity is extremely important since it influences the films' ability to release the API, and the patient comfort. The diffusion rate of the biologically active compounds from the Kalanchoe juice incorporated in buccal films to an oral mucosa will be defined, among other characteristics, by the ability to absorb water and create a gel-like layer. The diffusion rate allows compounds to be entrapped within films and prevents from being released all at once. This capacity is extremely useful in the inflammatory periodontal disease situations since it allow the wound exudate to be absorbed, improving the overall treatment and reducing the bacterial burden.

It is necessary to ensure that buccal films do not disintegrate instantaneously because buccal films' purpose is the continuous release of incorporated biologycally active compounds into the buccal cavity. So, the disintegration time was assessed in the artificial saliva (pH 6.9), being quantified in 119 min for the Carbopol films, with differences ($p < 0.05$) for the HPMC K100LV ones (128 min) and for HPMC+PVP (140). Such data is consistent with a swelling capacity determined for

all films (60.57, 52.48%, and 55.35% respectively). As buccal films swell upon contact with the artificial saliva, it is possible to observe modifications in the structure that enable films disintegration and the API release. So, obtained films with higher swelling capacity disintegrates faster. Also, lighter and thinner films tend to disintegrate more quickly which is confirmed by literature data [14].

The mechanical properties of buccal films obtained

Ideal buccal films should exhibit adequate elasticity and flexibility, being malleable to prevent breaking from oral activity movements and the handling, but not too flexible that deforms or extends easily during a cutting process or the packaging. The integrity and performance of films can be evaluated by the elongation, the resistance to extension, and the Young's Modulus. Such parameters are deeply affected by films' compositions, namely the polymer used, the polymer concentration and the type of plasticizer, and the API. Table 3.3 summarizes the buccal films mechanical properties.

Table 3.3

Mechanical properties of the formulated buccal films with the Kalanchoe juice: percent of elongation, resistance to extension, and Young's modulus

Sample number	Percent of elongation, %	Resistance to extension, N	Young's modulus, MPa
F1	23.15 ± 2.92	7.91 ± 2.57	1940 ± 510
F2	27.24 ± 3.26	8.29 ± 1.98	2120 ± 450
F3	30.25 ± 3.14	9.11 ± 2.02	2560 ± 420
F4	18.87 ± 2.34	6.21 ± 2.01	1670 ± 380
F5	20.95 ± 2.29	6.94 ± 1.27	1790 ± 410
F6	21.84 ± 2.36	7.22 ± 1.45	1840 ± 360
F7	25.10 ± 3.02	8.56 ± 1.91	2590 ± 390
F8	28.56 ± 2.91	9.54 ± 1.28	2710 ± 290
F9	32.90 ± 2.88	10.35 ± 1.94	2830 ± 340

The percent of the elongation measure the buccal films deformation before it breaks or fails, indicating the ability of films to conform to the oral cavity contours or the flexibility, or to withstand the deformation without fracturing. The polymer type and content of films, the amount of the API and plasticizers have the profound effect on films percent of elongation [14]. The HPMC K100LV buccal films with the Kalanchoe juice exhibited a significantly lower percent of elongation than the HPMC K100LV plus PVP K-17 buccal films with the Kalanchoe juice (21.84% *vs* 32.90 %). This probably occurs due to the influens of the PVP K-17 polymer, contributing to the polymer chain sliding during mechanical evaluations.

The tensile strength, also known as resistance to extension, intends to evaluate the maximum load or force that films may withstand before the breaking or undergoing the permanent deformation [14], reflecting the films durability and mechanical strength. According to Table 3.3, no significant differences were observed between the Carbopol 940 buccal films and the HPMC+PVP films (9.11 N and 10.35 N, respectively). The types of plasticizers and their quantity influence the resistance to extension. So, since the Carbopol 940 buccal films and the HPMC+PVP K-17 films have the same amount of plasticizer (glycerol), the resistance to extension was similar.

The elastic modulus or the Young's modulus, also known as stiffness, represents films resistance to the deformation under applied stress and measures films ability to return to their original shape after the removal stress. The buccal films with HPMC K100LV, PVP K-17 and the Kalanchoe juice displayed a significantly higher Young's Modulus (2830 MPa) than the HPMC K100LV buccal films (1840 MPa). It indicated that the HPMC K100LV buccal films without PVP is stiffer, less deformable, and more resistant to stretching or bending. Different physical features of buccal films may influence this mechanical property [14]. For example, the Young's modulus tends to increase when films are thicker or heavier. The heavier and thicker films can have the denser matrix of the polymer and they are, therefore, richer in intramolecular and intermolecular interactions, leading to the stiffness films and higher Young's modulus. The hydration ability may also play the

crucial role in the film elasticity, since a mobility of polymers chains can be influenced by the water molecules presence in the polymeric matrix.

Given the mechanical properties of buccal films obtained, it can be affirmed that the Kalanchoe juice buccal films with HPMC K100LV, PVP K-17 polymers are resistant, ensuring their resistance to administration, handling, transportation, and minimizing the risk of failure or damage. The developed buccal films can resist to tension or stress during application or removal from the packaging.

Buccal films of polymer compositions (F1–F9) were found to be soft, dry, translucent, peeling off from the Petri dish, and non-sticky. No spots were found on the obtained buccal films. The films prepared were homogeneous upon visual inspection. In addition, it was found that the Kalanchoe juice films prepared did not stick when pressed between paper layers for one minute.

Determination of pH

The pH of films was determined potentiometrically in accordance with the requirements of the SPU [3–4]. The aqueous solutions of the film samples (F1–F9) were prepared to determine the pH; 50 ml of the solutions was taken from the flask with the dissolved film sample and the pH was determined, using the pH meter.

Alkaline or acidic pH may irritate the buccal mucosa and affect the degree of hydration of different polymers. Therefore, it is preferable to maintain the pH value of the formulations with Kalanchoe juice as close to the buccal pH as possible. The films prepared had the pH range of 6–7, which is comparable to the buccal pH and is unlikely to cause the irritation.

***In vitro* mucoadhesion evaluation of the films with Kalanchoe juice**

Mucoadhesion of the buccal films is of significant importance to pharmaceutical forms that are designed to be mucoadhesive in the oral cavity. This is more important for pharmaceutical dosage forms indicated for prolonged API release, whereby the mucoadhesive strength (the strength of adherence), and the retention time (the time taken for detachment) should be sufficient to facilitate API

release over the prolonged time period. The several methods have been developed by scintists to evaluate mucoadhesion of the buccal films *in vitro*.

The adhesion time was determined by determining the time during which the film with the Kalanchoe juice would remain on the wall of a glass beaker in a medium of purified water at t = 37 ºC (Fig. 3.1).

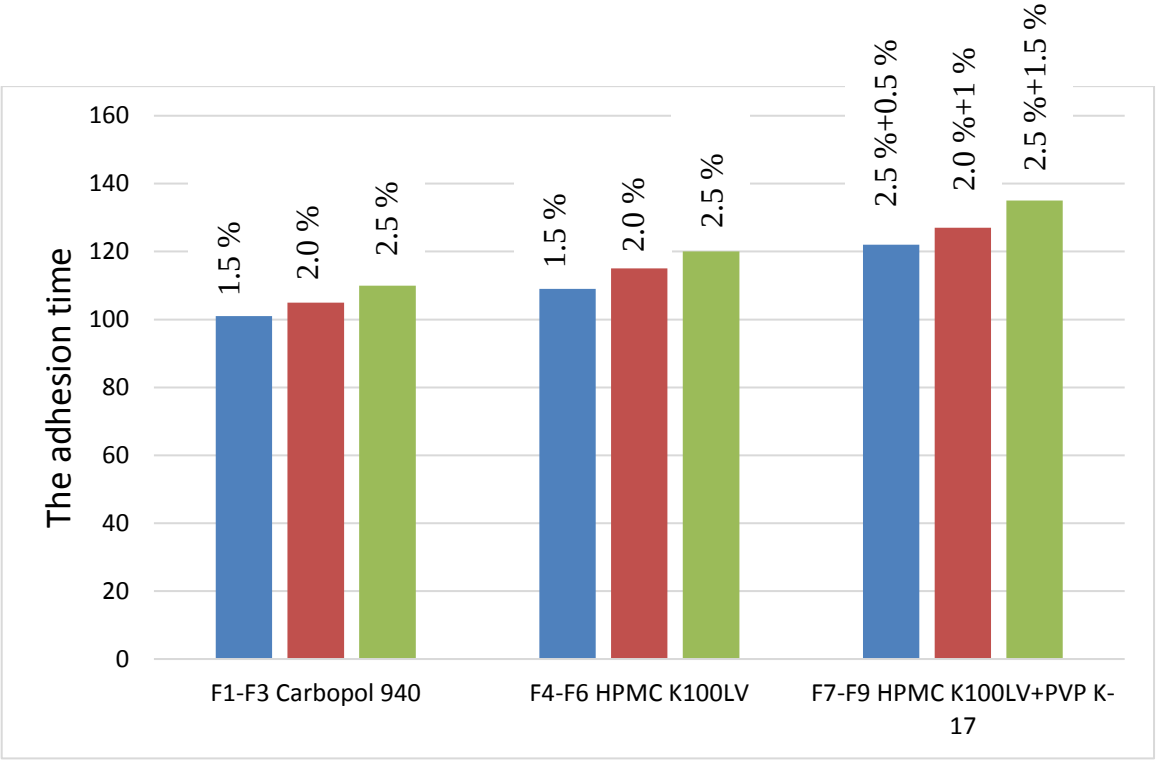

Fig. 3.1. The results of adhesion time determination of the films with the Kalanchoe juice

The mucoadhesion studies *in vitro* were performed, suggesting that increasing the Carbopol 940 and HPMC content increases the mucoadhesion time. However, the observed values shawed that the mucoadhesion time of such films was not sufficient, and that's why PVP K-17 was added to the composition of buccal films with HPMC K100 LV the mucoadhesion time of which was more than films with Carbopol 940.

Changing the amount of PVP K-17 affects the adhesion times of the prepared films. The adhesion time of the HPMC K100LV films was (109–120 min), and the films with HPMC K100LV and PVP K-17 have higher mucoadhesive capacity, the adhesion time of which was for F7 composition (122±14 min), for F8 composition

(127±18 min), and for F9 composition (135±18 min). Buccal films with Kalanchoe juice that obtained from 2.5 % solution of HPMC K100LV, 1.5 % solution of PVP K-17 were selected for further study. The film adhesion time depended on the film disintegration. Films with slower disintegration rate showed higher mucoadhesion time.

Thus, theoretically and experimentally justified the composition of the Kalanchoe juice buccal films. Such composition of the buccal films was offered (Table 3.5). The table below shows the content (g) of each component in dry films.

Table 3.4

Composition of the Kalanchoe juice buccal films

Components, g	Content, g	Function
Kalanchoe pinnata juice (in terms of dry matter)	0,1000 (0,020)	API
HPMC K100LV	0.029	Polymer basis
PVP K-17	0.017	Polymer basis
Glycerol	0.034	Plasticizer

3.3. Development of technology of the Kalanchoe juice buccal films by the solvent casting

The flowshart of the Kalanchoe juice buccal films obtaining is presented in Fig. 3.2.

The buccal films production technology was proposed. The technology includes such technological stages as raw material preparation, preparation of the polymers solution in Kalanchoe juice, introduction of the plasticizer, casting to the underlay, drying, cutting, labeling and packaging.

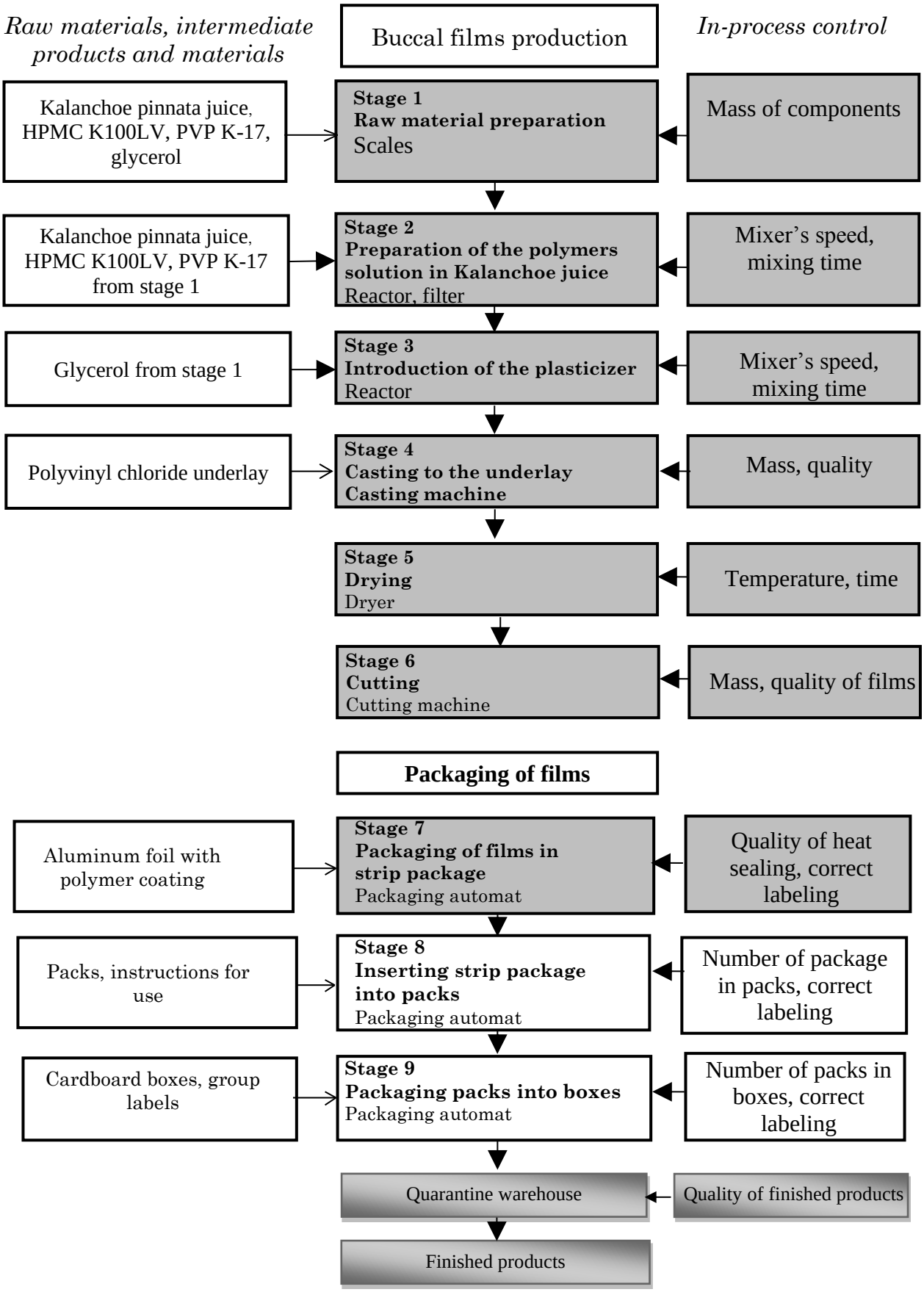

Fig. 3.2. The flowshart of the Kalanchoe juice buccal films

Stage 1. Raw material preparation

Weighing of Kalanchoe pinnata juice, HPMC K100LV, PVP K-17, glycerol, water is on the scales.

Stage 2. Preparation of the polymers solution in Kalanchoe juice

The polymers solution is prepared as follows: the initial components (film-forming agents (HPMC K100LV, PVP K-17), Kalanchoe juice) weighed are dissolved in the Kalanchoe juice while stirring until a homogeneous mass is obtained in the reactor.

Stage 3. Introduction of the plasticizer

Glycerol is added while stirring until a homogeneous mass is obtained in the reactor. Deaeration is carried out under vacuum.

Stage 4. Casting to the underlay

The resulting solution is applied in one layer through a slit onto the polyvinyl chloride underlay on a metal strip treated with ethyl alcohol and moving at a speed of 0.13-0.14 m/min using a special casting machine.

Stage 5. Drying

The dried at a temperature of approximately 70°C for approximately 4 min.

The resulting film is dried in a chamber dryer with five drying zones from 40 to 48 ^{0}C, cooled to 38^{0}C and the film is removed from the metal tape.

Stage 6. Cutting

The obtained Kalanchoe buccal films are cutted into 4 cm^2 portions (2 × 2 cm) by the cutting machine.

Stage 7-9. Labeling and packaging

The cell-less strip package (aluminum foil with polymer coating) is recommended for packaging buccal films. This will ensure tightness, which will prevent the ready product from drying out or swelling. Recommended packaging is 10 pcs. in a strip package, 3 strip packages in a pack. Ready products can also be packaged into cardboard boxes for storage.

Studies on the stability of the Kalanchoe buccal films are ongoing. The additional research of their qualitative and quantitative formulation is proposed to

carried out for the quality of the films developed. Additional study on microbiological stability and organoleptic characteristics are possible also in the future.

Conclusions to chapter 3

1. The buccal films with Kalanchoe juice has been developed.

2. The rational component composition of the film basis has been established.

3. The technological flowshart for obtaining films with Kalanchoe juice has been developed.

CONCLUSIONS

1. The data of scientific literature on the urgent problem of modern dentistry – inflammatory periodontal disease – were analyzed and summarized.

2. The therapeutic values of *K. pinnata* mostly lie on the presence of phytochemicals which possess high potential as a natural antimicrobial immunomodulatory, and anti-inflammatory agent.

3. In the present research, the formulation of buccal films with the Kalanchoe juice was achieved. The buccal films obtained presented adequate physical properties (thickness, weight, folding endurance, moisture content, disintegration time, and swelling capacity) and were easy to handle.

4. The mechanical features of buccal films with the Kalanchoe juice were also assessed, and the resistance to stress and the flexibility were proven.

5. This work showed the potential formulation of buccal films containing the Kalanchoe juice. Further studies should be carried out, including the analysis and long-term storage, the antimicrobial and anti-inflammatory properties of the films obtained and, most important, assays to ensure the compounds bioavailability.

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ANNEX

Annex A

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ГРАМОТА

нагороджується

ZOURHRI Ayyoub

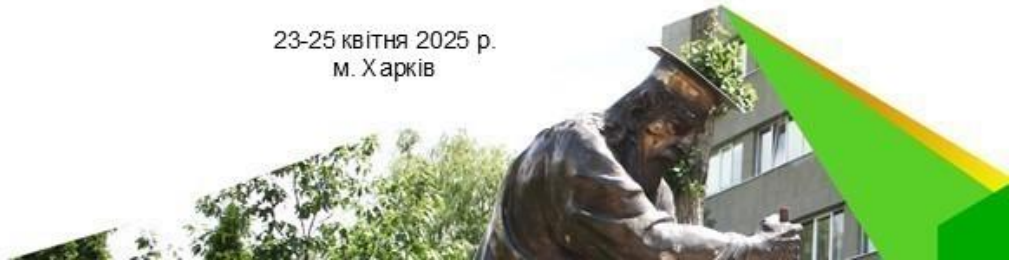
у секційному засіданні студентського наукового товариства кафедри
промислової технології ліків та косметичних засобів

XXXI Міжнародна науково-практична конференція
молодих вчених та студентів
«Актуальні питання створення нових лікарських засобів»

В.о. ректора
Національного фармацевтичного університету

Алла КОТВІЦЬКА

23-25 квітня 2025 р.
м. Харків



Ф А 2.2.1–32-366

National University of Pharmacy

Faculty pharmaceutical
Department of industrial technology of medicines and cosmetics

Level of higher education master

Specialty 226 Pharmacy, industrial pharmacy
Educational- professional program Pharmacy

APPROVED
The Head of Department
of Industrial Technology
of Medicines and
Cosmetics

_____

Olena RUBAN
"_26_" of _September 2024

ASSIGNMENT
FOR QUALIFICATION WORK
OF AN APPLICANT FOR HIGHER EDUCATION

Ayyoub ZOURHRI

1. Topic of qualification work: «Justification of the composition and technology of buccal films with Kalanchoe juice», supervisor of qualification work: Antonina SICHKAR, PhD, assoc. prof.

approved by order of NUPh from "27th" 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 analyze the data of literature sources about medicines for the treatment of inflammations of the oral cavity mucosa and gums, about application and active chemical compounds of *Kalanchoe pinnata*, theoretically and experimentally justify the composition and technology of buccal films with Kalanchoe juice and to study influence of pharmaceutical excipients on properties of the obtained films _____

4. Contents of the settlement and explanatory note (list of questions that need to be developed): literature review, objects and methods, experimental part, references _____

_____

5. List of graphic material (with exact indication of the required drawings):
Tables – 4, pictures – 6 _____

6. Consultants of chapters of qualification work

Chapters	Name, SURNAME, position of consultant	Signature, date	
		assignment was issued	assignment was received
1	Antonina SICHKAR, professor of higher education institution of department of industrial technology of medicines and cosmetics	26.09.2024	26.09.2024
2	Antonina SICHKAR, professor of higher education institution of department of Industrial Technology of Medicines and Cosmetics	22.11.2024	22.11.2024
3	Antonina SICHKAR, professor of higher education institution of department of Industrial Technology of Medicines and Cosmetics	22.12.2024	22.12.2024

7. Date of issue of the assignment: «_26___» ___ September _____2024.

CALENDAR PLAN

№ з/п	Name of stages of qualification work	Deadline for the stages of qualification work	Notes
1.	Literature review	September	**done**
2.	Experiment planning	October	**done**
3.	Experiment execution	November-February	**done**
4.	Processing of results	March-April	**done**
5.	Submission to EC	April	**done**

An applicant of higher education _____ Ayyoub ZOURHRI

Supervisor of qualification work _____ Antonina SICHKAR

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				
Зурхрі Аюб	Обгрунтування складу і технології букальних плівок з соком каланхое	Justification of the composition and technology of buccal films with Kalanchoe juice	доц. Січкар А.А.	доц. Буряк М. В.

Ректор
Вірно. Секретар

ФА2.8-03-317

ВИСНОВОК

експертної комісії про проведену експертизу
щодо академічного плагіату у кваліфікаційній роботі

здобувача вищої освіти

«06» травня 2025 р. № 331502933

Проаналізувавши кваліфікаційну роботу здобувача вищої освіти Зурхрі Аюб, групи Фм20(4,10д.)англ-02, спеціальності 226 Фармація, промислова фармація, освітньої програми «Фармація» на тему: «Обгрунтування складу і технології букальних плівок з соком каланхое / Justification of the composition and technology of buccal films with Kalanchoe juice», 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

Ayyoub ZOURHRI

on the topic: «Justification of the composition and technology of buccal films with Kalanchoe juice»

Relevance of the topic. Given the current state of medicines prescribed for the treatment aphthous stomatitis, and gingivitis in convenient forms, advantages of the Kalanchoe juice, the development of the new phytopreparation based on the Kalanchoe juice is relevant.

Practical value of conclusions, recommendations and their validity is the possibility of using the results of research for the further introduction into the industrial production of composition for obtaining buccal films with Kalanchoe juice.

Assessment of work. According to the form and content the qualification work corresponds to the current requirements, is an independent study, in which the student showed knowledge about a particular subject of research, the ability to receive information using modern scientific methods, the ability to comprehend the information received and submit it in an acceptable form.

General conclusion and recommendations on admission to defend. In general, the qualification work on the topic «Justification of the composition and technology of buccal films with Kalanchoe juice» deserves a positive assessment, and its author Ayyoub Zourhri — admission to the defense of the qualification work.

Scientific supervisor _____ Antonina SICHKAR

«_6_» of June 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

Ayyoub ZOURHRI

on the topic: «Justification of the composition and technology of buccal films with Kalanchoe juice»

Relevance of the topic. Today, the treatment of stomatitis and gingivitis is a common problem. A number of herbal medicines are used to treat the oral cavity. In dental practice, Kalanchoe juice is used for acute diffuse catarrhal gingivitis, subacute and chronic forms of hypertrophic catarrhal gingivitis, inflammatory-dystrophic form of periodontitis of the II-III degree, and recurrent chronic aphthous stomatitis. The juice is applied in the form of applications (gauze wipes or cotton wool) soaked in juice, but this is not convenient. Therefore, the development of a new dosage form of buccal films with Kalanchoe juice is relevant.

Theoretical level of work. The student of higher education independently conducted an analysis of the current state of buccal films manufacture, carried out the development of the composition of films with Kalanchoe juice based on the results of physico-chemical and technological studies.

Author's suggestions on the research topic. The author developed suggestions for solving the problem of obtaining buccal films with Kalanchoe juice.

Practical value of conclusions, recommendations and their validity is the possibility of using the research results for the further introduction into the industrial production of technology of buccal films with Kalanchoe juice.

Disadvantages of work. Minor, namely, disproportionate placement of material, presented in separate sections, were revealed. However, these disadvantages are not important and should not affect the overall assessment of work.

General conclusion and assessment of the work. The qualification work is executed on an urgent topic, because it covers the issues of developing the composition and technology of new buccal films with Kalanchoe juice. The work as a whole meets the requirements of the qualification level and deserves an excellent assessment.

Reviewer _____assoc. prof. Marina BURYAK

«_09__» of _June___ 2025

Ф А2.2.1-91-287

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

Витяг з протоколу
засідання кафедри промислової технології ліків та косметичних засобів НФаУ
№ 14 від 09 червня 2025 року

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

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

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

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: «Обгрунтування складу і технології букальних плівок з соком каланхое»

здобувача вищої освіти випускного курсу Фм19(4,10д.)англ-05 групи НФаУ 2024 року випуску _____Аюб ЗУРХРІ_____
(ім'я, прізвище)
Науковий (-ві) керівник (-ки) к.фарм.н., доц. Антоніна СІЧКАР
Рецензент_____к.фарм.н., доц. Марина БУРЯК_____

УХВАЛИЛИ: Рекомендувати до захисту кваліфікаційну роботу здобувача вищої освіти 5 курсу Фм20(4,10д.)англ-02 групи Аюб ЗУРХРІ
(ім'я, прізвище)
на тему: «Обгрунтування складу і технології букальних плівок з соком каланхое»

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

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

Ф А2.2.1-32-042

НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ПОДАННЯ
ГОЛОВІ ЕКЗАМЕНАЦІЙНОЇ КОМІСІЇ
ЩОДО ЗАХИСТУ КВАЛІФІКАЦІЙНОЇ РОБОТИ

Направляється здобувач вищої освіти Зурхрі Аюб до захисту кваліфікаційної роботи
за галуззю знань 22 Охорона здоров'я
спеціальністю 226 Фармація, промислова фармація
освітньо-професійною програмою Фармація
на тему: «Обгрунтування складу і технології букальних плівок з соком каланхое».

Кваліфікаційна робота і рецензія додаються.

Декан факультету _____ / Микола ГОЛІК /

Висновок керівника кваліфікаційної роботи

Здобувач вищої освіти Зурхрі Аюб виконала кваліфікаційну роботу на високому рівні, з логічним викладенням матеріалу та обговоренням, оформлення роботи відповідає вимогам НФаУ до випускних кваліфікаційних робіт та може бути рекомендований до захисту в Екзаменаційній комісії НФаУ.

Керівник кваліфікаційної роботи

_____ Антоніна СІЧКАР

«_6__» __червня_____ 2025 року

Висновок кафедри про кваліфікаційну роботу

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

Завідувач кафедри
технологій фармацевтичних препаратів

_____ Олена РУБАН

« _9_» _червня____ 2025 року

Qualification work was defended

of Examination commission on

« _____ » _____ 2025

With the grade _____

Head of the State Examination commission,

DPharmSc, Professor

_____ / Volodymyr YAKOVENKO /