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**MINISTRY OF HEALTH OF UKRAINE**
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# QUALIFICATION WORK

on the topic: «**Research on the creation of films with anibacterial and anti-inflamatory effects**»

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## ANNOTATION

The assortment and properties of auxiliary substances used in medicinal films were described. On the basis of complex physico-mechanical and pharmacotechnological studies, the composition of medicinal films made of chlorhexidine bigluconate, sodium hyaluronate, and dry meadowsweet's flower extract was substantiated. As a result of the study of the physical and chemical properties of medicinal films, their compliance with the specification standards was established. Technology for production of medicinal films was proposed. The master's thesis is presented on 54 pages, and consists of an introduction, a literature review, 2 sections of the experimental part, general conclusions, a list of used literary sources and appendices. The bibliography includes 46 literature sources. The work is illustrated with 6 tables and 4 figures.

*Key words*: medicinal films, drug technology, chlorhexidine bigluconate, sodium hyaluronate, dry meadowsweet's flower extract.

## АНОТАЦІЯ

Наведено характеристику асортименту та властивостей допоміжних речовин, які використовуються в складі лікарських плівок. На основі комплексних фізико-механічних і фармакотехнологічних досліджень обґрунтовано склад лікарських плівок з хлоргекседину биглюконатом, натрію гіалуронатом, екстрактом квітів лабазника сухим. В результаті дослідження фізико-хімічних властивостей лікарських плівок встановлено їх відповідність специфікаційним нормам. Запропонована технологія виробництва лікарських плівок. Магістерська робота викладена на 54 сторінках, і складається зі вступу, огляду літератури, 2 розділів експериментальної частини, загальних висновків, списку використаних літературних джерел та додатків. Бібліографія включає 46 джерел літератури. Робота ілюстрована 6 таблицями та 4 рисунками.

*Ключові слова*: лікарські плівки, технологія ліків, хлоргекседину біглюконат, натрію гіалуронат, екстракт квітів лабазика сухий.

# CONTENT

## LIST OF ABBREVIATIONS

CMC – carboxymethylcellulose

DF – dosage form

EP – European Pharmacopoeia

HPMC – hydroxypropyl methylcellulose

HMVS – high-molecular-weight substances

INN – international non-proprietary name

MF – medicinal film

MPF – medicinal phytofilm

MS – medicinal substance

Na-CMC – sodium carboxymethylcellulose

PF – phytofilms

PVA – polyvinyl alcohol

PVP – polyvinylpyrrolidone

PAA – polyacrylamide

PEO – polyethylene oxide

SPU – State Pharmacopoeia of Ukraine

AA – adhesive agent

API – active pharmaceutical ingredient

MTS – matrix therapeutic system

TTC – transdermal therapeutic system

# INTRODUCTION

**Relevance of the work**. Introduction of drugs into the body through transdermal therapeutic systems is an alternative method for drugs that cannot be administered otherwise, or if the traditional method of administration is less effective. Modern TTSs are becoming increasingly popular because they are economical, as targeted use of drugs allows for a reduction in the required amount by over 100 times while maintaining pharmacological effect. This makes treatment cheaper and more accessible. Currently, no existing type of drug formulation provides the same level of dose regulation as TTSs [10,16].

The activity of such systems depends on the controlled ability of sustained drug release through diffusion across a membrane from a reservoir into an adhesive layer, and then through the skin into the systemic circulation. The feature of TTSs is the maintenance of drug concentration at a certain level for a prolonged time through the release of certain doses, which depend on the pharmacokinetics of the drug [15,16].

TTSs for local use are traditionally produced in the form of films, patches, or strips. Two approaches are used to prolong the effect of drugs. The first involves reducing the diffusion of the low-molecular-weight drug by chemical bonding with a carrier macromolecule. This increases the duration of the therapeutic effect of the drug on the body through slow diffusion of the macromolecule and the associated drug molecules [12,13, 21].

The second approach to regulating drug diffusion is achieved by incorporating it into a polymer semi-permeable membrane. This approach is used in the development of prolonged-release drugs [21].

Considering the absence of combined composition films on the pharmaceutical market, the development of drugs in the form of films that combine several drugs with different effects (antibacterial, antifungal, reparative, anti-inflammatory, antioxidant) is relevant.

**The purpose and tasks of work.** The purpose of this master's thesis was to develop the composition of an application combined drug with antibacterial and anti-inflammatory effects. To achieve this, the following tasks needed to be addressed:

1. Analyze and summarize the literature on the use, composition, and technology of transdermal therapeutic systems.
2. Characterize the range of auxiliary substances used in the composition of application drugs.
3. Develop the composition and investigate the properties of the application drug (in the form of films).

*The object of research* is the bases and dental films, active pharmaceutical ingredients: sodium hyaluronate, chlorhexidine digluconate, dry extract of lily-of-the-valley flowers, auxiliary substances: high molecular weight compounds (HMWC), film-forming agents, solvents.

*The subject of research* is the theoretical and experimental justification of the composition of the application drug form for the treatment of infectious-inflammatory diseases of the oral mucosa. Determining the optimal concentration of auxiliary substances, studying the physicochemical and pharmacotechnological properties of the developed composition.

**Research methods.** The development of the composition and technology of an application drug in the form of a film with a complex of antibacterial and anti-inflammatory agents using various methods of organoleptic (uniformity, smell, color), physicochemical (pH), pharmacotechnological (homogeneity and shine of films, their relative elongation, strength and elasticity) and mathematical (statistical processing of results) studies, which allow evaluating the quality indicators of experimental film samples and selecting the rational composition of the drug.

**Scope and structure of work.** The master's thesis is presented on pages and consists of an introduction, literature review, 2 sections of the experimental part, general conclusions, a list of references, and appendices. The bibliography includes literary sources. The work is illustrated with 6 tables and 4 figures.

# SECTION I
# MODERN TRANSDERMAL THERAPEUTIC SYSTEMS

## 1.1 General characteristics and classification of transdermal therapeutic systems

Introduction of medicinal substances into the body through transdermal therapeutic systems (TTS) is an alternative method of introducing substances that cannot be introduced otherwise, or a traditional method of introduction is less effective.

The history of transdermal (topical) drug forms has ancient roots. In medicine, in the V-IV centuries BC, poultices of raw or boiled plants, grounded with oil or wine, were used; ointments with various substances of plant, animal, and mineral origin based on oil, honey, lard, thickened juices, and plant infusions. Later, compresses and plasters appeared

Most of the named drug forms have reached our days, but they do not fully meet modern requirements for drug forms. This is primarily due to the fact that, unlike modern polymeric TTS, they do not regulate the rate of APIs entry and concentration in the body and do not have a prolonged effect. These tasks are solved by using TTS, which have certain structural features that allow dosing of drugs gradually over a necessary time interval [20, 41].

TTS is a form of introducing medicinal substances into the large circle of blood circulation through undamaged skin. The principle of action of transdermal TTS is that due to the concentration gradient, medicinal substances diffuse from the matrix or diffusion medium and penetrate the human body through passive diffusion through the skin or mucous membranes [10].

Modern transdermal therapeutic systems (TTS) are becoming more and more popular due to their economic efficiency. The targeted use of active pharmaceutical ingredients allows a reduction in their required amount by over 100 times, while still maintaining the desired effect. This makes treatment cheaper and

more accessible. Currently, no other existing type of medication provides the same level of dose control as TTS [10, 12].

The application of TTS to the skin or mucous membranes allows the use of terms such as «application», «transdermal», or «percutaneous» to denote this group of medication forms.

The development of TTS was based on several positive properties of this group of medication forms, such as:

- the ability to reduce the therapeutic active dose;
- a resorptive effect on internal organs and systems;
- a constant concentration of the active ingredient in the blood over a long period of time;
- safety of the medication as the entire dose remains outside the body and can be removed at any time;
- higher delivery precision;
- reduced or eliminated side effects and overdosing due to the use of small doses;
- protection of active ingredients from destruction in the gastrointestinal tract;
- lack of irritant effects on the gastrointestinal tract;
- painless administration of medication, and convenience of use for children and elderly patients;
- less frequent medication intake and self-application;
- increased dosage accuracy and medication comfort compared to other transdermal medication forms (such as ointments, gels,embrocation) [16].

According to the United States Pharmacopeia (USP, 23, NF 18) – TTS (Transdermal Therapeutic System) are dosed drug forms that ensure the penetration of drugs through the skin into the systemic bloodstream.

Macromolecular TTS are a type of sustained-release drug form. Their functioning is based on relatively low diffusion rates.

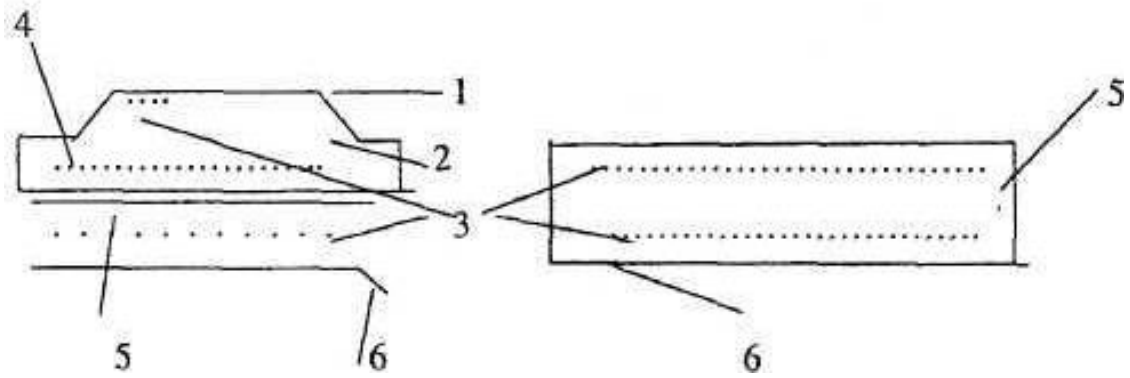
All TTS work on the principle of passive diffusion. Biologically active compounds (BACs) penetrate through the mucous membrane or skin along the concentration gradient on both sides of the semi-permeable membrane, in this case, the skin (or mucous membrane). The amount of drug substance that will enter the body is regulated by the TTS area. TTS usually consist of an external coating (barrier), a reservoir with a drug substance that may have a membrane that controls the release of the drug substance, and contact adhesive coatings in some or all parts of the skin covering. The activity of such systems depends on the regulated ability of a long-acting drug substance released by diffusion through a membrane from a reservoir into an adhesive layer, and then through the skin into the systemic bloodstream. The feature of TTS is the maintenance of the drug substance concentration at a certain level for a long time by releasing certain doses that depend on the pharmacokinetics of the drug substance [13,35,43].

TTS for local use are traditionally released in the form of patches or strips.

There are two approaches to prolonging the action of drugs. The first involves reducing the diffusion of the low-molecular-weight drug substance by chemical bonding with a carrier macromolecule. In this case, the increase in the therapeutic impact time of the drug substance on organisms is determined by the slow diffusion of macromolecule and the drug substance molecules associated with it. The second approach to regulating the diffusion of API is achieved by incorporating it into a polymeric semi-permeable membrane. This approach is used in the creation of extended-release (prolonged action) drugs [37,34].

### 1.2 Classification of application dosage forms

TTC (application dosage forms) divided into two groups: matrix and membrane (ravioli) (fig. 3).




**A** **B**

Fig. 1.1 A – membrane TTS (ravioli), B – matrix TTS: 1 – covering film, 2 – reservoir, 3 – drug molecules, 4 – membrane, 5 – matrix, 6 – protective adhesive film (removed before application to the skin).

**Membrane TTS (known as ravioli**) consist of an impermeable backing, a reservoir containing the medication, a membrane that regulates the release of the drug, and an adhesive layer (the drug can be in the reservoir in the form of a suspension in liquid or gel covered by a polymeric membrane). The reservoir is located between the impermeable backing and the membrane made of porous polymeric foil, which determines the rate of drug release. These are called membrane patches (or reservoir membrane systems).

**Matrix TTS.** In these systems, the medication is dissolved or dissociated throughout the volume of the polymeric body, placed in a matrix consisting of a gel or polymeric film. Drug release from such a system is determined by its diffusion from the matrix material [12,10].

TTS are also classified by other characteristics.

For example, scientists proposed using a classification system similar to the classification of ophthalmic preparations to unify therapeutic systems in dentistry:

- Reservoir systems (with APIs diffusion through membranes);
- Matrix systems (with drug release through diffusion);
- Eroding systems (drug release occurs by diffusion with simultaneous TS erosion);
- Osmotic mini-pumps;

- Infusion pumps [34].

A similar classification is also used for therapeutic systems used vaginally.

Other classification system for therapeutic transdermal systems (TTS) is used based on the method of influencing the macroorganism:

- Local action;
- Systemic (general) effect.

According to M. Lamb's classification (1987), TTS are usually divided into two groups, which are distinguished by the principles that determine their physiological activity. The first group uses the physiological activity of TTS themselves. The mechanism of action is not related to their breakdown but is determined by the properties of the macromolecule (for example, based on polypeptides). The second group includes TTS in which a low-molecular-weight medicinal substance is attached (grafted) to the polymer chain (graft-type drug films). They can be considered as complex systems that have physiological activity depending on the attached active substance.

Based on the type of bond between molecules of active substances and the carrier, there are four groups that differ in the dynamics of release of the active substance:

1. Active substances are covalently attached to the side chain of a polymer;
2. Active substances are included in the main chain of a polymer;
3. Active substances are included in a spherical or cylindrical shell for implantation or oral use (no chemical bond with the polymer);
4. The drug is uniformly distributed in a polymer solution or in a block of polymer in the form of a solid solution or dissolved in a polymer solution (no covalent bond) [40, 21].

Taking into account the research conducted in the creation of matrix transdermal therapeutic systems (TTS) in the form of drug films (DF), another classification can be given:

- TTS – patches.

- TTS – drug films (DF), which are further divided as follows:

a – DF with natural (plant-derived) substances;

b – DF with synthetic substances [18]

At present, both groups of TTS based on this classification are represented by a fairly diverse range of DF, which requires independent classification. This primarily applies to the subgroup of DF with natural (plant-derived) substances.

Drug films containing botanical active substances are called phytofilms (PF), which are a type of TTS. PFs differ from synthetic polymer therapeutic systems in that PF are made in the form of matrix TTS on natural carriers (bone carriers such as collagen, gelatin, sodium alginate, agar-agar, etc.). Due to the natural origin of the polymer, they are safer and more compatible with living organisms. In addition to the aforementioned differences, drug films do not contain an adhesive layer. Their adhesion to the surface to which they are applied occurs due to the viscosity, stickiness, and other adhesive properties in the carrier matrix, unlike traditional macromolecular TTS, which are released in the form of patches or strips with a mandatory presence of an adhesive layer [39,35].

The PF are thin sticky plates of different sizes with extracts from medicinal plant raw materials, added to film-forming agents. The thickness of the films does not exceed 5 mm. They are intended for local or resorptive action and are matrix TTS.

PF can be divided into the following groups:

• by structural features:

- monolayer (monolithic) PF;
- bilayer (multilayer) PF;

• by the number of active substances:

- single-component PF;
- multicomponent FP.

There is a classification of PF by behavior in the focus of pathology (by the method of absorption):

I. Biodestructible (those that dissolve):

• biodegradable;

• bioerodible.

II. Bionondestructible (requiring removal).

Biodegradable PF differs from bioerodible by the nature of dissolution. If the destruction of TTS occurs due to the erosion of the surface, it is called bioerodible. If the external environment quickly penetrates the polymer and the destruction occurs throughout the volume of the polymer, then in this case, it is biodegradable TTS [35].

There are four possible mechanisms of biodegradation:

1 - dissociation of polymer-polymeric complexes (PPC);

2 - enzymatic degradation;

3 - dissolution or nonspecific hydrolysis of polymers in tissue fluids;

4 - intermolecular catalysis of the breakdown of PPC or intramolecular breakdown of water-soluble polymers with the formation of soluble fragments.

Quite widely used the classification of medicinal PF by the area or place of application:

- ophthalmic;
- dental;
- gynecological;
- otorhinolaryngological;
- dermatological (including surgical).

According to the dispersological classification, pharmaceutical films can be classified as bound-dispersed systems with a conditionally solid dispersion medium and a dispersed phase [17].

Currently, sustained-release dosage forms are divided into two groups based on their mechanism of prolongation: sustaining and repeat action [15]. The mechanism of sustaining action is more suitable, for example, for antimicrobial drugs. The mechanism of repeat action is more suitable for toning and stimulating drugs.

However, all the above types of classification are conditional.

## 1.3 Composition of application dosage forms

The effectiveness of drugs that are part of TTS (transdermal therapeutic systems) is increased due to their uniform entry into the systemic bloodstream, as well as the elimination of presystemic metabolism in the gastrointestinal tract and liver, which is especially important for drugs such as scopolamine («Scopoderm», «Transderm»), organic nitrates («Nitroderm»), clonidine («Catapress»), enzymes and other drugs.

Researchers proved that to ensure absorption through the skin, the drug substance must be in the form of a solution. The high degree of lipophilicity of drugs is ideal for their penetration into the upper horny layers of the skin [13,43].

The following requirements must be met for drug substances to be included in TTS:

- have sufficient solubility in hydrophobic and hydrophilic environments;
- good permeability through the skin (the drug substance should be related to the hydrophobic horny layer and the hydrophilic dermis);
- neutral molecule (as charge can hinder its penetration through the hydrophobic environment);
- molecular weight should not exceed 500 Dalton;
- high effectiveness in small doses;
- good compatibility with the skin;
- suitable for preventive, long-term therapeutic use, or replacement therapy [19].

## 1.4 Excipients in the technology of TTC

The term «excipients» includes a large group of natural and synthetic substances used in pharmaceutical technology. They should possess formative ability and be inert to the macroorganism and medicinal substances.

Excipients are essential ingredients in almost all pharmaceutical dosage forms. They are subject to several requirements:

- ensuring the necessary bioavailability and desired therapeutic effect of the drug at minimal concentration;
- maximum inertness to the macroorganism and medicinal substances;
- physical and chemical stability against light, moisture, air, temperature, and time;
- lack of taste, color, and odor;
- microbiological purity;
- availability [15, 21, 41].

Currently, there are about 400 different excipients used in pharmaceutical technology, and some of them are used in transdermal therapeutic systems (TTS).

Excipients used in TTS can be classified based on various criteria, with functional classification being one of the main ones. The main groups include:

- forming agents (film-forming agents);
- solubilizers;
- plasticizers;
- adhesives;
- penetrators;
- preservatives;
- flavorings.

The need to use a sufficient amount of auxiliary substances is explained by the fact that it is impossible to obtain a high-quality drug from a single base polymer. Other auxiliary substances are required to modify (improve) certain physical or physicochemical properties of the drug delivery systems (DDS), such as adhesion, elasticity, and others. However, this classification, like any other, is relative, as the same auxiliary substance can perform different functions [10, 18-20].

For example, hydrophilic substances such as PEG, PVP, starch, glycerin, and others are introduced to increase the adhesive properties, which can also act as

plasticizers and penetrators. When including them in the DDS composition, it is taken into account that a significant increase in the hydrophilic properties of the DDS leads to a decrease in their adhesion. Various auxiliary substances belonging to different classification groups can be used in the creation of DDS [12, 43]

Therefore, as the main auxiliary substances, the following polymers of natural, semi-synthetic, and synthetic origin are used:

1) of natural origin, which are also represented by various groups:

- of animal origin (chitosan, collagen, gelatin, elastin);
- of plant origin (alginates, agar-agar);
- of microbial origin (dextran).

2) of semi-synthetic origin (methylcellulose (MC), sodium carboxymethylcellulose (Na-CMC), hydroxypropyl cellulose (HPC), and others);

3) synthetic (polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), polyethylene oxide (PEO, PEG), polyacrylamides (PAA), and others) [19,44].

However, in addition to the aforementioned auxiliary substances, various other transdermal therapeutic systems (TTS) are also used. For example:

- The nitroglycerin matrix TTS «Nitrodisc», developed by the company Searle, is characterized by a large number of micro-inclusions from a mixture of nitroglycerin and lactose in an aqueous solution of PEG-400. The size of such inclusions ranges from 10 to 200 microns. They are pressed into a matrix made of a silicone-organic polymer compound.

- The Nitro-Dur matrix TTS with nitroglycerin, developed by Key Pharmaceuticals, is also known as a «transdermal infusion system». Nitroglycerin is adsorbed on lactose and dispersed in a hydrogel consisting of water, glycerin, PVS and PVP.

- The German company Schwarz GmbH has developed a nitroglycerin matrix TTS called «Deponit» in the form of a polymer film made of polyisobutylene and a resinous substance applied to a foil substrate. The matrix consists of 7 layers. Each layer contains a different concentration of nitroglycerin adsorbed on lactose.

Etherified fatty acids (in transdermal therapeutic systems such as «Climara», «FemPatch», and «Minitran»), oleic acid and propylene glycol (in «Menorest» and «Vivelle»), sorbitan monooleate («Alora»), glyceryl monooleate, methyl laurate, ethyl alcohol, and glycerin (in «Androderm») are used as solvents in TTS.

## 1.5 Ways of obtaining application dosage forms

The production of transdermal therapeutic systems (TTS) is relatively simple and economically justified, as it does not require complex equipment or materials.

In general, the technology of matrix TTS involves the preparation of a mixture of active and auxiliary substances, which are then applied to a tissue or other base. Alternatively, TTS can be made by pouring the mixture onto special backing forms, followed by drying under different conditions (at room temperature, at 40°C for 8 hours, at 50°C for 8 hours, etc.) [11].

For diffusion TTS, each function is provided separately by one of the components. The technology involves introducing a solution or gel containing the active ingredient into the space between the main membrane and the reservoir containing the drug. They are then thermally sealed with the membrane, which controls the level of drug release. The system is covered with adhesive around the perimeter to adhere it to the application surface, and the whole system is protected from external influences by a cover film [11,13].

However, such TTS are too bulky and inconvenient. Therefore, a new technology for matrix systems has been developed, in which the adhesive that bonds the system to the surface performs several functions, such as adhesion, storage, drug release, and control of the level of release. The technology for such TTS is relatively simple, and the TTS themselves are very thin. However, there are problems with selecting an adhesive that can dissolve the active substance and release it without crystallization for the entire duration of the TTS action. The dissolution and release of the active substance may also lead to a reduction in the adhesive strength to the application surface [20].

Thus, the delivery of medicinal substances through the skin is subject to significant interrelationships that limit the wide application of this technology.

**Conclusions to section 1**

1. Modern TTS are becoming more and more common due to the fact that they are economical, as the targeted use of active substances allows to reduce their required amount by more than 100 times while maintaining the effect, which makes the treatment cheaper and more accessible.

2. Currently, various approaches are being investigated in order to overcome the barrier properties of the skin, increase its permeability, and improve the application possibilities of TTS.

# SECTION 2
# OBJECTS AND METHODS OF THE RESEARCH

## 2.1 Objects of the research

The quality of the API film composition includes sodium hyaluronate and chlorhexidine digluconate as active ingredients. In developing the film composition, carboxymethylcellulose (CMC), polyacrylamide (PAA), polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), glycerin, and purified water were used.

**Sodium hyaluronate (PhEur 9.0)** is the sodium salt of hyaluronic acid, a polysaccharide composed of D-glucuronic acid and N-acetyl-D-glucosamine disaccharide units linked by glycosidic bonds. It is a hygroscopic powder or granules of white color. It is moderately soluble in water and practically insoluble in 96% ethanol and acetone. Its pH (0.5% aqueous solution) is 5.0-8.5. The loss on drying is not more than 20% [24].

**Chlorhexidine digluconate (Chlorhexidine) (N,N''-bis(4-chlorophenyl)-3,12-diimino-2,4,11,13-tetraazatetradecandiamide bigluconate) (EurPh)** is a cationic surfactant, a salt of a quaternary ammonium base and a derivative of biguanide, which has significant antimicrobial activity. It is a powder of white to yellow color. Chlorhexidine digluconate solutions are transparent, colorless, odorless, and have a bitter taste. It is effective against Staphylococci, Streptococci, Escherichia coli, and other bacteria and Candida albicans fungus. Depending on the concentration, chlorhexidine has bacteriostatic or bactericidal activity against gram-positive and gram-negative bacteria [25, 29, 33,45].

**Dry extract of meadowsweet flowers (production of Germany).**

Meadowsweet has long been known for its medicinal properties. The herb contains essential oil, tannins, salicylic acid, and vitamin C. The root of labaznik contains methyl salicylate, tannin, and essential oil. The plant's flowers contain coumarins, ascorbic acid, phenol glycosides (monotropitin, spirein, isosalicin),

flavonoids (spireozide - quercetin glucoside), tannins, microelements, avicularin, quercetin, and methyl ether of salicylic acid [32].

The medicinal properties of meadowsweet have a wide range of applications in traditional medicine. The root, flowers, and leaves are used, which have anti-inflammatory, hemostatic, anti-hemorrhoidal, diuretic, urine-promoting, analgesic, soothing, binding, fever-reducing, and wound-healing properties.

The dry extract is a white powder with a weak, nonspecific odor. It is easily soluble in hot water and polysorbate-80 [30,32]. It exhibits antibacterial, anti-inflammatory, antioxidant, and regenerating effects. The recommended dosage is 1-4%.

## 2.2 Methods of the research

The physical-mechanical methods for studying medicinal phytopharmaceutical films were carried out according to the methods described in scientific publications.

The effort to break was studied using the ZM10 instrument, which allows for the determination of tensile strength (mm) and total elastic deformation of the MFs stretch.

For the tensile experiment of the samples, a clamping speed of 7.5 x 10-4 m/s was used. The calculation was carried out using formula (2.1):

$G = P_{max} / F_o$, (2.1)

where:

G – tensile strength, kgf/cm2;

Fo – initial cross-sectional area, $см^2$ .

Pmax – the maximum force that the sample can withstand, кgf;

*Relative elongation*. The tensile strength index is related to such a characteristic of elasticity as relative elongation. It was determined by the difference in the length of the film samples before and after determining the tensile strength index according to the formula (2.2):

$E = G = L_1 - L_0 / L_0 \cdot 100\%$, (2.2)

where: E – relative elongation, %;

$L_0$ – the initial lenth of the film sample, mm.

$L_1$ – length of the film sample after rupture, mm [1,8];

*The continuity* of the films was determined using a defectoscope of the LKD-1 type. The operation of the device is based on an electrocontact method, which involves measuring the electrical resistance of the area of the surface being studied. The film was placed on a metal plate, which was connected to the defectoscope. Before the tests, the surface of the sensor had to be wetted with an isotonic solution of sodium chloride, which fills the defects on the surface of the film during the movement of the brush sensor. In the case of defects on the film (pores, cracks, through-thickness defects), the surface resistance changes, and this is detected by the electronic circuit of the device. The presence of through-thickness defects is determined visually by the deflection of the microammeter needle and by a sound signal [8].

*Adhesion.* The investigation of film adhesion was determined by establishing the force required to peel the film off the surface, or the force of resistance that overcomes the adhesion of the film to the surface. In the investigation, the film was applied to glass and parallel incisions were made with a scalpel to obtain a grid of 25 squares with a distance of 1 mm between the cutting lines.

Adhesion was determined by the number of squares of the film that adhered to the glass and did not come off during cutting and subsequent friction with the dull side of a scalpel after the film had dried. Complete delamination of the film from the glass was visually observed [8].

*The glossiness* of the film was measured using a photometric glossmeter (FB-2, RF). It is designed to determine the reflected gloss of a given sample, which is compared to a standard (glass with a reflected gloss of 65% is used as the standard).

*The average weight* of the film was determined by weighing 10 films on analytical scales, then weighing each of the 10 films separately and calculating the average weight of each film. The allowable deviation from the average weight of the film should be within ±10%; only one film may exceed the allowable deviation limits, but not more than twice. If the investigated films do not meet the requirements, the study is repeated and carried out on 20 films, of which 2 may exceed the allowable deviation limits, but not more than twice [3,4, 13, 27].

During storage and drying, the films may experience weight loss. The determination of *weight loss during drying* was carried out for each series by taking 40 films, placing them in an open container (previously dried to a constant weight), and then drying them at a temperature of 100-105°C to a constant weight. The weight loss during drying of the film should not exceed 8-9% [13, 27].

Measurement of film thickness was carried out using a thickness gauge (according to the State Standard of Ukraine 6507-78 standard) with an accuracy of 10 micrometers.

*The dissolution time* of the films was determined by pouring 10 ml of water into a 50 ml flask with a stopper and heating it on a water bath at 37±1 °C. Then, a film sample with a size of 1 cm2 was added to the flask, vigorously shaken, and placed back into the water bath to observe the dissolution of the film.

*The osmotic activity* of the samples was studied using a semi-permeable membrane (cellophane film) at a temperature of 34±1 °C using a TS-80 M-2 thermostat.

The measurement of *the mass of the internal cylinders* was carried out at 0.5, 1, 2, 4, 8, 12, and 24 hours on analytical scales (ADV-200M) with an accuracy of 0.001 g, after wiping them from the outside. The volume of purified water in the dialysis chamber was brought to the initial level. The amount of liquid absorbed was determined by the difference in weight between two weighings [13, 26].

*Rheological studies* were conducted using the «Rheotest-2» instrument (Germany) at various temperatures. The temperature was measured by a laboratory thermometer with a scale division of 0.1 °C. Temperature control was performed using an ultra-thermostat, which is included in the instrument's kit.

The kinetic parameters of the film were determined using the *in vitro* method by dialyzing through a semi-permeable membrane (cellophane film of grade V 8079, according to the State Standard of Ukraine 7730-79 standard).

For this purpose, a chamber consisting of two cylinders with diameters of 50 and 70 mm, respectively, was used. The inner cylinder with the sample (5 g) of gel or 1 cm2 of MF was placed in a dialysis chamber with a certain amount of purified water (100 ml) at a temperature of 34±1 ºC. After sampling (10 ml), the volume of water in the dialysis chamber was periodically brought back to the initial level (100 ml). Samples were taken at 30, 60, 120, 180, 240, 300, 360 minutes. The temperature was maintained using a spiral heat exchanger connected to an ultra-thermostat – UT-15. The chamber was placed between the heat exchanger pipes and the entire system was covered with a special box made of foam, which provided thermal insulation.

**Conclusions to section 2**

1. The physical and chemical properties and characteristics of active and auxiliary substances used in the development of dental films are presented. To ensure the necessary organoleptic, consumer, and physicochemical properties, consistency, and osmotic properties of the films, a film-forming agent and high-molecular-weight compounds and other auxiliary substances are selected for the

composition of the films, which provide the necessary complex of consumer and physicochemical properties of the medication.

2. The research methods used in the development and investigation of dental films are presented.

# SECTION 3
# JUSTIFICATION OF COMPOSITION AND STUDIES OF MEDICINAL FILMS

## 3.1 Theoretical justification of the choice of API and excipients to the films composition

Pharmaceutical films are a new generation of drugs with controlled release of active pharmaceutical ingredients (APIs). They belong to matrix therapeutic systems (MTS). As noted in the literature review, polymers that swell or gradually dissolve in biological environments are the basis for creating matrices, providing prolonged diffusion of APIs from the polymer carrier. The use of films allows for precise dosing compared to, for example, creams and gels, achieving constant optimal API concentration at the application site, necessary therapeutic effectiveness, and prolonged action [34, 43].

An important stage in the pharmaceutical development of films is the justification of the choice of the base. The optimal base composition, due to the properties of film-forming agents, allows achieving the necessary physical and chemical properties of the film matrix and varying the pharmacokinetic parameters of the API, primarily dissolution and release.

Based on the analysis of literary sources, it has been established that the following are used as bases for matrix therapeutic systems:

- inert – polyethylene, PVC, vinyl chloride copolymers, vinyl acetate copolymers, etc.;
- hydrophilic – cellulose derivatives, alginic acid derivatives, agar-agar, collagen, gelatin, acrylic acid derivatives, etc.;
- hydrophobic – natural waxes, synthetic triglycerides, higher fatty alcohols, etc.;
- inorganic – bentonites, zeolites, calcium phosphate, barium sulfate, etc. [10, 12, 18-20].

The next important component of MTS is a plasticizer. Glycerin and its ethers, polyoxyalkyl ether of fatty acids and alcohols, and others are used as plasticizers. Typically, their content does not exceed 10% of the mass of the solution of the film-forming base in films [20]. We have conducted an analysis of scientific literary sources to determine the nomenclature of the most commonly used auxiliary substances in films.

For example, based on the literature sources, it was established that the bioavailability of hinazol and gentamicin sulfate from vaginal films is influenced by the nature of the base-carrier and plasticizer [14]. The scientist has proven that necessary release of the active pharmaceutical ingredient occurs when using a base containing 5% gelatin and 2% glycerin as a plasticizer. The optimal base for the release of ethonium, sodium sulfacyl and miramistin from the composition of vaginal MTS is PEO-400. For left-sided chlorhexidine bigluconate, it is advisable to use a base containing Na-CMC: glycerin: gelatin: polyvinylpyrrolidone: DMSO: water in a ratio of 8.15:9.6:16.35:1.6:0.65:63.65 [46].

The influence of glycerin, introduced as a plasticizer, on the degree of release of miramistin from films has been demonstrated. It has been established that an increase in the glycerin content increases the release of active pharmaceutical ingredient from the film [46].

Films containing antimicrobial agents and proteolytic enzymes as the base, to which a mixture of biodegradable poly-ε-caprolactone and poly-3-hydroxybutyrate ethers has been added, have been developed [37].

Natural polysaccharides chitin and chitosan are promising polymers in the technology of MTS. By chemical structure, chitin is a linear amino polysaccharide in which a small part of N-acetylglucoside units are hydrolyzed to glucosamine units. A composition has been developed and the possibility of producing pharmaceutical films based on chitosan with gentamicin, cefazolin and ceftriaxone, furacilin, tinidazole, and nonsteroidal anti-inflammatory drugs has been proven [2].

The use of bases containing ichthyocol, methylcellulose, NaCMC, gelatin, and chitosan with glycerin as a plasticizer was justified in the development of films with phytosubstances by researchers. Based on the results of the properties of film samples, it was determined that films containing chitosan, gelatin, and methylcellulose had the greatest elasticity and strength, and this mixture was chosen for the composition of phytofilms [39].

Scientists proposed a composition of films containing 1% dry extracts of oak bark, St. John's wort, sage, and aloe on a base containing 3% Na-CMC, 2% glycerin, and 94% purified water. In the development of wound-healing films containing aloe extract as a base, benecel was used in combination with collidon 90F and glycerin as a plasticizer [35].

Previously conducted reseaches studied the influence of the nature and concentration of the plasticizer on medicinal films containing 3 and 7% gelatin, 3% PVP, 3% PVC, 3 and 4% Na-CMC, 3% HPMC, as well as a combination of 3% HPMC and Na-CMC in ratios of 1:1 and 1:3 as the base. It was determined that the optimal concentration of glycerin in the film base is 5% of the solution's mass. At a lower concentration of glycerin, the films dried quickly, and at a higher concentration, they were sticky and greasy to the touch. The authors found that the use of 5% PEG-400 and Tween-80 did not serve as a plasticizer for the investigated films [38].

However, it has been established that the addition of ofloxacin and tween-80 to the base of the film results in a more complete and uniform distribution of the API in the base. This in turn promotes a stable concentration of the active ingredient at the site of application [ 40].

Recently, publications have emerged on the development of films with natural BACs.

The production of films with plant components requires the mandatory addition of antimicrobial preservatives to the composition of the MF. Studies indicate the expediency of using miramistin, which provides sufficient protection of the film from microbial contamination and serves as a preservative [39].

In the development of films based on polyvinyl alcohol with sodium alginate and tetraborate, with an antiseptic agent – a derivative of polyhexamethylene guanidine and proteolytic enzymes, a positive effect of sodium alginate on the activity of enzymes has been established. It has been found that the rate of desorption and the amount of antimicrobial substance released from the film decreases with the addition of tetraborate and sodium alginate to the composition of the film. This can be explained by the fact that the antimicrobial substance is fixed in the polymer network [18]. In addition to the mentioned components, other groups of auxiliary substances can be included in the composition of films – adhesive substances, prolongators, stabilizers, etc.

The effectiveness of using a mixture of nipagine and nipasol in a ratio of 3:1 as preservatives in the composition of drugs has been confirmed.

One direction of film modification is the creation of multilayer compositions. Based on the previous researches of Davtyan L.L., technological methods have been developed for creating two-layer films based on gelatin solution, HPMC, Na-CMC, and others, which provide step-by-step release of APIs from each layer of the film to affect various stages of the pathological process [2, 3].

### 3.2 Experimental justification of API and excipients choice for the films composition

Based on the analysis of literary sources, the main medical-biological requirements for dental medicinal phytofilms (MPFs) have been established: biocompatibility with the oral mucosa, adhesion to the oral mucosa, swelling of the film in the oral cavity, absence of allergenic and local irritant effects, matching the pH of the film to the pH of saliva, optimal shape and size of the film, prolonged action, simplicity and technological capabilities of manufacturing, and ease of storage [39, 40, 44].

In justifying the creation of the basis for MPFs, the requirements developed for dental MPF were followed. It is advisable to create films in the form of strips with a size of 9.0x4.5x0.35 mm for dentistry.

The main role of the polymer is to create a film-matrix. The drying rate of the films depends on the nature and concentration of the polymer and solvent, and the amount of plasticizer. Literature analysis has shown that purified water, ethanol, and their mixture are used as solvents. The rate of evaporation depends on the type of solvent. The use of ethanol, or an increase in its content, promotes its rapid evaporation. In addition, the rate of evaporation decreases with an increase in the concentration of the film-forming agent. It should be noted that the kinetics of evaporation also depends on the composition of MPFs, temperature, and humidity of the environment. Previous studies have shown that water is the optimal solvent that provides optimal quality and consumer properties of MPF. The use of volatile solvents (water-ethanol) accelerates the drying of films and the technological process but worsens the quality of the films [31, 34]. Therefore, purified water was chosen as the solvent in our research in the creation of MPF.

To improve the physical and mechanical parameters of MPFs, namely glossiness, we introduced PVP into the composition of the film basis. This is because improving glossiness reduces cracks and micropores. The optimal introduction of PVP is 2-4 %.

Therefore, in justifying the composition of the films, we used data from the literature and the following synthetic high molecular weight compounds (polymers) were chosen as film formers: PVP, PVA, PAA, and semi-synthetic CMC. Glycerin was used as a plasticizer, which is the most commonly used plasticizer in films, and purified water was used as a solvent.

Based on the results of other researchers' studies and our own observations, in justifying and choosing the base for medicinal films, it was established that base #1, which contains PAA, PVA, PVP, glycerin, and purified water, provides controlled release of API for 2 days. It should be noted that in the development of extended-release films, without basic barrier properties, the above-mentioned

auxiliary substances require some correction. The introduction of such water-soluble polymers as CMC, NaCMC, etc. should contribute to increased solubility.

We chose carboxymethyl cellulose (CMC) as the film former because this polymer has been shown by many studies to be able to create a film matrix. The concentration of the polymer significantly affects the solubility of the films. The concentration of 1.5 % CMC was chosen.

The optimal physical and mechanical properties of the films are achieved by adding a plasticizer to the composition. Glycerin, propylene glycol (PG), polyethylene oxide-400 (PEO-400, PEG-400), or their mixture are used as plasticizers in the film composition. In developing the base composition for comparative analysis, bases were used that contained synthetic polymers with the addition of CMC, as well as bases containing CMC, glycerin, and purified water with additional synthetic film formers. Model samples of the medicinal product composition containing different ratios of PAA, PVS, PVP, and CMC are shown in Table 3.1. The investigation of the physical and mechanical properties of the medicinal product, the composition of which is shown in Table 3.1, was conducted using the methods outlined in Section 2.

*Table 3.1*

**Composition of model film bases**

| Name of ingredients | Quantitative content of ingredients, (%) | | | | | |
|---|---|---|---|---|---|---|
| | Model base | | | | | |
| | 1 | 2 | 3 | 4 | 5 | 6 |
| PAA | 2 | 2 | 2 | 3 | 4 | 2 |
| PVA | 2 | 4 | 3 | 2 | 2 | - |
| PVP | 2 | - | - | - | - | 4 |
| CMC | - | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| glycerin | 3 | | | | | |
| purified water | up to 100 | | | | | |

To justify the choice of a rational composition for films that would have the necessary properties, the integrity and gloss of the films, their relative elongation, tensile strength, and elasticity were investigated. These indicators affect the consumer quality of the films. The benchmark values for the films were selected from the literature: tensile strength – 70-90 kgf/cm2; relative elongation – 55-100%; integrity – 6-14 μA; adhesion strength – not less than 90%.

The gloss of the films was determined using a gloss meter, which is designed to determine the reflected glossiness of a test sample. The obtained values were compared with the benchmark – glass, glossiness of which was taken as 65%.

During the study, it was found that the sample according to specification #1 did not meet the requirements for external appearance and physico-mechanical properties, and therefore was not used in further research. The results of the study are presented in Table 3.2.

Analysis of the research results presented in Table 4.2 shows that the average tensile strength of the test samples of the films is within the range of 79.8 to 90.5 kgf/cm$^2$.

*Table 3.2*

**Physico-chemical properties of model bases of films**

| Model samples | Physico-chemical parameters, dimensions | | | |
|---|---|---|---|---|
| | Adhesion strength, % | Tensile strength, кgf/cm$^2$ | Relative elonglation,% | Solidity |
| 1 | 68.3 ± 0.3 | 50.4 ± 0.5 | 28.4 ± 0.5 | 5.3 ± 0.3 |
| 2 | 98.2 ± 0.5 | 89.5 ± 0.3 | 85.2 ±0.5 | 7.5 ± 0.2 |
| 3 | 85.6 ± 0.4 | 81.3 ± 0.2 | 48.6 ± 0.2 | 8.1 ± 0.3 |
| 4 | 82.1 ± 0.4 | 79.9 ± 0.1 | 36.1 ± 0.3 | 8.4 ± 0.3 |
| 5 | 78.8 ± 0.3 | 82.6 ± 0.3 | 46.5 ± 0.3 | 9.6 ± 0.4 |
| 6 | 96.3 ± 0.4 | 90.6 ± 0.5 | 65.7 ± 0.4 | 7.9 ± 0.1 |
| Optimal values | ≥90 | 80-90 | 55-100 % | 6-14 |

One of the indicators that characterizes the quality of medicinal films is their integrity. The lower the values of this indicator (between 16 and 139), the higher the quality of the films, as they are free from pores and microcracks. Integrity is also a factor that characterizes the glossiness of the films. The lower the integrity values, the higher the glossiness and quality of the films [13]. The research results on the integrity indicators showed that all of them fall within the recommended values, except for sample No. 1. For sample No. 2, the value is 7.6 and for sample No. 6, it is 7, both in micron. In contrast, samples No. 3 and 4 have values exceeding 8 micron, and sample No. 5 approaches 10 micron.

Adhesion is another important quality indicator of medicinal films. According to the specificity of their application, this value should exceed 90%. The research showed that the highest adhesion values were found for samples No. 2 and 6, at 98.2% and 96.2%, respectively. For all other samples, the adhesion value was less than 90% and outside the specifications for medicinal films.

Thus, based on the generalized results of the physical and mechanical properties of the model film samples, samples No. 2 and 6 were chosen for further research due to their optimal indicators falling within the specifications of medicinal films, such as adhesion, tensile strength, elongation at break, and integrity.

In addition to physical and mechanical properties, another important quality indicator of medicinal films is their osmotic activity. For topical medications, osmotic activity is a crucial factor because it affects their therapeutic effect, ability to absorb exudate, and promote faster inflammation healing [10]. The osmotic activity was determined by the dialysis method through a semi-permeable membrane according to the methodology described in section 2.

We studied the osmotic activity of the samples (Fig. 3.1).

It has been established that the osmotic activity of the model samples has the same dynamics and practically does not differ from each other, and is at the level of 80-84%. It is known that the osmotic activity is influenced by hydrophilic aqueous solvent.

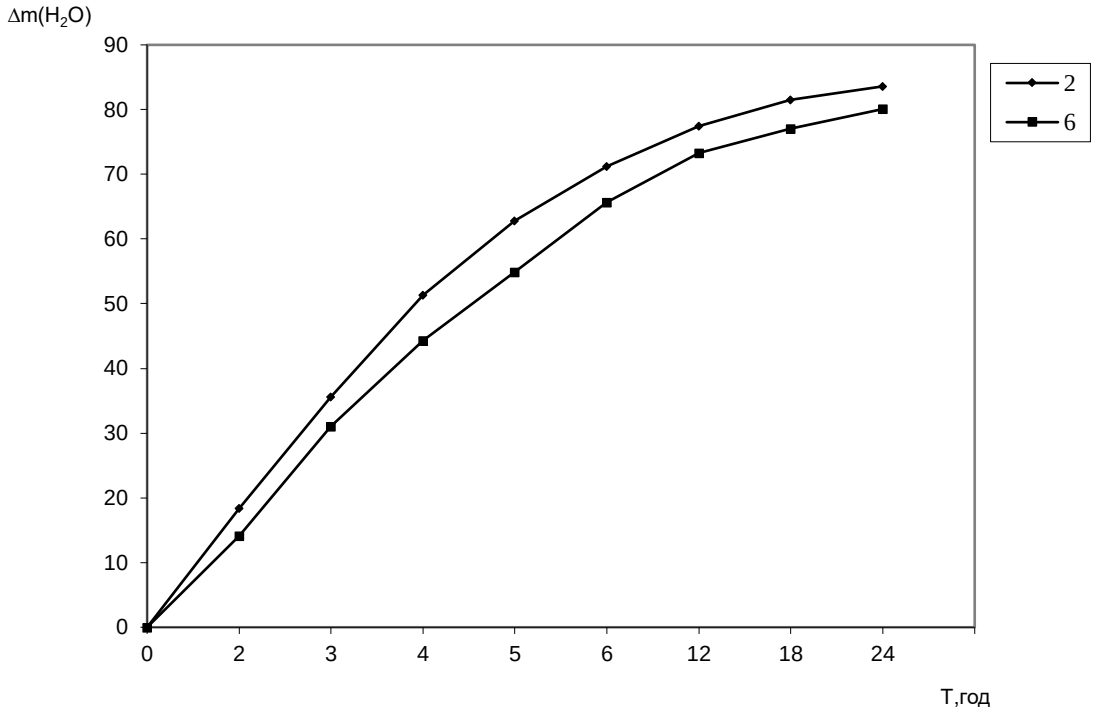



Рис. 3.1 Absorption capacity of experimental film samples

We studied the effect of glycerin on the osmotic activity of films. In the selected sample No. 2 (Table 3.2), the concentration of glycerin was varied, using 1% (sample 1) and 5% (sample 3), compared to 3% in sample 2.

It has been established that reducing the concentration to 1% decreases the absorption capacity by 5%. Increasing the concentration of glycerin to 5% caused an increase in osmosis by 13% to 97%, which corresponds to the requirements according to the specification characteristics for medicinal products. Such a level of osmotic activity can help eliminate purulent discharge and reduce swelling.

An important quality indicator and stability of medicinal films is their resistance to drying out. The loss of moisture was determined by the results of the reduction in mass of the medicinal product.

The loss of mass in the medicinal films may indicate their resistance to drying out, which is an important indicator for medicinal films. It has been established that the smallest loss of moisture is observed for the sample with 5%

glycerin, where after 24 hours of drying, the loss of mass is 18% compared to 24% in the sample containing 1% glycerin.

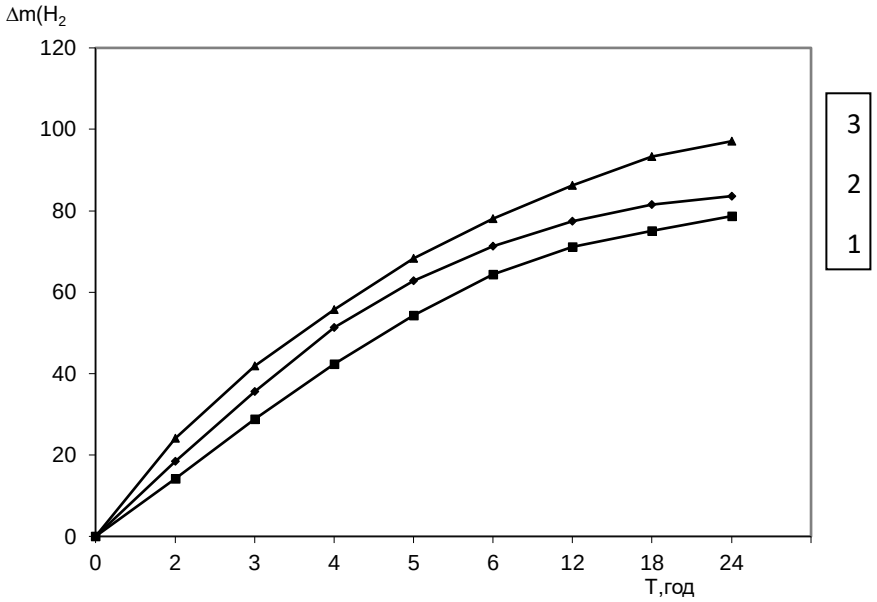



Рис. 3.2 The absorbency capacity of films depending on glycerin concentration

Small losses of mass are observed for the sample with 3% glycerin. However, it is predicted that increasing the glycerin content to 5% reduces the loss of mass during drying (Fig. 3.3).

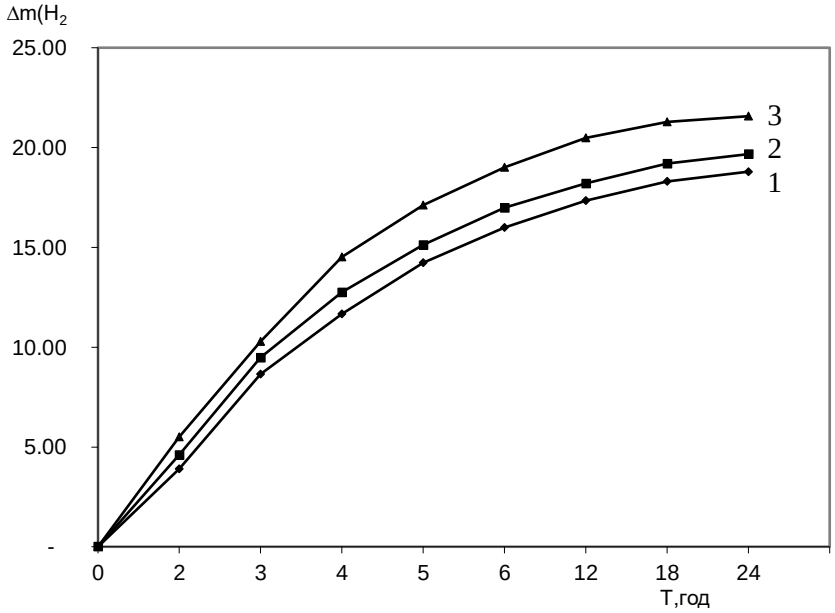



Рис. 3.3 Investigation of moisture retention capacity of films depending on glycerin concentration

Based on the research results, the most optimal concentration for use in the composition of the medicinal film is 5% glycerin. Films dried out too quickly at lower concentrations of glycerin, and were sticky to the touch at higher concentrations. Therefore, for further research, we will use a base that includes: PAA 2%, PVS 2%, CMC 1.5%, glycerin 5%, purified water up to 100.0.

As the analysis of literary sources and the composition of medicinal films has shown, the following active pharmaceutical ingredients (APIs) are used in the development of dental and oral films: caffeine, diphenhydramine hydrochloride, pseudoephedrine hydrochloride, loratadine, phenylephrine hydrochloride, chlorpheniramine maleate, azatadine maleate, brompheniramine maleate, paracetamol, meloxicam, triprolidine hydrochloride, acrivastine, dextromethorphan hydrochloride, ketoprofen, sumatriptan succinate, zolmitriptan, loperamide, omeprazole, salbutamol sulfate, nicotine, and so on [10, 21, 34, 41].

To ensure the necessary pharmacological effect, antimicrobial components must be added to the composition of the medicinal film. APIs are chosen from the group of antiseptics derived from halogens, which are divided into chlorine-containing and iodine-containing. Chlorine-containing halogens are antiseptics with antimicrobial action that have a long-lasting effect and do not irritate tissues. This group includes 0.5-1% iodine chloride solution, 1.5% chloramine solution, and 0.5% chloramine B solution. This group of antiseptics has certain drawbacks, such as a strong chlorine odor, and they also irritate mucous membranes at high concentrations.

Iodine-containing preparations such as 1% iodinol solution and 5% alcohol solution of iodine are used. Iodine has a rapid and strong disinfectant effect due to protein coagulation.

Cationic QACs (quaternary ammonium compounds) are fourth-generation ammonium bases. These compounds, due to their positive charge, neutralize the activity and pathogenicity of negatively charged shells of microorganisms by adhering to them. From the numerical group of cationic QACs, the following are

used: 0.01-0.05 % miramistin solution, 0.5 % ethonium solution, 0.25-2 % DMSO solution [33, 29].

Antiseptic cationic QACs also include salts of quaternary ammonium bases such as chlorhexidine digluconate, cetylpyridinium chloride, and miramistin monohydrate.

Chlorhexidine digluconate is an antiseptic, a derivative of biguanide, which has pronounced antimicrobial activity (even at high dilutions) and low toxicity. It is effective against staphylococci, streptococci, E. coli, and a range of other aerobic and anaerobic bacteria as well as the yeast-like fungus Candida albicans. Depending on the concentration, chlorhexidine has a bacteriostatic or bactericidal effect on gram-positive and gram-negative bacteria. It has a bacteriostatic effect in aqueous and alcohol solutions at a concentration of 0.01%; bactericidal effect – above 0.01%; fungicidal effect – 0.05%. In dentistry, 1% and 2% solutions are used [33, 29, 25, 42].

Cetylpyridinium chloride is an antiseptic from the group of quaternary ammonium compounds and belongs to cationic surfactants. It has a bactericidal effect on a wide range of gram-positive and, to a lesser extent, gram-negative bacteria. The antimicrobial activity of cetylpyridinium is due to its nonspecific interaction with various components of the bacterial cell: membrane, ribosomes, proteins, and enzymes. Cetylpyridinium chloride also inhibits some groups of viruses and fungi. It is inactive against bacterial spores [26].

Miramistin monohydrate is an antiseptic with a wide range of action, effective in the prevention and treatment of bacterial, fungal, and viral infections. A 0.01% solution of miramistin is used for gingivitis, which exhibits antimicrobial and antiviral activity, as well as wound-healing properties [9].

The anti-inflammatory activity of the developed pharmaceutical formulations can be fully realized through extracts from the following plant raw materials: calendula and meadowsweet flowers, tansy herb, birch leaves, nettle, linden, black currant, and immortelle grass.

The following active pharmaceutical ingredients (APIs) were chosen for inclusion in the developed dental films: chlorhexidine bigluconate antiseptic and sodium hyaluronate + dry meadowsweet extract.

Hyaluronic acid (HA) is a component of the extracellular matrix. It reduces inflammatory reactions and stimulates tissue healing. This substance is extremely effective for the prevention and treatment of periodontal diseases, especially in individuals prone to periodontal destruction and poor gum healing after mechanical treatment of the oral cavity [36].

It is known that the mechanical and pharmacotechnological properties of pharmaceuticals may change upon introduction of active pharmaceutical ingredients (APIs). Therefore, we studied the effect of each API on the physical and mechanical properties of the model sample of the pharmaceutical film. The composition and properties of the films are presented in Tables 3.3 and 3.4.

*Таблиця 3.3*

**The composition of experimental films samples**

<table>
<tr><td rowspan="3">Names of ingredients</td><td colspan="4">Quanitative content of ingredient, (%)</td></tr>
<tr><td colspan="4">Model base</td></tr>
<tr><td>1</td><td>2</td><td>3</td><td>4</td></tr>
<tr><td>PAA</td><td colspan="4">2</td></tr>
<tr><td>PVA</td><td colspan="4">2</td></tr>
<tr><td>CMC</td><td colspan="4">1,5</td></tr>
<tr><td>grycerin</td><td colspan="4">5</td></tr>
<tr><td>chlorhexidine digluconate</td><td>-</td><td>0.05</td><td>-</td><td>0.05</td></tr>
<tr><td>sodium hyaluronate</td><td>-</td><td>-</td><td>0.2</td><td>0.2</td></tr>
<tr><td>dry extract of meadowsweet flowers</td><td>-</td><td colspan="3">1.0</td></tr>
<tr><td>purified water</td><td colspan="4">Up to 100</td></tr>
</table>

Chlorhexidine bigluconate, sodium hyaluronate, and dry meadowsweet flowers extract were added to the film composition after previous dissolution in water. Meadowsweet extract was dissolved in purified water heated to a temperature of 75 ± 5 °C. The results of the study of the physical and mechanical properties of the films before and after the addition of the API showed that the model samples practically did not differ in the studied properties.

*Таблиця 3.4*

**Physico-chemical properties of model films**

| Model samples | Physico-chemical parameters, dimensions | | | |
|---|---|---|---|---|
| | Adhesion strength, % | Tensile strength, кgf/cm$^2$ | Relative elongation,% | Solidity, micron |
| 1 | 98.3 ± 0.4 | 89.4 ± 0.2 | 85.1 ±0.3 | 7.7 ± 0.2 |
| 2 | 98.5 ± 0.3 | 89.2 ± 0.4 | 84.6 ± 0.2 | 7.8 ± 0.3 |
| 3 | 98.7 ± 0.2 | 92.1 ± 0.1 | 88.5 ± 0.4 | 8.0 ± 0.2 |
| 4 | 98.4 ± 0.2 | 89.2 ± 0.3 | 86.1 ± 0.2 | 7.7 ± 0.1 |
| Optimal values | ≥90 | 80-90 | 55-100 % | 6-14 |

The values of all parameters are within ±5% deviations, which indicates the practical absence of API influence on the physical and mechanical properties of the samples. This may be due to the properties (solubility in water) and low doses of API in the composition of a medication.

The obtained results correspond to the specification parameters of medication: relative elongation – 55.0-100.0%; tensile strength – 80.0 - 90.0 kgf/cm2; solidity – 6 - 14 micron, adhesion strength – not < 90%.

Thus, according to the results of the conducted research, the composition of dental films is proposed (Table 3.5).

*Table 3.5*

**Compostition of dental films**

| **Names of ingredients** | Quantitative content of ingredients, (%) | Functional purpose |
|---|---|---|
| PAA | 2 | film former |
| PVA | 4 | film former |
| CMC | 1.5 | film former |
| glycerin | 5 | moisturizer |
| chlorhexidine bigluconate | 0.05 | API, antiseptic |
| sodium hyaluronate | 0.2 | API, moisturizing, reparative effect |
| dry extract of meadowsweet flowers | 0.5 | BAS, antibacterial effect |

### 3.3 Technology of medicinal films and study of the medicinal films' stability

The results of the physico-chemical and pharmacotechnological studies of films made it possible to build a technological sequence of processes, which is the basis of the technological process of the production of a medication.

The production of FP was carried out by the irrigation method in accordance with the requirements of the Instruction ST-N of the Ministry of Health 42-4.5:2015 «Requirements for the manufacture of non-sterile medicinal products in pharmacies» [7].

The main stages of film production are:

– preparation of a solution of film-forming polymers;

– obtaining a solution of API (in a minimum amount of water) with PVP and glycerin;

– deaeration;

– filtering;

– bottling;

– drying;

– cutting;

– packaging;

– labeling.

In order to study the stability of the films and their compliance with the defined specific requirements, their quality was studied during 6 months of storage in foil packed in polyethylene bags at temperatures of 5±3˚C ˚C and 25±2˚C.Results of the research are presented in table 3.6.

*Table 3.6*

**Results of study of dental films during storage**

| Model samples | Фізико-хімічні показники, розмірність | | | |
|---|---|---|---|---|
| | Adhesion strength, % | Tensile strength, кgf/cm$^2$ | Relative alongation,% | Solidity, micron |
| Optimal values | ≥90 | 80-90 | 55-100 % | 6-14 |
| Initial values | 98.2 ± 0.3 | 89.4 ± 0.2 | 86.1 ± 0.3 | 7.7 ± 0.2 |
| at temperature 5±3˚C | | | | |
| 1 | 98.2 ± 0.2 | 89.5 ± 0.2 | 85.2 ±0.5 | 7.6 ± 0.3 |
| 3 | 98,4 ± 0.3 | 89.4 ± 0.2 | 85.2 ±0.2 | 7.7 ± 0.2 |
| 6 | 98.1 ± 0.2 | 89.3 ± 0.3 | 84.9 ± 0.3 | 7.6 ± 0.2 |
| at temperature 25±2˚C | | | | |
| 1 | 98.2 ± 0.3 | 91.1 ± 0.1 | 85.5 ± 0.2 | 8.0 ± 0.2 |
| 3 | 98.3 ± 0.3 | 89.3 ± 0.2 | 86.1 ± 0.2 | 7.8 ± 0.2 |
| 6 | 98.2 ± 0.2 | 89.2 ± 0.2 | 86.0 ± 0.3 | 7.6 ± 0.3 |

The analysis of the results showed that MF remain stable in all samples studied during 6 months of storage at a temperature range from 2 to 27 ˚C.

**Conclusions to section 3**

1. On the basis of complex pharmacotechnological, physico-mechanical research, the composition of medicinal films was substantiated: PAA 2%, PVA 4%, CMC 1.5%, glycerin 5%, chlorhexidine bigluconate 0.05%, sodium hyaluronate 0.2%, dry extract of meadowsweet flowers 1.0%.
2. As a result of the study of the physical and chemical properties of medicinal films, their compliance with the specification norms was established.
3. The technology of production of medicinal films was proposed.
4. The stability of medicinal films during storage for 6 months at a temperature of up to 25 °C in foil, packed in food-grade cellophane was studied.

## GENERAL CONCLUSIONS

1. Literature sources on transdermal therapeutic systems have been analyzed and summarized.
2. The assortment of auxiliary substances used in the composition of topical pharmaceutical products is described.
3. The composition of medicinal films is substantiated based on complex pharmaco-technological and physico-mechanical research: PAA 2%, PVA 4%, CMC 1.5%, glycerin 5%, chlorhexidine bigluconate 0.05%, sodium hyaluronate 0.2%, dry extract of meadowsweet flowers 1.0%.
4. As a result of research on the physico-chemical properties of medicinal films, their compliance with specification standards has been established.
5. A technology for the production of medicinal films is proposed.
6. Quality indicators and stability of medicinal films during storage for 6 months have been studied. As a result of the research, a shelf life of 6 months at a temperature of up to 25 °C in food-grade cellophane packaging has been established.
7. Conference abstracts have been published based on the results of the study. *Polovko N.P., Kanun Elmehdi* THE USE OF EXCIPIENTS IN TRANSDERMAL THERAPEUTIC SYSTEMS. Modern achievements of pharmaceutical technology: Collection of X International Scientific-Practical Conference, dedicated to the 60th anniversary of the birth of Doctor of Pharmaceutical Sciences, Professor Gladukh Ievgenii Volodymyrovych, Kharkiv, May 10-11, 2023. Kharkiv : NUPh, 2023. P. 90.

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# APPENDICES

*Appendices A*


МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

# ГРАМОТА

нагороджується

## Канун Ельмехді

у секційному засіданні студентського наукового товариства кафедри аптечної технології ліків

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

В.о. ректора
Національного фармацевтичного університету

Алла КОТВІЦЬКА

19-21 квітня 2023 р.
м. Харків

*Appendices Б*

National University of Pharmacy
*Національний фармацевтичний університет*
Department of Technologies of Pharmaceutical preparations
*Кафедра технологій фармацевтичних препаратів*

# CERTIFICATE № 160

*СЕРТИФІКАТ*

This is to certify that
*Цим засвідчується, що*

## Канун Ельмехді

has participated in the X International Scientific-Practical Conference
*брав(ла) участь у X Міжнародній науково-практичній конференції*
**"MODERN ACHIEVEMENTS OF PHARMACEUTICAL TECHNOLOGY"**
**«СУЧАСНІ ДОСЯГНЕННЯ ФАРМАЦЕВТИЧНОЇ ТЕХНОЛОГІЇ»**
dedicated to the 60th anniversary of the birth of Doctor of Pharmaceutical Sciences, Professor Gladukh Ievgenii Volodymyrovych
*присвяченої 60-річчю з дня народження доктора фармацевтичних наук, професора Гладуха Євгенія Володимировича*

May 10-11, 2023, Kharkiv, Ukraine
*10-11 травня 2023 року, Харків, Україна*

**Rector of the NUPh, prof.**
*Ректор НФаУ, проф.*
**Alla KOTVITSKA**
*Алла КОТВІЦЬКА*

**Head of the Department of Technologies of Pharmaceutical preparations, prof.**
*Завідувач кафедри технологій фармацевтичних препаратів, проф.*
**Oleksandr KUKHTENKO**
*Олександр КУХТЕНКО*

*Appendices B*

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
МІНІСТЕРСТВО ОСВІТИ І НАУКИ УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ
НАЦІОНАЛЬНА АКАДЕМІЯ НАУК ВИЩОЇ ОСВІТИ УКРАЇНИ
КАФЕДРА ТЕХНОЛОГІЇ ФАРМАЦЕВТИЧНИХ ПРЕПАРАТІВ

MINISTRY OF HEALTH OF UKRAINE
MINISTRY OF EDUCATION AND SCIENCE OF UKRAINE
NATIONAL UNIVERSITY OF PHARMACY
NATIONAL ACADEMY OF HIGHER EDUCATION SCIENCES OF UKRAINE
DEPARTMENT OF TECHNOLOGIES OF PHARMACEUTICAL PREPARATIONS

# X МІЖНАРОДНА НАУКОВО-ПРАКТИЧНА КОНФЕРЕНЦІЯ «СУЧАСНІ ДОСЯГНЕННЯ ФАРМАЦЕВТИЧНОЇ ТЕХНОЛОГІЇ»

присвячена 60-річчю з дня народження
доктора фармацевтичних наук,
професора Гладуха Євгенія Володимировича

# X INTERNATIONAL SCIENTIFIC-PRACTICAL CONFERENCE «MODERN ACHIEVEMENTS OF PHARMACEUTICAL TECHNOLOGY»

dedicated to the 60th anniversary of the birth of
Doctor of Pharmaceutical Sciences,
Professor Gladukh Ievgenii Volodymyrovych

ЗБІРНИК НАУКОВИХ ПРАЦЬ
COLLECTION OF SCIENTIFIC WORKS

ХАРКІВ
KHARKIV
2023

*Appendices B*

*Appendices B*

«Сучасні досягнення фармацевтичної технології» (10-11 травня 2023 р., м. Харків)

**THE USE OF EXCIPIENTS IN TRANSDERMAL THERAPEUTIC SYSTEMS**

***Polovko N.P., Kanun Elmehdi***
**National University of Pharmacy, Kharkiv, Ukraine**

Excipients in the composition of transdermal therapeutic systems (TTS) are classified according to various characteristics, one of the main ones being classification according to functional purpose. The main groups are mold-forming (film-forming) substances; solubilizers, plasticizers, adhesives, penetrants, preservatives and flavors. The need to use a sufficiently large number of auxiliary substances is explained by the fact that it is impossible to obtain a high-quality drug from one basic polymer. There is a need to use other excipients to modify certain physical or physicochemical properties of TTS, such as, for example, adhesiveness, elasticity, and others. The same excipient can perform different functions.

For example, to increase the adhesive properties, PEG, PVP, starch, glycerin and other hydrophilic substances that can act as plasticizers and penetrants are introduced. When creating TTS, excipients belonging to different classification groups can be used.

Polymers of natural origin are used as the main (basic) auxiliary substances and are represented by different groups: of animal (chitosan, collagen, gelatin, elastin); plant (alginates, agar-agar) and microbial origin (dextrin, xanthan gum). The group of polymers of semi-synthetic origin, which are used in the composition of TTS, is represented by methyl cellulose, sodium-carboxy-methylcellulose, oxypropylethylcellulose, etc.; synthetic (polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene oxide, polyacrylamides, etc.). Along with the specified auxiliary substances, various other excipients are used. Hydrophilic non-aqueous solvents such as propylene glycol, glycerin, ethanol are used as solvents and co-solvents in TTS. Esterified fatty acids, sorbitan monooleate, glyceryl monooleate, methyl laurate, etc. are used as solubilizers and plasticizers.

*Ф А 2.2.1–32-366*

**National University of Pharmacy**

Faculty for foreign citizens' education
Department department drug technology

Level of higher education master

Specialty 226 Pharmacy, industrial pharmacy
Educational program Pharmacy

**APPROVED**
**The Head of Department**
**department drug technology**

**_____**

**Liliia VYSHNEVSKA**
"28" september 2022

**ASSIGNMENT**
**FOR QUALIFICATION WORK**
**OF AN APPLICANT FOR HIGHER EDUCATION**

## Elmehdi KANOUN

1. Topic of qualification work: «Research on the creation of films with anibacterial and anti-inflammatory effects», supervisor of qualification work: Natalia POLOVKO, Doctor of Pharmaceutical Sciences, prof.,

approved by order of NUPh from "6th" of February 2023 № 35

2. Deadline for submission of qualification work by the applicant for higher education: April 2023.

3. Outgoing data for qualification work: the composition of a combined application drug with antibacterial and anti-inflammatory effects was developed

4. Contents of the settlement and explanatory note (list of questions that need to be developed):
- analyze and summarize the literature on the use, composition, and technology of transdermal therapeutic systems.
- characterize the range of auxiliary substances used in the composition of application drugs.
- develop the composition and investigate the properties of the application drug (in the form of films).

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

6. Consultants of chapters of qualification work

| **Chapters** | **Name, SURNAME, position of consultant** | **Signature, date** | |
|---|---|---|---|
| | | **assignment was issued** | **assignment was received** |
| 1 | Natalia POLOVKO, professor of higher education institution of department of department drug technology | 28.09.2022 | 28.09.2022 |
| 2 | Natalia POLOVKO, professor of higher education institution of department drug technology | 07.10.2022 | 07.10.2022 |
| 3 | Natalia POLOVKO, professor of higher education institution of department drug technology | 16.11.2022 | 16.11.2022 |

7. Date of issue of the assignment: «28th» of September 2022

**CALENDAR PLAN**

| **№** | **Name of stages of qualification work** | **Deadline for the stages of qualification work** | **Notes** |
|---|---|---|---|
| 1 | Topic selection | September 2022 | **done** |
| 2 | Literature analysis | September-December 2022 | **done** |
| 3 | Conducting of experimental studies | January – February 2023 | **done** |
| 4 | Formatting of the work | March 2023 | **done** |
| 5 | Submission of finished work to the commission | April 2023 | **done** |

**An applicant of higher education** _____ Elmehdi KANOUN

**Supervisor of qualification work** _____ Natalia POLOVKO

**ВИТЯГ З НАКАЗУ № 35**
**По Національному фармацевтичному університету**
**від 06 лютого 2023 року**

нижченаведеним студентам 5-го курсу 2022-2023 навчального року, навчання за освітнім ступенем «магістр», галузь знань 22 охорона здоров'я, спеціальності 226 – фармація, промислова фармація, освітня програма – фармація, денна форма здобуття освіти (термін навчання 4 роки 10 місяців та 3 роки 10 місяців), які навчаються за контрактом, затвердити теми кваліфікаційних робіт:

| Прізвище студента | Тема кваліфікаційної роботи | | Посада, прізвище та ініціали керівника | Рецензент кваліфікаційної роботи |
|---|---|---|---|---|
| • **по кафедрі аптечної технології ліків** | | | | |
| Канун Ельмехді | Дослідження зі створення плівок антибактеріальної і протизапальної дії | Research on the creation of antibacterial and anti-inflammatory films | проф. Половко Н.П. | проф. Рубан О.А. |

Підстава: подання деканату, згода ректора

Ректор

**Вірно**. Секретар

*Ф А2.8-47-110*

**ВИСНОВОК**

**Комісії з академічної доброчесності про проведену експертизу**

**щодо академічного плагіату у кваліфікаційній роботі**

**здобувача вищої освіти**

№ 113210 від «10 » травня 2023 р.

Проаналізувавши випускну кваліфікаційну роботу за магістерським рівнем здобувача вищої освіти денної форми навчання Канун Ельмехді, 5 курсу, 3 групи, спеціальності 226 Фармація, промислова фармація, на тему: «Дослідження зі створення плівок антибактеріальної і протизапальної дії / Research on the creation of antibacterial and anti-inflammatory films», Комісія з академічної доброчесності дійшла висновку, що робота, представлена до Екзаменаційної комісії для захисту, виконана самостійно і не містить елементів академічного плагіату (компіляції).

**Голова комісії,**
**професор** **Інна ВЛАДИМИРОВА**

**0%**

**28%**

*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**

**Elmehdi KANOUN**

**on the topic: «Research on the creation of films with antibacterial and anti-inflammatory effects»**

**Relevance of the topic.** An alternative method of administering medicinal substances into the body is through the use of transdermal therapeutic systems (TTS). Modern TTS are becoming increasingly popular due to their cost-effectiveness, as targeted use of medicinal substances allows for a reduction in the required quantity, making treatment cheaper and more accessible. TTS for local use are traditionally available in the form of films, patches, or strips. Considering the absence of combination film formulations in the pharmaceutical market, the development of medicinal products in the form of films that combine several active substances with antibacterial, antifungal, reparative, anti-inflammatory, and antioxidant effects is currently relevant.

**Practical value of conclusions, recommendations and their validity.** The applicant for higher education has analyzed and summarized the literary sources regarding medicinal films. The characterization of the assortment and properties of excipients used in the composition of medicinal films has been provided. Based on comprehensive physico-mechanical and pharmaco-technological studies, the composition of medicinal films containing chlorhexidine bigluconate, sodium hyaluronate, and dried meadowsweet flower extract has been substantiated. The research of the physicochemical properties of medicinal films has confirmed their compliance with the specified standards. A technology for the production of medicinal films has been proposed.

**Assessment of work**. The thesis, in terms of its volume of theoretical and practical research, fully meets the requirements for the formatting of qualification works.

**General conclusion and recommendations on admission to defend.** The thesis of Kanun ELMEHDI is eligible for submission to the Examination Commission of the National Pharmaceutical University for the award of a Master's degree.

Scientific supervisor _____ Natalia POLOVKO

«12th» of April 2023

*Ф А 2.2.1-32-356*

**REVIEW**

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

**Elmehdi KANOUN**

**on the topic: «Research on the creation of films with antibacterial and anti-inflammatory effects »**

**Relevance of the topic.** A promising direction in the development of modern pharmacy is the utilization of transdermal therapeutic systems (TTS). TTS films enable targeted delivery of pharmaceutical substances, reducing their quantity, cost, and ensuring the safety of treatment. Since combined films are currently absent on the pharmaceutical market, it is relevant to create films that contain a complex of active pharmaceutical ingredients (APIs) combining multiple pharmacological effects, such as antibacterial, reparative, anti-inflammatory, and antioxidant properties.

**Theoretical level of work.** The work is done at the required theoretical level.

**Author's suggestions on the research topic.** The applicant for higher education has summarized the literature sources on pharmaceutical films; provided a characterization and analyzed the range and properties of excipients used in pharmaceutical films; based on experimental research, justified the composition of pharmaceutical films containing sodium hyaluronate, chlorhexidine bigluconate, and dried meadowsweet flower extract. A technology for pharmaceutical films has been developed. The properties of the pharmaceutical films have been investigated, and their compliance with regulatory requirements has been established.

**Practical value of conclusions, recommendations and their validity.** The work has been carried out using modern methods. The results have been statistically processed, and the conclusions are based on an appropriate amount of rese
The obtained results have practical implications.

**Disadvantages of work.** In terms of volume and content, it meets the requirements for qualification works.

**General conclusion and assessment of the work.** The qualification paper of Kanun ELMEHDI can be presented for defense to the Examination Commission of the National Pharmaceutical University for the award of a master's educational qualification level.

Reviewer _____ prof. Olena RUBAN

«19th» of April 2023

**МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ**
**НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ**

**ВИТЯГ З ПРОТОКОЛУ № 9**
«26» квітня 2023 року
м. Харків

**онлайн-засідання кафедри**
**аптечної технології ліків**
(назва кафедри)

**Голова:** завідувачка кафедри, професор Вишневська Л. І.
**Секретар:** докт. філ., асистент Коноваленко І. С.

**ПРИСУТНІ:**
Богуцька О. Є., Зуйкіна С. С., Ковальова Т. М., Крюкова А. І., Марченко М. В., Половко Н.П., Семченко К. В.

**ПОРЯДОК ДЕННИЙ:**
1. Про представлення до захисту кваліфікаційних робіт здобувачів вищої освіти.

**СЛУХАЛИ: проф. Вишневську Л. І.** – про представлення до захисту до Екзаменаційної комісії кваліфікаційних робіт здобувачів вищої освіти.

**ВИСТУПИЛИ:** Здобувач вищої освіти групи Фм18(5,0д)анг-03 спеціальності 226 Фармація, промислова фармація освітньої програми Фармація Канун Ельмехді – з доповіддю на тему «Research on the creation of films with anibacterial and anti-inflamatory effects/ Дослідження зі створення плівок антибактеріальної і протизапальної дії» (науковий керівник, проф. Половко Н. П.).

**УХВАЛИЛИ:** Рекомендувати до захисту кваліфікаційну роботу.

**Голова**
Завідувачка кафедри, проф. _____ **Лілія ВИШНЕВСЬКА**

**Секретар**
Асистент _____ **Ілона КОНОВАЛЕНКО**

*Ф А2.2.1-32-042*

# НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

## ПОДАННЯ
## ГОЛОВІ ЕКЗАМЕНАЦІЙНОЇ КОМІСІЇ
## ЩОДО ЗАХИСТУ КВАЛІФІКАЦІЙНОЇ РОБОТИ

Направляється здобувач вищої освіти КАНУН Ельмехді до захисту кваліфікаційної роботи
за галуззю знань 22 Охорона здоров'я
спеціальністю 226 Фармація, промислова фармація
освітньою програмою Фармація
на тему: «Дослідження зі створення плівок антибактеріальної і протизапальної дії».

Кваліфікаційна робота і рецензія додаються.

Декан факультету _____ / Світлана КАЛАЙЧЕВА /

### Висновок керівника кваліфікаційної роботи

Здобувач вищої освіти КАНУН Ельмехді представив кваліфікаційну роботу, яка за об'ємом теоретичних і практичних досліджень повністю відповідає вимогам до оформлення кваліфікаційних робіт.

Керівник кваліфікаційної роботи

_____ Наталя ПОЛОВКО

«12» квітня 2023 р.

### Висновок кафедри про кваліфікаційну роботу

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

Завідувачка кафедри
аптечної технології ліків

_____ Лілія ВИШНЕВСЬКА

«26» квітня 2023 р.

Qualification work was defended

of Examination commission on

«____» June 2023

With the grade _____

Head of the State Examination commission,

DPharmSc, Professor

_____ / Oleh SHPYCHAK /