*F A 2.2.1-32-367*

**MINISTRY OF HEALTH OF UKRAINE**
**NATIONAL UNIVERSITY OF PHARMACY**

**faculty for foreign citizens' education**

**department Technology of Drugs**

**QUALIFICATION WORK**

on the topic

# DEVELOPMENT OF THE COMPOSITION OF SUPPOSITORIES FOR THE TREATMENT OF CANDIDIASIS

**Prepared by:** higher education graduate of group Phm17 (4.10d) - 06 English
specialty 226 Pharmacy, industrial pharmacy
educational program Pharmacy
Hajar BIKECH
**Supervisor:** associate professor of higher education institution of department Technology of Drugs, PhD, associate professor Ganna YURIEVA
**Reviewer**: associate professor of higher education institution of department of Industrial drug technology, PhD, associate professor Natalia GERBINA

**Kharkiv – 2022 year**

## SUMMARY

The relevance of the development of extemporaneous suppositories with fluconazole for use in the treatment of candidiasis is theoretically and experimentally substantiated in the master 's thesis. Based on the results of experimental studies, in particular organoleptic, physicochemical and biopharmaceutical, the optimal composition of the new drug is substantiated. Quality parameters of model samples were determined according to methods of SPhU. The work is presented on 42 pages, includes 6 tables, 4 figures and 71 sources of literature.

*Key words:* suppositories, composition, technology, candidiasis, antifungal drug.



## АНОТАЦІЯ

В магістерській роботі теоретично та експериментально обґрунтована актуальність розробки екстемпоральних супозиторіїв з флуконазолом для застосування в лікуванні кандидозу. На основі результатів експериментальних досліджень, зокрема органолептичних, фізико-хімічних та біофармацевтичних, обґрунтовано оптимальний склад нового препарату. Показники якості модельних зразків визначали за методикою ДФУ. Робота викладена на 42 сторінках, містить 6 таблиць, 4 рисунки та 71 джерело літератури.

*Ключові слова:* супозиторії, склад, технологія, кандидоз, протигрибковий препарат.

**CONTENTS**

# INTRODUCTION

**Actuality of topic.** Fungal infections are one of the leading groups diseases in the world. According to the WHO, every fifth inhabitant of the planet suffers from any mycosis. The frequency of these infections is associated with deteriorating environmental conditions, widespread use of antibiotics, increasing the number of patients with disorders of the immune system, etc.

In recent years, the prevalence of fungal infections has increased, caused by fungi of the genus *Candida*. Clinicians note the trend of steady increase in the incidence of this pathology, frequent recurrence and point out that the problem is acute medical and social nature, affecting the health of different age groups and segments of the population, negatively affects them efficiency [17, 23].

Therefore, over the past decade, there has been interest in the treatment and prevention of candidiasis of the mucous membranes in such fields of medicine as gynecology, dentistry, ophthalmology. An analysis of the literature shows that in recent decades the problem of infection has acquired the status of an important medical and social problem. The number of patients with superficial forms of candidiasis - the mucous membranes of the vagina, which are registered as a separate disease, and as a concomitant of other infections. This negatively affects the quality of life of patients, leads to significant financial costs associated with treatment and rehabilitation [37, 38].

The pronounced tendency to spread candidiasis emphasizes the need for appropriate therapy aimed at eliminating the infectious agent, short-term treatment, achieving high concentrations of the substance in the cell, safety and prevention of inactivation of the drug in the liver. Despite the large range and choice of antifungal drugs, the treatment of candidiasis is still relevant and requires for its solution the introduction of new, more effective pharmacological substances, as well as the creation of combined drugs based on them.

Among the groups of modern synthetic anti-fungal agents that used in the treatment of candidiasis of mucous membranes, triazole compounds dominate. Of

these, a special place belongs to fluconazole. Its high bioavailability, relevance and possibility of use in dosage forms of different localization of candidiasis has been confirmed in clinical practice [8, 12, 40, 43, 46, 47, 53, 54, 71].

It is known that in the treatment of candidiasis of the mucous membranes are widely used oral and parenteral methods of administration of antifungal drugs, including fluconazole. However, the local application of this group of drugs also occupies a niche [49].

Thus, in gynecology, one of the rational dosage forms are suppositories, which are prescribed not only for local effects on pathological areas of the vaginal mucosa, but also to achieve a general, resorptive effect on macroorganism. They are directly introduced into the lesion, where they create a high concentration of the active substance and allow to achieve a significant therapeutic effect with minimal side effects, and do not require special conditions for use [15, 18, 29].

**The purpose and objectives of research**

Theoretically and experimentally substantiate the composition and technology of extemporaneous suppositories with fluconazole for use in gynecological practice.

To achieve this goal it is necessary to solve the following **tasks**:

- to analyze the literature on the prospects for the use of fluconazole in the treatment of candidiasis;

- theoretically and experimentally substantiate the composition of suppositories with antifungal action;

- conduct physico-chemical, biopharmaceutical and microbiological examination of suppository samples;

- to develop the technology of making suppositories with fluconazole in pharmacies;

- to study the stability of the developed suppositories.

**Scientific novelty**

The composition and technology of extemporaneous suppositories with fluconazole for use in the local therapy of vaginal candidiasis have been developed.

**Theoretical and practical significance of the work**

The theoretical and practical significance of the master's thesis is that the choice of suppository base, excipients was experimentally substantiated and the composition and technology of extemporaneous drug in the form of vaginal suppositories.

**Implementation of results**

The main provisions of the qualification work are outlined and discussed at the International scientific-practical conference "Modern aspects of science, education, technology and society" (April 14, 2022, Poltava). Abstracts of the report have been published.

**Structure and scope of qualification work**.

Qualification work consists of an introduction, literature review (section 1), experimental part (sections 2 and 3), general conclusions, references, appendices. The work is presented on 42 pages, includes 6 tables, 4 figures, 71 sources of literature.

# CHAPTER I.
# MODERN APPROACHES TO THE PHARMACOTHERAPY OF CANDIDOS AND PROSPECTS OF SUPPOSITORIES APPLICATION IN GYNECOLOGICAL PRACTICE

## 1.1. The problem of candidiasis of mucous membranes in medical practice

Currently in medical science and practice with the growth of diseases accompanied by various immunodeficiency conditions, increased interest in lesions of various organs and tissues of the human body pathogenic and opportunistic fungal infections (mycoses). This stimulates the study of microbiological properties of fungi, microbiological responses to fungal invasion, the creation of new methods for diagnosing mycoses, improving schemes and forms of application of existing antifungal drugs, as well as the search for new ones [57, 61].

The most common pathogens of mycoses are opportunistic pathogens - fungi of the genus Candida. However, in certain conditions of the body, they can cause a wide range of diseases - from mild damage to the skin and mucous membranes to processes that can affect almost any organ, often life-threatening [23, 62].

At present, more than 150 biological species of yeasts have been described, and the degree of prevalence and pathogenicity of strains is quite diverse. The main role in human pathology is played by a limited number of species, with a sharp dominance of fungi (80-90%), which has such virulence factors as products, phospholipases, and the ability to produce mycelium.

In recent years, many authors have noted a tendency to increase the incidence of the disease, especially in chronic and active forms caused by other species of fungi [17, 20]. Infectious disease of the skin, mucous membranes and internal organs caused by fungi, which occurs against the background of reduced body defenses and refers to secondary mycoses is called candidiasis [23].

The most common type of pathology among such lesions of the human body - candidiasis of the mucous membranes. The mucous membranes of the urogenital, respiratory and digestive tracts are "open" systems that are in constant contact with the external environment, which explains the high prevalence of human carriers.

In healthy people, this fungus colonizes epithelial surfaces, resulting in the development of specific immunity. Violations of non-specific protection of the organism at the systemic and local level contribute to the occurrence of infection. The increase in the number of patients is affected by the impact of various environmental factors on the human body, such as: deterioration of the environmental situation, extensive use of chemicals, air pollution, frequent and prolonged emotional stress, exhausting physical activity, etc. [17].

The use of new medical technologies (intensive care, organ and tissue transplantation, diagnostic and medical procedures, etc.). Self-medication, taking broad-spectrum antibiotics that inhibit the growth of lactobacilli; HIV infection; autoimmune and allergic diseases, especially with corticosteroids; endocrinopathy; endogenous auto-infection from the intestine and/or oral cavity are also considered risk factors for candidiasis [43, 55].

Clinical manifestations of candidiasis are diverse and depend on the nature of the underlying disease and comorbidities, the stage of the pathological process, the characteristics of the background microbial content. The problem of treatment and prevention of candidiasis is quite narrow in all fields of medicine and, especially, in gynecological practice [40, 49, 57].

In women, inflammatory changes may be limited to the external genitalia or vagina (vaginitis), but combined lesions are more common, urethritis and cystitis are less common [58]. In the general structure of infectious pathology of the genitourinary tract due to fungal infection, according to various authors, range from 30% to 50%. But the most common manifestation of candidiasis of the mucous membranes in gynecology is vaginal, which is firmly in the lead in gynecology among specific infections of the reproductive organs, second only to bacterial [40]. Studies show that about 75 % of women have at least one episode of vaginal can-

didiasis during their lifetime, 50 % have recurrent, and up to 20% of patients have chronic candidiasis [44].

Vaginal candidiasis (VC) is not a sexually transmitted infection, but may indicate changes in immune and / or hormonal status. In VC, the infectious process is most often localized in the superficial layers of the vaginal epithelium and causes changes in the biocenosis of the vagina. This creates optimal conditions for a sharp increase in opportunistic flora, which becomes the main pathogen factor in the development of the disease. Microbiological studies show that in the pathological material there is a cluster of 10-15 or more yeast cells, mostly with buds, mycelium is contained in large quantities.

In acute forms of the disease predominate cellular forms, in chronic - clusters of mycelium. The main clinical symptoms of VC are abundant or moderate raw vaginal discharge, the formation of white plaque on the inflamed mucous membrane, itching and burning in the external genitalia. The mucous membrane is easy injured and bleeding on examination [10, 62].

The peculiarity of this infection is currently chronic, prolonged, prone to recurrence, the course of the process. Thus, almost 40% of women who have suffered from the disease have relapses, which adversely affects not only health but also quality of life in general - mushrooms without symptoms - about 20% healthy women are their carriers [53, 71].

Currently, the most common reports of "non albicans" vaginal lesions, which are referred to as the so-called complicated vaginal candidiasis associated with chronic recurrent forms of the disease. Clinicians note that chronic vaginal infections cause pathology not only of the lower but also of the upper urogenital organs, leading to infertility and abortion. The presence of candidiasis in women during pregnancy leads in 70 % of cases to the colonization of microorganisms in the oral cavity of children [44, 48, 49]. In connection with the above, this infection of the genitourinary system is an urgent problem of modern gynecology.

## 1.2. Modern approaches to the treatment of candidiasis of the mucous membranes

Due to the pronounced trend of candidiasis, the problem of its treatment is especially important, closely related to the choice of treatment regimen and drug. Medicines designed for both systemic and local action are currently used to treat candidiasis.

Systemic antifungal drugs are more commonly administered orally in the form of tablets and capsules, as well as injectable forms. Despite the widespread use of systemic oral antifungal drugs, the likelihood of side effects persists, mainly from the gastrointestinal tract, ranging from mild dyspepsia to the development of various forms of toxic hepatitis [68].

Before the systemic treatment of candidiasis of the mucous membranes, a number of advantages are acquired by local therapy, the preference of which is given in the acute form of the disease. Thus, the local action of drugs determines: minimal systemic absorption, and as a consequence, rare side effects and drug interactions; less likely to develop resistant forms of the pathogen; security; possibility of application at genital pathologies of pregnant women; creating a high concentration of active pharmaceutical ingredient (API) on the mucous membrane and providing a rapid therapeutic effect, which is expressed in the reduction of clinical symptoms; no effect of therapeutic concentrations of the drug on healthy tissues [16].

Drugs are divided into two groups: antibiotics and synthetic antifungal drugs. The first antifungal agents proposed for use in clinical practice were a number of antibiotics. However, they have such significant disadvantages as: high toxicity, low absorption rate of the gastrointestinal tract (for nystatin), not exceeding 3-5%, and so on.

The most common in the treatment of candidiasis, compared with this group, are synthetic drugs, including antifungals. Because the problem of treatment of candidiasis does not lose its relevance and requires its solution to introduce new

effective pharmacological substances, along with drugs of these groups, there are drugs of the triazole series: fluconazole, itraconazole, etc. [49, 54, 66, 71].

The antifungal drug selected for drug therapy must meet the following requirements:

- have selective antifungal action;
- have a minimum frequency of resistance in pathogens;
- have good compatibility with drugs of other pharmacological groups;
- be non-toxic even in the case of long-term use;
- be stable and well absorbed from the gastrointestinal tract;
- long action;
- be economically accessible [1, 61].

In the local treatment of candidiasis use such dosage forms as solutions, creams, ointments, gels, tablets, capsules, suppositories. They include antiseptics, antibiotics, antifungals and their combination one.

For local therapy continue to use, but less often antiseptics such as: 1-3% aqueous solutions of methylene blue, 10-20% solution of sodium tetraborate in glycerol, 1% iodinol, 2% solution of sodium bicarbonate, potassium permanganate solution (1: 5000 ), chlorhexidine solution. They are considered ineffective for the treatment of fungal diseases because they do not have fungicidal and antifungal action. In clinical practice, a 1% solution of "Candid" was tested, the effectiveness of which was noted in the treatment of fungal lesions of the mucous membranes. For treatment patients of reproductive age suffering from acute vaginal candidiasis use the drug in the form of vaginal cream with a content of 2 %. Its efficiency, which is 94.3%, has been experimentally established.

Clinical studies of patients with candidiasis of the skin and mucous membranes combined or simple ointment with clotrimazole allowed us to conclude about the higher efficiency of the combined ointment based on oleogels.

Ointment, in addition to the antifungal agent, which has a pronounced anti-inflammatory effect and metronidazole, which affects the anaerobic flora, which is often present together with fungi of the genus *Candida* on the skin and mucous

membranes [3, 7, 9, 71]. For the treatment of fungal or mixed diseases are also used vaginal tablets "Klion-D", which contain as active substances metronidazole and miconazole nitrate (antifungal agent) [37, 12]. Experiments *in vivo* studied the antifungal activity of tablets and gels containing miconazole nitrate in the amount of 10 mg and concentration 2% respectively. Analysis of the results of the comparison of the two dosage forms showed that the minimum predominant concentration of antifungal agent was achieved in a short period of time for both gel and tablets. Thus, today in the arsenal of clinicians there are a large number of effective tools for both systemic and local treatment of VC.

Despite the advantages of oral administration of antifungal agents, the search and development of new locally acting drugs that can create high concentrations at the injection site and provide a pronounced therapeutic effect, reducing side effects, continues to be relevant.

### 1.3. Fluconazole, its characteristics and use in the treatment of candidiasis

Of the entire arsenal of currently existing antifungal agents, drugs belonging to a new class of compounds have found wide application. Their appearance on the pharmaceutical market is compared with a revolutionary step in the treatment and prevention of fungal infections. The main properties of these drugs are high efficiency and bioavailability. One of the representatives of this group is fluconazole, the advantage of which over other antifungal agents has been confirmed by a number of studies [1, 45, 54, 71].

Fluconazole has a pronounced antifungal effect. It selectively acts on the fungal cell and, unlike other agents, does not affect the metabolism of hormones. The mechanism of action of the fluconazole is to inhibit the activity of fungal enzymes dependent on cytochrome P-450, blocking the transformation of fungal cells into a membrane cell lipid, increasing the permeability of the cell membrane, disrupting its growth and replication.

It has a wide spectrum of antifungal activity. The resistance of fungal strains during treatment rarely develops, usually with long-term treatment of chronic forms of candidiasis and low doses. The pharmacokinetic characteristics of fluconazole when administered orally and intravenously are similar, which distinguishes it from other antifungal agents.

Fluconazole has a high bioavailability, which reaches 94%. It is well absorbed in the gastrointestinal tract. Its plasma level after oral administration reaches 90 % of that with intravenous administration. Fluconazole, as a hydrophilic drug, freely penetrates into the vaginal secretion and has a fungicidal effect. Given the long period of elimination from plasma ($T_{1/2}$ = 30 hours), fluconazole can be administered once, which leads to its advantage over other drugs (therapeutic concentration in plasma is reached already 2 hours after administration, and after 8 hours - in the vaginal contents).

The drug is excreted from the body mainly by the kidneys. About 80% of the administered dose is excreted in the urine in a constant form [55, 62, 68].

On the Ukrainian pharmaceutical market, fluconazole is presented in the form of gelatin capsules (50, 100, 150 and 200 mg), tablets (50, 100 and 150 mg) and a solution for parenteral administration with a concentration of 2 mg/mL. The world authority in the creation of original drugs is the pharmacological company Pfizer. One of the most famous drugs of this company on the Ukrainian market is Diflucan capsules containing fluconazole as an active substance [37]. Studies have shown that fluconazole in a single dose of 150 mg is well tolerated by pregnant women and does not adversely affect the fetus [11, 44]. Guided by current international regulatory documents, practitioners suggest a single dose of fluconazole at a dose of 150 mg orally for primary VC [10, 45, 55].

### 1.4. Suppositories in the treatment of vaginal candidiasis

Suppositories as an external dosage form have quite positive characteristics. With the right choice of excipients, they provide high bioavailability; painlessness

and ease of use; the possibility of using medicinal substances of different pharmacological groups; absence or minimum side effects of API; compactness [15, 29, 51].

The advantages of suppositories and pessaries are shown in figure 1.1.

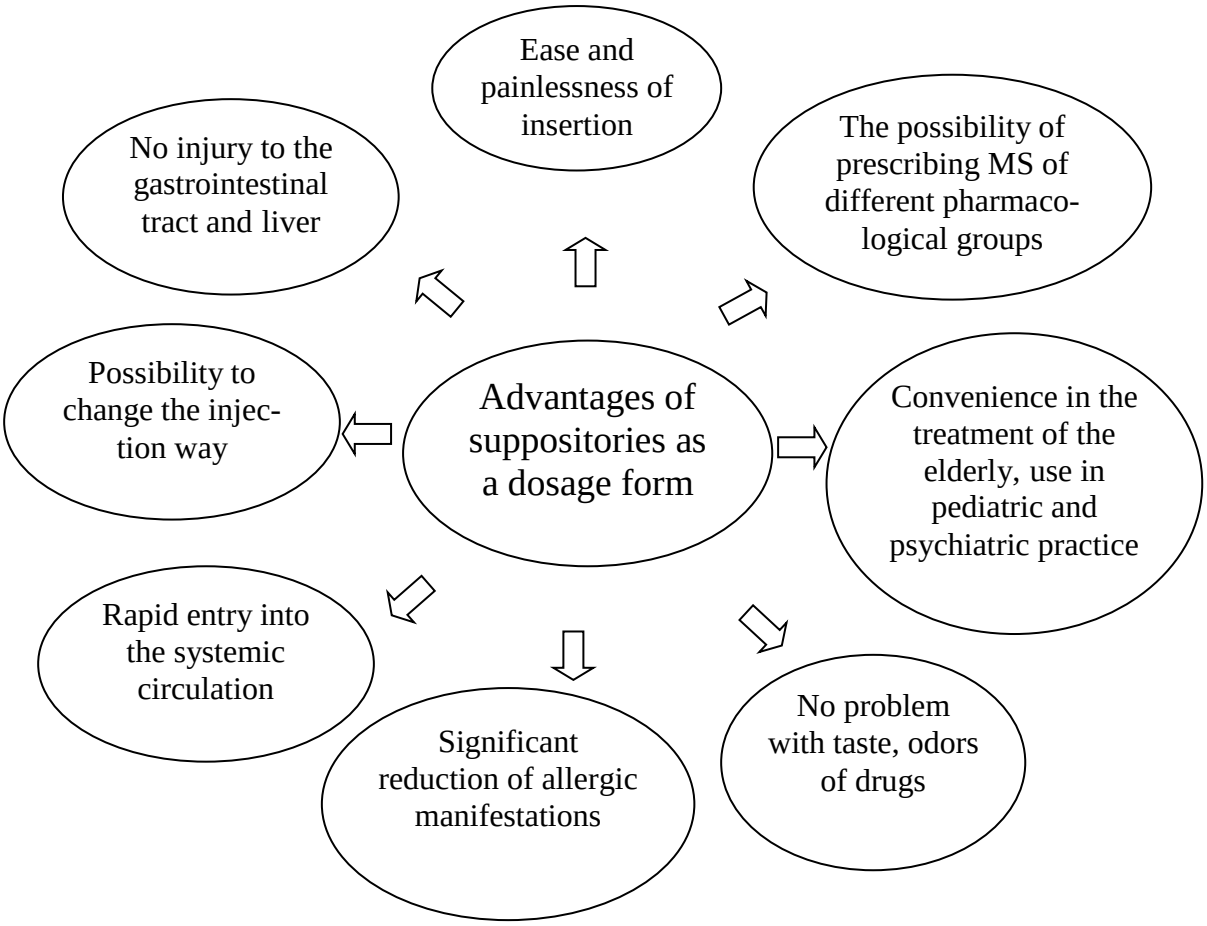


**Fig. 1.1. The advantages of suppositories and pessaries**

In addition, with topical administration, the concentration of API in the problem area is maximum, and the degree of absorption into the blood is very low. Unlike systemic drugs, vaginal suppositories act purposefully, in the focus of inflammation, without touching the gastrointestinal tract and other organs. The use of suppositories can reduce the level of allergic reactions, minimize the manifestations of toxic effects on the body and prolong the therapeutic effect, which in some cases can reduce the dose of the substance [69, 70].

All of the above qualities determine the popularity of the use of this dosage form in gynecology and the breadth of experimental studies on its development

and implementation in practice. A modern analysis of the results of bacteriological studies has shown that, along with monoinfection caused by fungi of the genus *Candida*, vaginal candidiasis can be combined with another infectious pathology caused by the presence of epidermal *Staphylococcus*, *Staphylococcus aureus*, pathogenic *Streptococcus*, *Escherichia coli*.

Given this, the treatment of candidiasis, as noted by practitioners, should depend not only on the severity of the clinical course of the disease, but also on the presence of infection and concomitant diseases.

Therefore, in treatment regimens, along with antifungal agents are prescribed drugs of antibacterial and antiseptic action, and in domestic and foreign developments, the results of research into the creation of dosage forms that combine substances of the indicated action groups[47].

For the treatment of inflammatory diseases of the female reproductive organs caused by fungi, bacteria, *Trichomonas* or combinations the drug Neo-Penotran Forte (Turkey) has been developed, which is a vaginal suppository containing a combination of antibacterial and antifungal agents - metronidazole and miconazole. For the treatment of vaginal candidiasis, suppositories with sodium tetraborate and dry extract of medicinal plant raw materials were proposed to prepare on a gelatin-glycerol basis in pharmacies and on the basis of witepsol W-35 - for industrial production. They have anti-inflammatory, antispasmodic, analgesic and antibacterial effects, and also help to eliminate secretions from the vaginal mucosa [13, 37, 39].

In the treatment of genecological diseases, suppositories containing a combination of an antifungal drug and an antiseptics are used. These drugs include "Iodoxide", containing 0.2 g of iodine as an active ingredient. A contraceptive vaginal remedy is proposed in the form of suppositories based on witepsol containing benzoic acid and benzalkonium chloride.

In addition to the main action of the drug, it has been proven that the API exhibits bactericidal effect on a whole range of bacteria, however, no less active in relation to pathogenic fungi. Benzoic acid is a pH regulator and inhibits the growth

of pathogenic fungi. A pharmaceutical company has developed a new combined drug "Depantol" in the form of vaginal suppositories containing dexpanthenol and chlorhexidine bigluconate at a dose of 0.1 g and 0.016 g per suppository, respectively. This drug is recommended for use as an additional agent for the treatment of candidiasis with mixed infection [37-40].

Thus, the study of the literature and the range of drugs presented on the pharmaceutical market, used externally for the treatment of vaginal infections, leaves no doubt that suppositories are one of the most popular and effective dosage forms.

## CONCLUSIONS

1. The analysis of the literature data revealed that in recent decades the problem of fungal infection has acquired the status of an important medical and social problem, which negatively affects the quality of life of patients, leads to significant financial costs associated with treatment and rehabilitation.
2. It has been established that in the arsenal of existing antifungal agents, a special place is occupied by fluconazole, recommended as the drug of choice for candidiasis and are presented mainly in oral and parenteral dosage forms, which are known to have certain disadvantages.
3. The therapeutic properties of fluconazole as an API, as well as the lack of local dosage forms based on it, indicate the prospects for their development.
4. The feasibility and relevance of creating pharmaceutical suppositories in order to expand the range of available domestic drugs for use in gynecology, in particular the treatment of candidiasis, has been proved.

# EXPERIMENTAL PART

# CHAPTER II

# OBJECTS AND METHODS OF RESEARCH

Substances and excipients that meet the requirements of SPhU and NTDs were used in the development of extemporaneous suppositories with fluconazole

## 2.1. Objects of researches

Objects of the study were the active pharmaceutical ingredient (fluconazole), which met the requirements of SPhU, as well as model samples of suppositories with different content of excipients.

### 2.1.1. Characteristics of active substances

**Fluconazole** (*CAAS № 514222-44-7*, 212.2 g / mol) is a white or almost white crystalline powder, easily soluble in methanol, moderately soluble in 96% ethanol, soluble in 0.1 M hydrochloric acid, slightly soluble in water. Has a pronounced antifungal effect. Included in capsules for internal use, tablets, solution for injection. Store in tightly closed vials in a dry, cool and well-ventilated place.

### 2.1.2. Characteristics of excipients

**Witepsol H-15** (EPh, 2005, 5th ed., Joint monograph of hydrophobic excipients) - is a white, solid and brittle mass without taste and odor; fusible at body temperature. The chemical composition is a mixture of saturated fatty acids and 1% mono - diglycerides of the same acids. The melting point is 33.5-35.5 °C. Curing temperature - 32.5-34.5 °C; iodine value should not exceed 3.0; acid number - not more than 0.2.

**Solid fat (**SPhU 2.0, Vol. 2, p. 608) is brittle homogeneous, solid, prickly mass from white to cream color, with a characteristic odor of fat. The chemical composition is a mixture of fatty acids that can be obtained by esterification of fatty acids of natural origin with glycerol. The melting point should not exceed 37 °C, curing temperature - not lower than 30 ° C. The acid number is 0.3, the hydroxyl

number is not more than 204 iodine number is not more than 3.0, the peroxide number is not more than 3.0. Transparent in molten form [32].

**Tween-80 (Polysorbate-80)** - (TU 6-14-938- 79) - surfactant. Obtained from sorbitol and fatty acids of olive oil. It is a liquid, oily, slightly viscous substance of light yellow or bright amber. color The smell is not strong, characteristic. Soluble in water and oils of vegetable and animal origin; well soluble in ethyl alcohol, benzene.

**Purified water** (SPhU 1.1, p. 308-309) is a colorless, transparent liquid, odorless and tasteless, pH 5.0-7.0 (potentiometrically).

## 2.2. Methods of researches

The development of the composition, technology and quality assessment of suppositories with fluconazole is due to research on the creation of new dosage forms antifungal activity, their standardization and stability control both in the manufacturing process and during storage.

*Organoleptic control.* Carried out visually. The shape, color, and homogeneity of the suppository mass were evaluated for the absence of inclusions on the longitudinal section.

*Average weight.* Determined by weighing 20 suppositories. The deviation in the average weight of individual suppositories should not exceed ± 5%.

*pH determination*. It was carried out potentiometrically (SPhU) [35].

Suppositories weighing 1.5 g were placed in a flask with a capacity of 50 ml, 15 ml of purified water, previously freed from carbon dioxide and cooled, were added. to (37±1)°C, shaken for 15 minutes. The aqueous extract was filtered, cooled to (20-25)°C and measured. Three parallel experiments were carried out.

*Microscopic analysis* of fluconazole particles was performed using a Granum R 4003 microscope with an 10x0.2 marking objective and an 8x measuring point. The separation price of the ruler was 0.6 μm. When determining the particle size in suppositories, a thin cross section was made, the sample was placed on a glass slide, a drop of vaseline oil was added, slightly heated until the base melted,

covered cover slip and viewed under a microscope in four fields of view of the segments formed by the diagonal of a square with a side of 15 mm applied to the reverse sides of the slide with a pencil. We looked at 500 particles. In the study of the substance fluconazole, the powder was placed on a glass slide, and 500 particles were examined.

*Determination of the melting point of suppositories* was carried out using the method described in the SPhU. The suppositories were melted in a water bath (at a temperature of 35°C) and the suppository mass was collected so that it filled the lower part of the capillary and formed a column about 10 mm high. The capillary was placed in a refrigerator for 1 hour, then the melting point was determined. According to the melting temperature (arithmetic average of 5 values), the one at which the substance column became transparent, rare and rose through the capillary. This operation was repeated with four other capillary tubes and the result was calculated as the average of five measurements.

*The time of complete deformation* of suppositories was studied for suppositories with a hydrophobic basis.

Suppositories, previously kept on ice for 15 minutes, were introduced into the tube under the rod and measure the time from inserting it into the tube until the rod appeared at the bottom of the narrowing of the tube. This time was taken as the time of complete deformation of the suppositories. Three parallel experiments were carried out.

*The dissolution time* was determined for suppositories made on a hydrophilic basis. Suppositories were placed in a vessel with a capacity of 100 ml, poured 50 ml purified water with a temperature of (37±1)°C. The vessel is shaken every 5 minutes until complete dissolution.

*Determination of the inverse substitution coefficient of fluconazole.* For the preparation of suppositories, a form with a cells volume of 1.5 g was used. From the suppository base, 10 suppositories without medicinal substance were obtained by pouring and weighed. In a porcelain cup on the water bath, a pure base was melted in an amount equal to approximately 80 % of the mass of 10 suppositories.

Weighed and pre-crushed fluconazole powder was added to the melted base, thoroughly mixed, and the suppository mass was poured evenly into the same mold. Then the cells were filled molten remaining base (20 % by weight of 10 suppositories without medicinal substance), the excess of which was carefully removed with a spatula. The form with suppositories was placed in the refrigerator for 10 minutes. The frozen suppositories were weighed. The replacement factor was calculated by the formula:

$$F = \frac{P - Q}{A} + 1$$

where: P is the weight of 10 suppositories without drug substance, g;

Q is the weight of 10 suppositories with the drug substance, g;

A - the total mass of the drug contained in 10 suppositories, g.

Calculation of the amount of base (L) required for cooking suppositories, taking into account the substitution factor was performed according to the following formula:

$$L = P - F \times A$$

*Biopharmaceutical research of flukonazol release.*

Biopharmaceutical studies on the release of flukonazol from suppositories were carried out in vitro by dialysis through a semi-permeable membrane. A cellophane film with a layer thickness of 45 μm was used as a dialysis membrane. Dialysis was performed in 70% ethanol in a TV 3-25 thermostat at a temperature of 40 ± 1°C.

Dialysate sampling was performed at 15 - 240 minutes. The sample volume was 5 ml. The same amount of dialyzer was immediately replenished with dialysis medium. The taken samples were subjected to spectrophotometric analysis for content flukonazol.

*Statistical processing of research results.* Reliability of the received research results were determined by the method of mathematical statistics, calculating the metrological characteristics of the results: arithmetic mean variance value, standard deviation size, confidence interval, relative error.

Statistical processing of the obtained data was performed on personal computer using a software package using Student's criterion. Differences were considered significant at $p < 0.05$.

# CONCLUSIONS

1. The object of study was an antifungal agent - fluconazole, as well as model samples of suppositories on various bases.
2. In the development of suppositories with fluconazole were used organo-leptic, physical, chemical and biopharmaceutical research methods.

# CHAPTER III.
# DEVELOPMENT OF THE COMPOSITION AND TECHNOLOGY OF SUPPOSITORIES WITH FLUCONAZOLE FOR THE TREATMENT OF CANDIDOS

## 3.1. Development of the composition of suppositories with fluconazole

### 3.1.1. Rationale for the choice of suppository base, dose of fluconazole and method of its introduction into the suppository

One of the objectives of the study is to develop the composition of suppositories that contain as an active substance an antifungal agent that causes the specific action of the dosage form. Justification of its content in suppositories, as well as the choice of the optimal suppository base was made on the basis of the study of literature data and the results of experimental studies.

Recently, antifungal drugs have proven to be quite reliable and effective, among which fluconazole has a special place. Analysis of literature data shows that the content of antifungal agents in suppositories is often 150 mg, rarely 300 mg per suppository. When choosing the therapeutic concentration of fluconazole, the following factors were taken into account: first, the antifungal group of the triazole series, compared with representatives of other groups have greater efficiency and bioavailability; secondly, when creating dosage forms intended for vaginal and rectal administration, usually guided by the doses set for oral administration. Accordingly, in medical practice there is no difference between vaginal and oral single and daily doses in most drugs. Fluconazole is most often administered orally in capsules with a dosage of 150 mg. Therefore, regarding the possibility of creating a new dosage form for fluconazole, it was administered at the rate of 150 mg per suppository [37, 38].

It is known that one of the factors that has a significant impact on the action of drugs substances in suppositories, there is a suppository base and its constituent

components. While choosing the ingredients of the base must take into account a number of requirements, in particular: no irritating effect on the mucous membrane, even distribution on it surfaces, compatibility with API and the ability to release them, storage stability [19, 26, 27].

In addition, the base must provide good technological performance, namely, in the molten state to have a certain viscosity, to prevent sedimentation of suspended particles in the dosing of the suppository mass, and poured into the sockets form molten mass should harden quickly and easily separated from their surface [30, 60].

Today in the international pharmaceutical market under well-known brands are suppository bases of various kinds - hydrophilic, hydrophobic, diphilic [2, 51]. The list of bases used for the manufacture of suppositories or pessaries is given in table 3.1.

Table 3.1

**Suppository bases**

| № | Basis | Composition, properties | Note |
|---|---|---|---|
| | | ***Hydrophilic bases*** | |
| 1 | Polyethylene oxide of various brands (400, 1500, 4000, 6000) or macrogols of different brands | PEO 400 (liquid) in relation to other brands PEO 1500, etc. | Used as a base for suppositories or pessaries |
| 2 | Propylene glycol | Propane-1,2-diol | Used as bases for suppositories or pessaries |
| 3 | Gelatin and glycerin | Gelatin 1.0<br>Glycerin 5.0<br>Water 2.0 | Used as a basis for suppositories |
| 4 | Soap-glycerin | Glycerin 60.0; | It is used as a base |

| | | | |
|---|---|---|---|
| | | sodium carbonate 2.6; stearin acid 5.0 | for laxative suppositories |
| ***Hydrophobic bases*** | | | |
| 1 | Solid fat | A mixture of mono -, di -, trilicerides of fatty acids | Used as a base for suppositories or pessaries |
| 2 | Witepsol | A mixture of tri-glycerides of saturated fatty acids with 1% mono - and diglycerides of the same acids | Used as a base for suppositories or pessaries |
| 3 | Cocoa butter (natural base) | A mixture of glycerides of glycerol esters and higher fatty acids | Used as a base for suppositories or pessaries |

A characteristic feature of hydrophilic bases is their good solubility. The process of absorption of API from bases is independent of their melting point, because it is due to the rate of dissolution of the bases themselves and the rate of diffusion of API from them.

The most striking representative of this class of bases are polyethylene oxide (PEO) bases. Combining different consistency of PEO, you can get bases with the necessary structural and mechanical properties. The most common suppository bases are obtained by fusing PEO-400 and PEO-1500 in the ratios (1: 9) and (2: 8) [18, 29]. The basis of PEO is also characterized by the presence of osmotic activity and weak bactericidal action. It actively adsorbs exudate, reduces swelling of tissues and mucous membranes [4, 69]. The hydrophobic suppository bases include fats, fat-like substances of natural and semi-synthetic origin, melting at body temperature. As substitutes for the classic base - cocoa butter, used for the manufacture of suppositories by extemporaneous rolling method, various pharmacopoeias around the world have accepted and widely used hydrogenated fats, alloys of hy-

drogenated fats with fat-like substances, emulsifiers or hydrocarbons. This group of bases includes butyrol and complex fatty bases [51].

Witepsol, which has a number of positive properties, is widely used in the manufacture of suppositories in industrial production. It is indifferent, does not form polymorphic modifications, emulsifies hydrogen well solutions, after melting hardens quickly [5, 12, 33].

The following bases are used in the master's thesis: witepsol H-15; alloy PEO-400 and PEO-1500 (in the ratio 2: 8); solid fat; butyrol (alloy of cocoa butter: paraffin: hydrogenated fat in a ratio of 30:20:50, respectively).

The listed suppository bases meet the above requirements and have the necessary structural and mechanical properties; the optimal ratio of melting point and curing temperature; when entering the body cavity, some are able to melt, others dissolve in the secretions of mucous membranes.

In the manufacture of the dosage form were guided by the main provisions of the article "Suppositories and pessaries made in pharmacies" (SPhU 2.0) [34]. When developing the technology of making suppositories with fluconazole, the nature and physical chemical properties of both API and suppository bases were taken into account.

For the experiment, model samples of suppositories were prepared by the method of casting, using molds with a cell volume of 1.5 g. Previously, the inverse substitution factor was established experimentally for fluconazole, which was equal 0.62, as its content in suppositories exceeded 5 %.

The base components of the combined type were melted in a porcelain cup in a water bath, taking into account their melting point, and the one-component bases were melted. Numerous results of experimental studies have proved the importance of studying such a factor as the degree of dispersion of the medicinal substance. It affects the homogeneity of the suppository mass, the uniformity of the distribution of the API in it and the accuracy of the dosage, as well as the bioavailability associated with the release process and the completeness of the manifestation of the therapeutic effect of the drug as a whole [6, 59].

Taking into account the physical and chemical properties of fluconazole (the substance does not dissolve in the base, it is slightly soluble in water), in the manufacture of suppository it was introduced as a suspension type, previously crushed in a mortar. Suppositories made on the above bases with crushed fluconazole, studied using a microscopic method according to the method described in chapter 2. The results are shown in table. 3.2.

Table 3.2

**The results of the analysis of variance of fluconazole in the substance and experimental samples of suppositories**

| Object of study | Fractions with a particle size (μm) of fluconazole | | | |
|---|---|---|---|---|
| | up to 10 | from 11 to 30 | from 31 to 50 | from 51 and more |
| Fluconazole substance before grinding | 2% | 6% | 27% | 65% |
| Fluconazole substance after grinding | 19% | 58% | 23% | - |
| Suppositories based on Butyrol | 19% | 59% | 22% | - |
| Suppositories based on Witepsol H-15 | 20% | 60% | 20% | - |
| Suppositories on solid fat | 16% | 66% | 18% | - |
| PEO-based suppositories | 18% | 63% | 19% | - |

The experimental results follows that the preliminary grinding of fluconazole significantly changes the fractional composition of the particles. After grinding, there are no particles larger than 50 μm in the field of view, while the particles of the same fraction in the original, not crushed substance, is 65%. An increase of about nine times in the number of particles up to 10 μm and from 11 to 30 μm was noted. With the introduction of crushed fluconazole into suppository bases and analysis of samples of experimental samples of suppositories made on the bases of

solid fat, witepsol H-15 and PEO, an insignificant effect of bases on the dispersity of the substance was established: the number of particles in the fraction size from 31 to 50) to 30 microns decreased. The main part of the particles falls on a fraction from 11 to 30 microns and ranges from 59 % to 66 %, depending on the suppository base.

To influence the dispersity of API, in order to improve the qualitative and quantitative characteristics of suppositories, it is possible not only using mechanical methods of grinding, but also by introducing surface-active agents (surfactants) into its composition [12, 30]. When developing suppositories with fluconazole, tween-80 (polysorbate 80) was used as a surfactant.

### 3.1.2. Rationale for the introduction of Tween-80 into suppositories

The results of numerous studies indicate that the dispersion of poorly and slowly soluble APIs is one of the main indicators that determine the time of their true solubility, determines the rate of absorption, and the bioavailability of APIs from the drug. The degree of dispersion of APIs can be changed by introducing surfactants (SASs) into the composition of suppository bases, which play the role of solvents and absorption activators.

As such a surfactant, tween-80 at a generally accepted concentration of 2% was used in the development of the dosage form [5, 33]. In the manufacture of suppositories, fluconazole pre-crushed in a mortar was ground with tween-80. The resulting pulp was mixed with a pre-prepared base, poured into molds and cooled. Samples of the substance and manufactured suppositories were subjected to microscopic evaluation, the results of which are shown in table. 3.3.

Table 3.3.

**The effect of tween-80 on the dispersion of fluconazole in the substance and experimental samples of suppositories**

| Object of study | Fractions with a particle size (μm) of fluconazole | | |
|---|---|---|---|
| | to 5 | from 6 to 10 | from 11 to 30 |

| | | | |
|---|---|---|---|
| Fluconazole substance after grinding with tween-80 | 20% | 62% | 18% |
| Suppositories based on butyrol | 20% | 63% | 17% |
| Suppositories based on witepsol H-15 | 21% | 61% | 18% |
| Suppositories on solid fat | 19% | 62% | 19% |
| PEO-based suppositories | 23% | 61% | 16% |

From a comparative analysis of the results of table. 3.3, it can be seen that the grinding of fluconazole with tween-80 at a concentration of 2 % affects the structure of the fractional composition of the particles. When using tween-80, there are no particles larger than 30 μm in the substance; the number of particles with a size of up to 10 μm increases by about four times. Therefore, according to the results obtained, it was found that the introduction of crushed fluconazole with 2 % tween-80 into the composition of suppositories leads to an increase in the fine particle fraction up to 5 μm and a decrease in the number of particles with a size of 11 to 3 μm. The impact of the base and the manufacturing process of suppositories on the dispersity of the medicinal substance has not been established.

### 3.1.3. The study of the release profile of fluconazole from suppositories by the method of equilibrium dialysis

Dialysis through a semipermeable membrane is one of the widely used biopharmaceutical methods of analysis. It allows taking into account the influence of pharmaceutical factors on the availability of a drug substance, choosing the most appropriate basis by analyzing the results of the process and the completeness of its release from the developed drug.

Dialysis through a semipermeable membrane was carried out according to

the method described in chapter 2. The studies were carried out with experimental samples of suppositories made without preliminary grinding and after grinding the active substance with tween-80. In samples of dialysate taken at certain intervals, the amount of fluconazole passed to the dialysate was determined.

To quantify the release of fluconazole from the dosage form used the method of spectrophotometry in the UV region. For this purpose, the optical density of the selected dialysate samples was measured at a wavelength of (261 ± 1) nm in a cuvette with a layer thickness of 1 cm.

A 0.1 M hydrochloric acid solution was used as a reference solution. In parallel, under the same conditions, the optical density of a standard sample solution (SS) of fluconazole was measured..

The amount of released fluconazole (%) was calculated by the formula:

$$X=\frac{A_1\times a_0\times 1\times 25\times 50\times m\times P}{A_0\times a_1\times 50\times 25\times 1\times 100},$$

where: $A_1$ is the optical density of the test solution;

$A_0$ is the optical density of SS;

$a_1$ is weighed amount of crushed suppository mass, g;

$a_0$ is weighed portion of SS fluconazole for solution preparation, g;

m is the average weight of the suppository, g;

P is the content of fluconazole in SS, %.

The content of fluconazole should be from 0.142 g to 0.158 g, calculated on the average weight of one suppository.

The results obtained are shown in fig. 3.1 and 3.2.

The analysis of the research results presented in the graphs indicates that both the nature of the base and the presence of surfactants play a significant role in the release of API, which contributed to a decrease in the particle size of the substance. The most complete and rapid release of the drug in the dialysate noted for suppositories made on a hydrophilic PEO base.

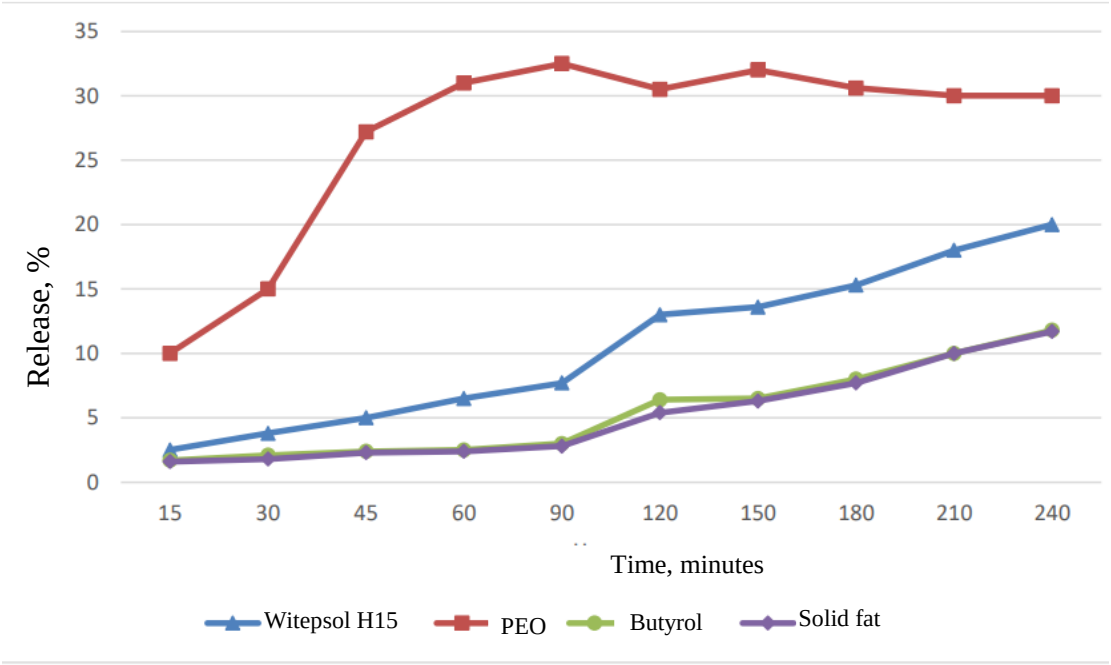


**Fig. 3.1. Profile of fluconazole release from suppositories without SAS addition**

The maximum concentration of the active substance in the dialysate with suppositories containing tween-80 was reached within the first 15 minutes. During the experiment with base, about 100% of fluconazole was released.

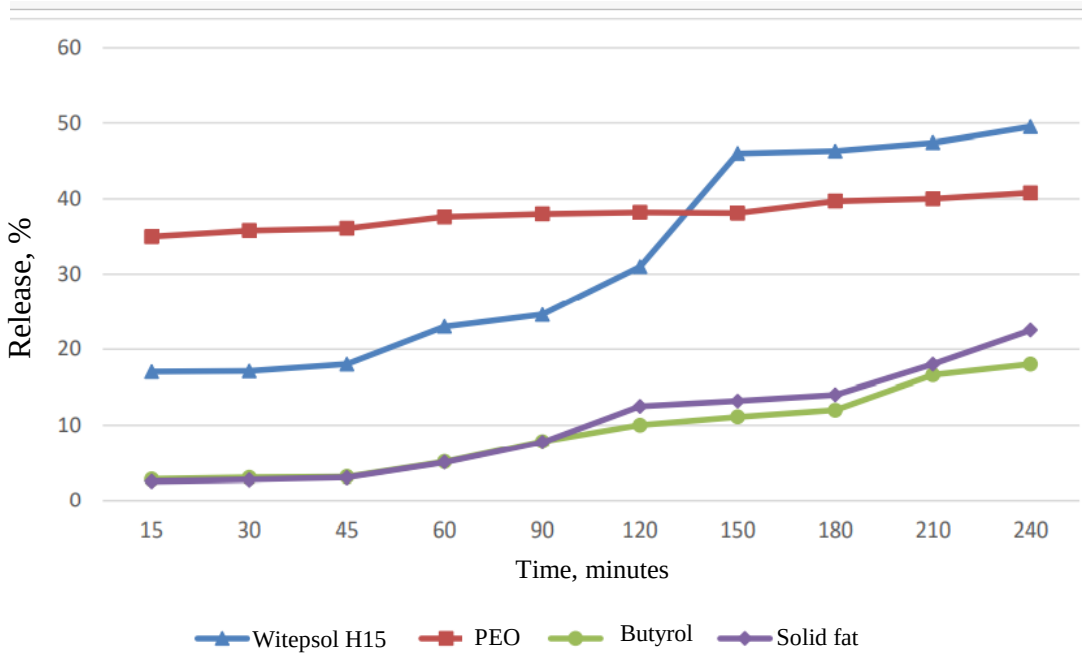


**Fig. 3.2. Profile of fluconazole release from suppositories with SAS addition**

From suppositories prepared on the same basis without surfactants, the maximum concentration of the substance in acceptor medium was noted after 45 min of the experiment, during which time 76 % of the API was released.

The second in terms of speed and completeness of the release of fluconazole is the base witepsol H15, containing a combination of surfactants. During the entire time of the experiment, a gradual increase in the concentration of API in acceptor medium. The presence of surfactants almost 2.5 times increases the completeness of the release of the drug from suppositories on the specified base, and at the end of the experiment in the dialysate, it was found to be about 100%.

Process the release of fluconazole from suppositories prepared on the same base, but without preliminary dispersion with surfactants, is rather slow. During the experiment, no pronounced completeness of API release was observed (only 36.6% in the dialysate). The lowest indications for the intensity and completeness of the release of API established for suppositories made on hydrophobic bases butyrol and solid fat. The completeness of the release of the drug into the dialysate from these bases was only 11.7 % and 12.0 %, respectively. Introduction of tween-80 into these bases led to only a slight increase in the concentration of API in the medium. However, the completeness of the output has not been achieved. The total content of the active substance was 18.0 % and 22.5 %, respectively.

Thus, the results obtained by the dialysis method indicate that the most optimal for the preparation of suppositories with fluconazole are PEO base and witepsol H-15. Dispersion of fluconazole with tween-80 contributed to a more rapid and complete release of the substance from these bases.

### 3.2. Development of the technology of suppositories with fluconazole

As you know, the technological process for obtaining suppositories includes the following stages: preparatory work, preparation of the base, obtaining the suppository mass, dosage of the suppository mass and the formation of suppositories, packaging and labeling of finished products. Technological scheme for the produc-

tion of suppositories with fluconazole on selected witepsol H-15 and PEO bases are presented in fig. 3.3.

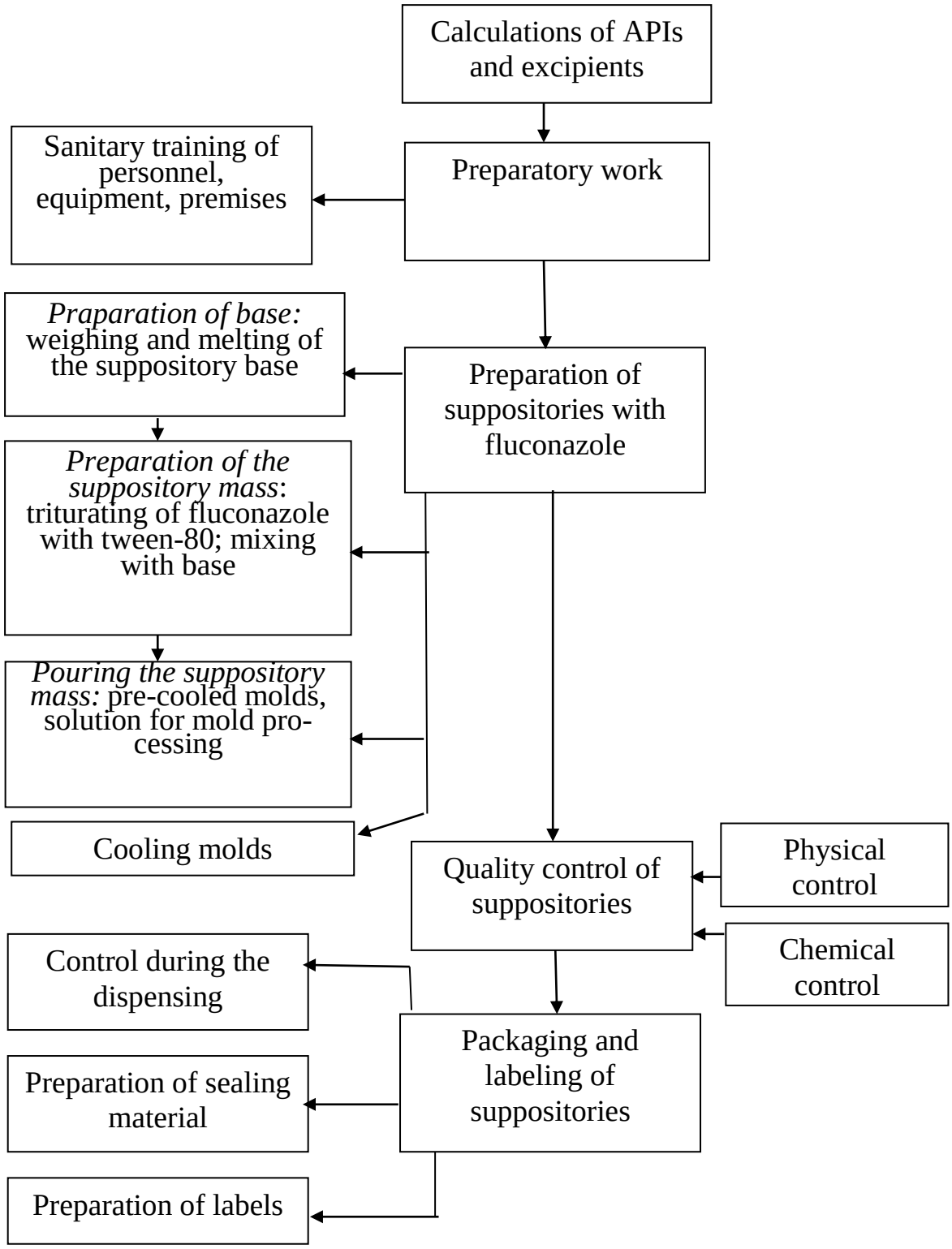


**Fig. 3.3. Technological scheme for the production of suppositories with fluconazole**

*Preparatory works*. Training of personnel, premises, equipment, auxiliary materials, medicines (grinding fluconazole in a mortar) and excipients were carried out in accordance with the requirements of the sanitary regime.

*Preparation of base.* In the manufacture of PEO-based suppositories of different molecular weights, they were fused in a porcelain cup, taking into account their melting points. In the manufacture of suppositories based on witepsol H-15, it was melted in a porcelain cup in a water bath.

*Preparation of the suppository mass*. The pre-ground fluconazole was subsequently triturated with tween-80. The resulting pulp of substances was introduced into the prepared bases with stirring.

*Dosage of the suppository mass and the formation of suppositories*. By controlling the temperature, the suppository mass was dosed, pouring into cooled forms, the cells of which were smeared with either soapy alcohol (when pouring a suppository mass based on witepsol H-15), or vaseline oil (when production on the base - PEO). After pouring the suppository mass, the form was placed in a refrigerator (4±1)°C, cooled until complete solidification and formation of suppositories.

*Packaging and labeling of suppositories.* The formed suppositories were taken out of the mold and packed in handkerchiefs or in individual suppository cells. Wrapped suppositories (pessaries) are placed in wide boxes with separate partitions. PEO-based suppositories (pessaries) are additionally labeled with a label: "Unfold, moisturize and insert" Suppositories and pessaries are stored at a temperature of 8-15 ˚C.

Suppositories prepared in this way were subject to evaluation according to the main criteria of normative documentation.

### 3.3. Evaluation of the quality of suppositories and the study of their stability

According to the quality rules, the GMP EU system has been introduced, which is intended for the production of medicines and guarantees that medicinal preparations are developed taking into account the requirements of good manufac-

turing practice. Therefore, it is necessary to obtain initial data for the validation of processes, as well as to manage quality risks in mass production. Attention should be paid to critical parameters in the development of suppositories, in particular:

- excess of the hydrogen phase in the composition of the drug, leading to fat oxidation, interaction between API and excipients, bacterial contamination;

- hygroscopicity (moisture absorption or it losses);

- API-excipients interaction (physical, chemical, pharmacological incompatibility);

- friability of the suppository mass;

- viscosity (slight viscosity of the base leads to API sedimentation);

- the nature of the substance that is used to lubricate the form;

- reduction (contraction) of volume.

According to the articles "Drugs for rectal use" or "Drugs for vaginal use" (SPhU), the quality indicators of suppositories should be studied, namely: organoleptic, physical and chemical, pharmacotechnological (osmotic properties, rheological characteristics and structural-mechanical), microbiological, establish the expiration date of this form.

Therefore, in order to control the quality of the obtained suppositories with fluconazole, we studied their quality both after manufacture and during storage (within 1 month). Applying organoleptic, physical, physico-chemical, technological, biopharmaceutical, microbiological methods of analysis, quality assessment was carried out according to the following criteria: appearance, average weight and deviation from it, melting temperature, full deformation time (for suppositories based on witepsol H15) or dissolution time (for suppositories based on PEO), value pH values of suppository extract, fluconazole particle size, microbiological purity [34, 59].

To monitor the stability of the suppositories, three series were prepared on each base. Before storage, a quality assessment was carried out, the results of which are shown in table 3.4.

Table 3.4

**Quality indicators of suppositories with fluconazole on different bases**

| **Indicator** | **Control results** | |
|---|---|---|
| | **witepsol H-15-based suppositories** | **PEO-based suppositories** |
| Appearance | homogeneous, white, with a smooth surface, no longitudinal incisions | |
| Average weight, ± 5% | 1.5 g | 1.48 g |
| Melting point, 37 ± 1 ° C | 35.8 ° C | --- |
| Time of full deformation, no more than 15 minutes | 10.5 minutes | - |
| Dissolution time, no more than 60 minutes | - | 11 minutes |
| The particle size of API | <30 μm | <30 μm |
| pH | 7.5 | 5.1 |

As noted earlier, the bioavailability of fluconazole from suppositories is largely determined by the size of its particles.

The developed compositions and technology of suppositories made it possible to significantly change the fractional composition of the particles of the fluconazole compared to the original substance. Their size does not exceed 30 μm, with a predominance of particle fractions (about 80%) up to 10 μm, which fully meets the requirements for this dosage form.

As can be seen from the results of the table in suppositories made on the bases - Witepsol N-15 and PEO, all the results of the analysis in terms of control indicators are within tolerance. This proves that the developed technology makes it possible to obtain suppositories of proper quality.

To monitor the stability and establish the expiration date, the suppositories

were stored at a temperature of (4±1)°C (refrigerator conditions). Samples were taken every 7 days for analysis and their quality was assessed.

The results that characterize the stability of suppositories during 1 month storage are presented in table. 3.5. and 3.6.

Table 3.5

**Stability of suppositories based witepsol H-15 during storage**

| **Indicator** | **Shelf life, days** | | | | | |
|---|---|---|---|---|---|---|
| | **start** | **7** | **14** | **21** | **28** | **35** |
| Appearance | homogeneous, white, with a smooth surface, on longitudinal section there are no inclusions | | | | | |
| Average weight, ± 5% | 1.50 ± 0.01 | 1.47 ± 0.02 | 1.51 ± 0.02 | 1.48 ± 0.01 | 1.47 ± 0.02 | 1.49 ± 0.02 |
| Melting point, 37 ± 1 ° C | 35.5 ± 0.2 | 35.8 ± 0.2 | 36.0 ± 0.1 | 35.0 ± 0.2 | 34.8 ± 0.1 | 36.1 ± 0.2 |
| Time of full deformation, no more than 15 min | 10.2 ± 0.2 | 11.2 ± 0.1 | 10.8 ± 0.2 | 11.0 ± 0.2 | 11.1 ± 0.1 | 10.5 ± 0.2 |
| API particle size, μm | <30 μm | <30 μm | <30 μm | <30 μm | <30 μm | <30 μm |
| pH | 7.1 ± 0.1 | 7.0 ± 0.2 | 6.8 ± 0.2 | 7.2 ± 0.1 | 7.0 ± 0.2 | 7.1 ± 0.1 |
| MBC: bacteria, fungi in 1.0 g not more than $10^2$ TAMC and $10^1$ TYMC | Corresponds | | | | | |

Analysis of the obtained results on the study of stability during storage of three series of suppositories based on Witepsol H-15 and PEO reliably indicates the stability of the indicators characterizing the developed dosage form.

Table 3.6

**Stability of suppositories PEO-based during storage**

| **Indicator** | **Shelf life, days** | | | | | |
|---|---|---|---|---|---|---|
| | **start** | **7** | **14** | **21** | **28** | **35** |
| Appearance | homogeneous, white, with a smooth surface, on longitudinal section there are no inclusions | | | | | |
| Average weight, ± 5% | 1.51± 0.01 | 1.49± 0.02 | 1.48± 0.02 | 1.47± 0.01 | 1.51± 0.02 | 1.50± 0.02 |
| Dissolution time, not> 60 minutes | 11 ± 0.5 | 13 ± 0.5 | 12 ± 0.5 | 15 ± 0.2 | 12 ± 0.5 | 11 ± 0.2 |
| API particle size, μm | <30 μm | <30 μm | <30 μm | <30 μm | <30 μm | <30 μm |
| pH | 5.5±0.1 | 5.2±0.2 | 5.0±0.2 | 5.6±0.1 | 5.1±0.2 | 5.5±0.1 |
| MBC: bacteria, fungi in 1.0 g not more than $10^2$ TAMC and $10^1$ TYMC | Corresponds | | | | | |

Thus, when controlling the stability of three series of samples of suppositories made on the basis of witepsol H15 and PEO, packed in contour cells stored in a refrigerator at a temperature of (4 ± 1) ° C, it was found that their quality meets the requirements of ND for 1 months. The proposed period differs from the well-known shelf life of extemporaneous suppositories, which is 10 days.

## CONCLUSIONS

1. The possibility of using the bases for the development of suppositories composition with an antifungal agent - fluconazole was studied. Witepsol H15 and an alloy of PEO-1500 and PEO 400 (8:2) are proposed to be used as the bases.
2. It has been established that preliminary grinding of the substance of fluconazole provides a more uniform fractional composition of the particles. Microscopic analysis of samples of model samples of suppositories showed a slight effect of the base and technology of their manufacture on the particle size of fluconazole that is introduced.
3. The effect of tween-80 on fluconazole fineness has been studied and established.
4. The release profile of fluconazole from suppositories was studied using the method of dialysis through a semipermeable membrane. It has been proven that the nature of the base and the presence of surfactant - tween 80 affect the release of API. The results of the experiment indicate that dispersion of fluconazole with tween-80 ensures its optimal release from suppositories, made on the bases of witepsol H15 and PEO.
5. As a result of the research, the composition and technology of suppositories with fluconazole in a pharmacy based on witepsol H15 and PEO were substantiated and developed, and their stability was studied for 1 month.

## GENERAL CONCLUSIONS

1. Based on the analysis of literature data, the need to create suppositories with antifungal action for use in the treatment of vaginal candidiasis is substantiated. Information on the properties of fluconazole, its benefits and methods of application is analyzed.
2. Compositions and technology of intravaginal fluconazole suppositories intended for prevention and treatment of candidiasis have been developed, theoretically and experimentally substantiated. It has been proved that witepsol H15 and PEO-1500 and PEO-400 alloy (8:2) are rational bases for suppository production.
3. On the basis of biopharmaceutical studies, the feasibility of introducing tween-80 into suppositories has been proved, which ensures the maximum degree of dispersion, uniformity of distribution and dosing accuracy.
4. The technology of suppositories preparation in pharmacy condition has been developed.
5. The stability of suppositories according to the developed quality indicators has been studied and their shelf life has been established.
6. Based on the results of the master's work, abstract was published in the collection of materials of the International scientific-practical conference "Modern aspects of science, education, technology and society" (April 14, 2022, Poltava).

## REFERENCES


1. Bioavailability enhancement: a review / H. Bajaj, S. Bisht, M. Yadav, V. Singh. Int. J. Pharm. Bio. Sei. 2011. Vol. 2, N 2. P. 202-216.
2. Chromatographic determination of clotrimazole, ketoconazole and fluconazole in pharmaceutical formulations / E.M. Abdel-Moety, F.I. Khattab, K.M. Kelani, A.M. AbouAI-Alamein. Farmaco. - 2002. - Vol. 57, N11.-P. 931-938.
3. Fluconazole for the management of invasive candidiasis: where do we stand after 15? / C. Charlier, E. Hart, A. Lefort [et al.]. J. Antimicrob. Chemother. 2016. Vol. 57. P. 384-410.
4. Formulation and evaluation of clotrimazole and ichtammol ointment / G. Rajalakshmi, N. Damodharan, C.V.Vaghajibhay, P. Janardhanreddy. Int. J. Pharm. Bio Sei. 2010. Vol. 1, N 4. P. 7-16.
5. Guedlines for treatment of candidiasis / P.G. Pappas, J.H. Rex, J.D. Sobel [et al.]. Clin. Infect. Dis. 2004. Vol. 38. P. 161-189.
6. Inman W. Safety of fluconazole in the treatment of vaginal candidiasis. A prescription-event monitoring study, with special reference to the outcome of pregnancy / W. Inman, G. Pearce, L. Wilton. Eur. J. Clin. Pharmacol. 1994. Vol. 46, N2.-P. 115-118.
7. In-vitro and in-vivo availability of mebeverine hydrochloride suppositories / B.N. AI-Dossary, O.M.N. AI-Gohary, M.M. EI-Khawaas. Sci. Pharm. 2006. N74. P. 31- 51.
8. Pfaller M.A. Twelve years of fluconazole in clinical practice: global trends in species distribution and fluconazole susceptibility of bloodstream isolates of Candida. International fungal surveillance participant group / M.A. Pfaller, D.J. Diekema J Clin. Microbiol. Infect. - 2014. -Vol. 10 Suppl. l.-P. 11-23. 52.

9. Rapp R.P. Treating fungal infections with triazole agents: pharmacokinetics, pharmacodynamics and drug interactions. Pharmacy Practice News [Electronic resource]. - 2007, September. - P. 1-8.
10. Sheehan, D.J. Current and emerging azole antifungal agents / D.J. Sheehan, C.A. Hitchcock, C.M. Silley. Clin. Microbiol. Rev. 2015. Vol. 12, N l. P. 40-79.
11. The United States Pharmacopoeia 40: The National Formulary 35. – New York, 2017. – 2569 p.
12. Treatment of vaginitis / S. Kukner, T. Ergin, N. Cicek [et al.]. Int. J. Gynecol. Obstet. - 2016. - Vol. 52. - P. 43-47.
13. In vitro активность флуконазола и вориконазола в отношении более 10000 штаммов дрожжей: результаты 5-летнего проспективного исследования ARTEMIS Disk в России / Н.В. Дмитриева, Р.С. Козлов, Н.Н. Климко [и др.]. Клин, микробиология и антимикробная химиотерапия. 2018. № 4. С. 345-354.
14. Абакарова, П.Р. Терапия вульвовагинального кандидоза с применением препарата «Гинофорт». Гинекология. 2006. № 1. С. 19-20.
15. Астраханова М.М., Охотникова В.Ф. Суппозитории как лекарственная форма высокой биологической доступности. Вопр. биол., мед. и фармацевт, химии. 2017. № 6. С. 9-12.
16. Байрамова Г.Р. Современные подходы к терапии вульвовагинального кандидоза. Гинекология. 2015. Т. 7, № 3. С. 164-166.
17. Баранов И.И. Экология влагалища и воспалительные заболевания половых органов. Гинекология. 2010. Т. 12, № 3. С. 4-6.
18. Биофармацевтические исследования суппозиториев для лечения вагинального кандидоза /О. А. Блинова, Н. А. Кондратьева, Т. Е. Рюмина, С. А. Коростелев. Фармация. 2019. № 4. С. 31-34.
19. Биофармацевтическое исследование суппозиториев парацетамола отечественных производителей / Т. В. Орлова и др. Разработка и регистрация лекарственных средств. 2016. № 2 (15). С. 70-75.

20. Буданов П.В. Нарушения микроценоза влагалища / П.В. Буданов, О.Р. Баев, В.М. Пашков. Вопр. гинекологии, акушерства и перинатологии. 2005. Т. 4, № 2. С. 78-88.
21. Влияние вспомогательных веществ на биофармацевтические характеристики мазей и суппозиториев /Т.Ю. Манджиоладзе, Н.А. Кечатова, Н.И. Кулибаба [и др.] // Разработка, исследование и маркетинг новой фармацевтической продукции : материалы 57-й межрегион. конф. по фармации, фармакологии. Пятигорск, 2012. - С. 54-55.
22. Гараничева О.В. Исследования состава суппозиториев с экстрактом стальника / О.В. Гараничева, В.И. Погорелов, В.А. Карпенко. Фармация. 2010. 2. С. 40-41.
23. Геппе Н.А. Кандидозы / Н.А. Геппе, Н.А. Белоусова. Consilium medicum. 2018. № 4. С. 34-38.
24. Демина Н. Б. Современные аспекты производства лекарственной формы суппозитории. Разработка и регистрация лекарственных средств. 2016. № 2 (15). С. 60-70.
25. Денисенко Ю. О. Выбор поверхностно-активных веществ в составе суппозиториев с экстрактом эхинацеи. Разработка, исследование и маркетинг новой фармацевтической продукции : сб. науч. тр. 2014. Вып. 73. С. 116-118.
26. Державна Фармакопея України : в 3 т. / ДП «Український науковий фармакопейний центр якості лікарських засобів». 2-е вид. Харків : Державне підприємство «Український науковий фармакопейний центр якості лікарських засобів», 2014. Т. 3. 732 с.
27. Державна Фармакопея України : в 3 т. / ДП «Український науковий фармакопейний центр якості лікарських засобів». 2-е вид. Харків : Державне підприємство «Український науковий фармакопейний центр якості лікарських засобів», 2014. Т. 2. 724 с.
28. Державна Фармакопея України : в 3 т. / ДП Український науковий фармакопейний центр якості лікарських засобів. 2–е вид. Харків : Дер-

жавне підприємство «Український науковий фармакопейний центр якості лікарських засобів», 2015. Т. 1. 1128 с.

29. Державна Фармакопея України : Супозиторії та песарії, виготовлені в аптеках / ДП «Науково-експертний фармакопейний центр». 2 вид. Х. : РІРЕГ, 2014. С. 716-723.
30. Державна Фармакопея України. Допов. 1. / ДП «Науково-експертний фармакопейний центр». 1–е вид. Харків : РІРЕГ, 2004. 520 с.
31. Державна Фармакопея України. Допов. 2. / ДП «Науково-експертний фармакопейний центр». 1–е вид. Харків : РІРЕГ, 2008. 618 с. 47.
32. Державний реєстр лікарських засобів України / МОЗ України, 2018. URL: http://www.drlz.com.ua/ (дата звернення: 01.05.2021).
33. Державний Формуляр лікарських засобів / МОЗ України. К., 2018. URL: http://mozdocs.kiev.ua/ (дата звернення: 20.05.2021).
34. Дзюба А. С. Российский рынок суппозиториев: оценка основных тенденцій. Ремедиум. 2013. № 9. С. 44-48.
35. Дижевская Е.В. Урогенитальные инфекции: современный взгляд / Е.В. Дижевская, Д.В. Блинов. Акушерство. Гинекология. Репродукция. 2011. Т. 5, № 4. С. 48-56.
36. Изучение стабильности суппозиториев с пантогамом / Н. С. Назаренко и др. Вестник ВГУ. 2008. № 1. С. 154-158.
37. Інструкція із санітарно-протиепідемічного режиму аптечних закладів : наказ МОЗ України № 275 від 15.05.2006 р. К., 2006. 21 с. URL: http://moz.gov.ua/ua/portal/dn_20060515_275.html (дата звернення: 26.02.2021).
38. Кандидозы в хирургической клинике: видовой состав возбудителей, чувствительность к антибиотикам, превентивная терапия // Анестезиология и реаниматология. 2011. № 5. С. 43-48.
39. Карапетян Т.Э. Беременность и вагинальный кандидоз: современное состояние проблемы (обзор литературы). Гинекология. 2018. № 2. С. 4-8.

40. Кира Е.Ф. Комбинированная терапия влагалищных инфекций. Гинекология. 2010. Т. 12, № 1. С. 26-29.
41. Кисина В.И. Оптимизация подходов к лечению кандидоза вульвы и влагалища. Клин, дерматология и венерология. 2010. № 2. С. 96-103.
42. Кисина В.И. Первичный и рецидивирующий кандидозный вульвовагинит: патогенез, терапия и профилактика. Гинекология. 2013. Т. 5, № 5. С. 185-187.
43. Кубась В.Г. Этиология, патогенез и лабораторная диагностика кандидоза. Пробл. мед. микологии. 2014. Т. 6, № 3. С. 10-12.
44. Кузьмин В.Н. Практические аспекты лечения неспецифических и кандидозных вульвовагинитов у женщин во время беременности. Гинекология. 2019. Т. 11, № 2. С. 12-15.
45. Лікарські засоби. Фармацевтична розробка (ICH Q8) : Настанова СТ-Н МОЗУ 42-3.0:2011 / М. Ляпунов, О. Безугла, Ю. Підпружніков та ін. - К.: МОЗ України, 2011. 42 с.
46. Літвінова О. М., Левачкова Ю. В., Чушенко В. М. Визначення показників якості та вивчення стабільності песаріїв з ацикловіром та ефірними оліями. Управління, економіка та забезпечення якості в фармації. 2017. № 3 (51). С. 14-18.
47. Літвінова О.М., Ярних Т.Г., Чушенко В.М., Левачкова Ю.В. Методологія фармацевтичної розробки супозиторіїв і песаріїв : метод.рек. Х., 2018. 30 с.
48. Мазуркевич М.В. Системная терапия кандидозного вульвовагинита. Клин, дерматология и венерология 2010. № 3. С. 37-41.
49. Маркова Т.П. Флуконазол в терапии кандидоза. РМЖ. 2002. № 15. С. 64-65.
50. Масюкова С.А. Глубокий кандидоз - актуальность и перспективы проблемы. РМЖ. 2004. №4. С. 189-195.

51. Мирзабалаева А.К. Кандидоз гениталий и бактериальный вагиноз в практике акушера-гинеколога. Пробл. мед. микологии. 2004. Т. 6, № 3. С. 18-24.
52. Нагорная В.Ф., Байло Н.В. Кандидозный вульвовагинит. Современный взгляд на проблему. Одеський медичний журнал. 2011. №1. С. 53-58.
53. Орлова Т.В., Панкрушева Т.А. Определение температуры плавления и времени полной деформации суппозиториев с нестероидными противовоспалительными средствами. Хим.-фармацевт. журн. 2010. Т. 44, № 7. С. 54-56.
54. Основы технологии суппозиториев - экстемпоральное изготовление / Т.Г. Ярных, Ю.В. Левачкова, М.В. Буряк, Н.В. Кубрина. Фармация. 2010. №2. С. 54-56.
55. Половко Н.П. Дослідження мікробіолопчної чистоти гелю з клотримазолом / Н.П. Половко, О.Г. Башура, О.П. Стрілець. Фармация. - 2010. Вип. 23, № 1. С. 73-75.
56. Потекаев Н.С., Гаджиев М.Н. Кандидоз. Consilium Medicum. 2012. Т. 4, № 5. - С. 230-233.
57. Прилепская В.Н. Клиника, диагностика и лечение вульвовагинального кандидоза (клиническая лекция). Гинекология. 2011. Т. 3, № 6. С. 201-205.
58. Про затвердження переліку допоміжних речовин та барвників, дозволених для застосування у виробництві лікарських засобів : Наказ МОЗ України № 8 від 15.01.2003 р. К., 2003. 34 с. URL : http://zakon2.rada.gov.ua/laws/show/z0069-03 (дата звернення: 16.10.17 р.).
59. Про затвердження Правил виробництва (виготовлення) та контролю якості лікарських засобів в аптеках : Наказ МОЗ України № 812 від 17.10.2012 р. К., 2012. 28 с. URL : http://moz.gov.ua/ua/portal/dn_20121017_812.html (дата звернення: 26.02.17 р.).

60. Проблема наукового обґрунтування технологій екстемпоральної рецептури та шляхи її вирішення. Пов. 2. Порівняльний аналіз сучасних фармакопейних вимог до технології і контролю якості екстемпоральних лікарських засобів / О. С. Соловйов та ін. Фармац. журн. 2014. № 2. С. 3-12.
61. Проблемы создания и стандартизации суппозиториев на современном этапе / Т. А. Панкрушева и др. Человек и его здоровье : Курский науч-практ. вестник. 2016. № 2. С. 108-112.
62. Просовецкая А.Л. Новые аспекты в лечении кандидозного вульвовагинита. Вестн. дерматологии и венерологии. 2016. № 6. С. 31-33.
63. Разработка вагинальных суппозиториев антимикробного действия с эфирными маслами / И.А. Пухальская, Н.Н. Малецкий, И.В Драч // Актуальні питания фармацевтичної та медичної науки та практики : зб. наук, статей. - Запоріжжя, 2009. - Вип. 22, Т. 2.-С. 134-137.
64. Разработка состава, технологии и изучение вагинальных суппозиториев для лечения специфических кольпитов / М.А. Захарова, Л.Н. Ерофеева, Н.Д. Афонина [и др.] // Курск, науч-практ. вестн. «Человек и его здоровье». 2011. № 2. С. 134-142.
65. Рецидивирующий урогенитальный кандидоз: лечение с использованием флуконазола / А.М. Савичева, З.М. Мартикайнен, Е.И. Абашова [и др.]. Журн. акушерства и женских болезней. 2018. Т. 57, вып. 1.-С. 41-46.
66. Розробка складу та дослідження песаріїв / Ю.В. Левачкова, Т.Г. Ярных, В.М. Чушенко, Л.М. Малоштан. Вісник фармації. 2011. № 1 (65). С. 6-8.
67. Роль вспомогательных веществ в обеспечении биодоступности суппозиториев парацетамола / Т.В. Орлова, Т.А. Панкрушева, А.В. Нестерова, Н.Д. Огнещикова. Науч. ведомости. Серия Медицина. Фармация. 2012.-Вып. 18/4, № 10 (129).-С. 114-118.

68. Флуконазол «Микосист» в лечении грибковых инфекций урогенитального тракта у онкологических больных / Н.В. Дмитриева, Е.Н. Соколова, И.Н. Петухова, Г.В. Варлан. РМЖ. 2006. № 14. С. 1020-1022.
69. Хамаганова И.В. Опыт применения сертаконазола при вульвовагинальном кандидозе / И.В. Хамаганова, В.В. Кальменсон. Вестн. дерматологии и гинекологии. 2007. № 3. С. 57-61.
70. Яремчук А.А Сравнительное изучение противогрибковой активности лекарственных средств / А.А Яремчук, Н.П. Половко, О.П. Стрилец // Вестник фармации. 2012. - № 1 (47). - С. 56-60.
71. Ярных Т.Г. Изучение ассортимента суппозиторных основ (обзор) / Т.Г. Ярных, Е.В Толочко, В.Н. Чушенко. Хим.-фармацевт. журн. 2010. № 10.-С. 21-26.

# APPENDIXES

**APPENDIX A**

**CENTER FOR FINANCIAL-ECONOMIC RESEARCH**
**ЦЕНТР ФІНАНСОВО-ЕКОНОМІЧНИХ НАУКОВИХ ДОСЛІДЖЕНЬ**

# CERTIFICATE OF PARTICIPATION
# СЕРТИФІКАТ УЧАСНИКА

підтверджує, що

**Hajar Bikech**

**взяв участь у роботі Міжнародної науково-практичної конференції**

«Сучасні аспекти науки, освіти, технологій та суспільства»

**International scientific-practical conference**

«Modern aspects of science, education, technology and society»

**Загальна кількість академічних годин: 6 год (0,2 кредита ECTS)**

Директор Центру фінансово-економічних наукових досліджень — Щербак В. Д.

14 квітня 2022 р.
April 14, 2022

м. Полтава, Україна
Poltava, Ukraine

**APPENDIX B**

ЦФЕНД ЦЕНТР ФІНАНСОВО-ЕКОНОМІЧНИХ НАУКОВИХ ДОСЛІДЖЕНЬ

**МІЖНАРОДНА НАУКОВО-ПРАКТИЧНА КОНФЕРЕНЦІЯ**
**INTERNATIONAL SCIENTIFIC-PRACTICAL CONFERENCE**

# СУЧАСНІ АСПЕКТИ НАУКИ, ОСВІТИ, ТЕХНОЛОГІЙ ТА СУСПІЛЬСТВА

# MODERN ASPECTS OF SCIENCE, EDUCATION, TECHNOLOGY AND SOCIETY

**Збірник тез доповідей**
**Book of abstracts**

**14 квітня 2022 р.**
**April 14, 2022**

**м. Полтава, Україна**
**Poltava, Ukraine**

**CONTINUATION OF APPENDIX B**

Збірник тез доповідей Міжнародної науково-практичної конференції
«Сучасні аспекти науки, освіти, технологій та суспільства»

**СЕКЦІЯ 6** | **ФАРМАЦЕВТИЧНІ НАУКИ**
**SECTION 6** | **PHARMACEUTICAL SCIENCES**

**UDC 615.454.21:615.322**

**Yurieva Ganna**
Candidate of Pharmacy,
Associate Professor,
Drugs Technology Department,
National University of Pharmacy
**Hajar Bikech**
Applicant for higher education,
National University of Pharmacy
**Nada Benfdil**
Applicant for higher education,
National University of Pharmacy

## STUDY OF THE INFLUENCE OF FLUCONAZOLE PARTICLE SIZE IN THE DEVELOPMENT OF THE COMPOSITION OF EXTEMPORANEOUS SUPPOSITORIES FOR THE TREATMENT OF CANDIDIASIS

In recent years, the prevalence of fungal infections has increased, caused by fungi of the genus *Candida*. Clinicians note the trend of steady increase in the incidence of this pathology, frequent recurrence point out that the problem is acute medical and social nature, affecting the health of different age groups and segments of the population, negatively affects them efficiency.

Therefore, over the past decade, there has been interest in the treatment and prevention of candidiasis of the mucous membranes in such fields of medicine as gynecology, dentistry, ophthalmology. An analysis of the literature shows that in recent decades the problem of infection has acquired the status of an important medical and social problem. The number of patients with superficial forms of candidiasis - the mucous membranes of the vagina, which are registered as a separate disease, and as a concomitant of other infections are increased. This negatively affects the quality of life of patients, leads to significant financial costs associated with treatment and rehabilitation [1, 2].

The pronounced tendency to spread candidiasis emphasizes the need for appropriate therapy aimed at eliminating the infectious agent, short-term treatment, achieving high concentrations of the substance in the target, safety and prevention of inactivation of the drug in the liver. Despite the large range and choice of antifungal

*F A 2.2.1–32-366*

**National University of Pharmacy**

Faculty for foreign citizens' education
Department Technology of Drugs

Level of higher education master

Specialty 226 Pharmacy, industrial pharmacy
Educational program Pharmacy

**APPROVED**
**The Head of Department**
**Technology of Drugs**
**Tatyana YARNYKH**

"_18_" of June 2021

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

1. Topic of qualification work: «Development of the composition of suppositories for the treatment of candidiasis», supervisor of qualification work: Ganna YURYEVA, PhD, assoc. prof.,

approved by order of NUPh from "17th" of February 2022 № 76.

2. Deadline for submission of qualification work by the applicant for higher education: April 2022.

3. Outgoing data for qualification work: Object of researches: fluconazol, model samples of suppositories with fluconazol

4. Contents of the settlement and explanatory note (list of questions that need to be developed):
- to analyze the literature on the prospects for the use of fluconazole in the treatment of candidiasis; - theoretically and experimentally substantiate the composition of suppositories with antifungal action; - conduct physico-chemical, biopharmaceutical and microbiological examination of suppository samples; - to develop the technology of making suppositories with fluconazole in pharmacies; - to study the stability of the developed suppositories.

5. List of graphic material (with exact indication of the required drawings):
tables – 6
figures – 4

6. Consultants of chapters of qualification work

| Chapters | Name, SURNAME, position of consultant | Signature, date | |
|---|---|---|---|
| | | assignment was issued | assignment was received |
| I Chapter | Ganna YURYEVA, ass. prof. of higher education institution of department Technology of Drugs | 18 June 2021 | 18 June 2021 |
| II Chapter | Ganna YURYEVA, ass. prof. of higher education institution of department Technology of Drugs | 10 September 2021 | 10 September 2021 |
| III Chapter | Ganna YURYEVA, ass. prof. of higher education institution of department Technology of Drugs | 5 December 2021 | 5 December 2021 |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |

7. Date of issue of the assignment: _____18 of June 2021_____

**CALENDAR PLAN**

| № з/п | Name of stages of qualification work | Deadline for the stages of qualification work | Notes |
|---|---|---|---|
| 1. | Analysis of literature data. | September – November 2021 | **done** |
| 2. | Researches of active substances and excipients | December 2021 – February 2022 | **done** |
| 3. | Justification of the results | March 2022 | **done** |
| 4. | Registration of qualification work | April 2022 | **done** |
| | | | |
| | | | |
| | | | |
| | | | |

**An applicant of higher education** _____ Hajar BIKECH

**Supervisor of qualification work** _____ Ganna YURYEVA

**ВИТЯГ З НАКАЗУ № 76**

**По Національному фармацевтичному університету**
**від 17 лютого 2022 року**

1. нижченаведеним студентам 5-го курсу 2021-2022 навчального року, навчання за освітньо-кваліфікаційним рівнем «магістр», галузь знань 22 охорона здоров'я, спеціальності 226 – фармація, промислова фармація освітня програма – фармація, денна форма навчання (термін навчання 4 роки 10 місяців), які навчаються за контрактом, затвердити теми магістерських робіт:

| № з/п | Прізвище студента | Тема магістерської роботи | Посада, прізвище та ініціали керівника | Рецензент магістерської роботи |
|---|---|---|---|---|
| **по кафедрі технології ліків** | | | | |
| 1. | Бікеш Хажар | Розробка складу супозиторіїв для лікування кандидозів Development of the composition of suppositories for the treatment of candidiasis | доц. Юр'єва Г.Б. | доц. Гербіна Н.А. |

Підстава: подання декана, згода ректора.

Ректор

Вірно. Секретар

# REVIEW

**of scientific supervisor for the qualification work of the master's level of higher education of the specialty 226 Pharmacy, industrial pharmacy**
**Hajar BIKECH**
**on the topic: «Development of the composition of suppositories for the treatment of candidiasis»**

**Relevance of the topic.** Currently, the spread of opportunistic yeast-like fungi of the genus *Candida* among sick and healthy individuals is increasing, as well as an increase in the incidence of candidiasis in people of different ages. Scientists estimate that about 20 % of women normally have *Candida* in the vagina without having any symptoms. Sometimes, *Candida* can multiply and cause an infection if the environment inside the vagina changes in a way that encourages its growth. This can happen because of hormones, medicines, or changes in the immune system.The use of antibiotics, especially a broad spectrum of action, contributes to the occurrence of intestinal dysbacteriosis, which can lead to the occurrence of severe systemic candidiasis. Fluconazole occupies a special status among antifungal drugs. It is distinguished by high bioavailability and efficiency in any localization of the process - from common skin lesions to meningitis, penetration into all biological fluids and tissues of the body, good effect of oral forms, the possibility of intravenous use in a serious condition of the patient and the introduction of a shock (double) dose on the first day of treatment , no toxicity and low frequency of adverse reactions.

**Practical value of conclusions, recommendations and their validity.** Experimental results are served as the basis for the creation of new extemporaneous drugs based on fluconazole in the form of suppositories, which will expand the range of medicines for the treatment of candidiasis.

**Assessment of work**. The research methodology is based on the main technological, physical and chemical principles reflected in the works of domestic and foreign authors. The study used a complex of organoleptic, physical -chemical and technological researches.

**General conclusion and recommendations on admission to defend.** The work was carried out at a high level, meets all requirements and can be submitted to the Examination Commission.

Scientific supervisor _____ Ganna YURYEVA

«12» of April 2022

*F A 2.2.1-32-356*

**REVIEW**

**for qualification work of the master's level of higher education, specialty 226 Pharmacy, industrial pharmacy**
**Hajar BIKECH**
**on the topic: «Development of the composition of suppositories for the treatment of candidiasis»**

**Relevance of the topic.** Scientific data from the National Institute of Allergy and Infectious Diseases tells us that nearly 75% of all adult American women have had at least one vaginal yeast infection in their lifetime. Candidiasis is an opportunistic infection. *Candida albicans* is present in healthy persons colonizing the oropharyngeal, esophageal, and gastrointestinal mucosa. *Candida albicans* can cause mucosal candidiasis in these areas where they usually are present in an immunocompromised host. Candida infections are treated with antifungal medications such as nystatin, clotrimazole, amphotericin B, miconazole. Mild or moderate genital Candida infections can have treatment with antifungal vaginal cream. In the treatment of vaginal candidiasis, a special place is given to drugs based on fluconazole, as a safe and highly effective agent. Fluconazole, as a hydrophilic drug, freely penetrates into the vaginal secretion and has a fungicidal effect. Thus, studies on the development of pharmaceutical dosage forms with fluconazole are promising and relevant.

**Theoretical level of work.** To generalize literary information about the modern state of candidiasis and usage of antifungal medicines for this purpose in the treatment of this patology. The place of fluconazole as a highly effective antifungal agent in the treatment of candidiasis has been determined.

**Author's suggestions on the research topic.** To carry out the complex of physical, chemical, biopharmaceutical and microbiological examination of suppository samples for development of the optimal composition.On the basis of obtained result the technology of suppositories in pharmacy condition has been proposed.

**Practical value of conclusions, recommendations and their validity.** During this work, the literature data has been analyzed, the physical, physical-chemical, and biopharmaceutical methods of research have been mastered. Results are of practical interest for the purpose to expand the range of available medicines

**Disadvantages of work.** There are spelling mistakes, technical errors in the work.

**General conclusion and assessment of the work.** Qualification work of Hajar BIKECH can be submitted to the Examination Commission for defense.

Reviewer _____ assoc. prof. Natalia GERBINA

«19» of April 2022

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

**ВИТЯГ З ПРОТОКОЛУ № _10_**
«28» квітня 2022 року
м. Харків

**засідання кафедри**
**___технології ліків___**

**Голова:** завідувачка кафедри, доктор фарм. наук, професор Тетяна ЯРНИХ
**Секретар:** канд. фарм. наук, доцент Володимир КОВАЛЬОВ

**ПРИСУТНІ:** професор Олександр КОТЕНКО, професор Юлія ЛЕВАЧКОВА, доцент Марина БУРЯК, доцент Оксана Данькевич, доцент Ганна ЮР'ЄВА, доцент Вікторія ПУЛЬ-ЛУЗАН, асистент Світлана ОЛІЙНИК

**ПОРЯДОК ДЕННИЙ**

1. **Про представлення до захисту до Екзаменаційної комісії кваліфікаційних робіт другого (магістерського) рівня вищої освіти**

**СЛУХАЛИ**:

Здобувача вищої освіти 5 курсу групи Фм17(4.10д)англ.-06 спеціальності 226 Фармація, промислова фармація Хажар БІКЕШ з доповіддю на тему «Розробка складу супозиторіїв для лікування кандидозів» (науковий керівник: доцент Ганна ЮР'ЄВА).

**УХВАЛИЛИ**:

Рекомендувати до захисту кваліфікаційну роботу.

**Голова засідання** **Тетяна ЯРНИХ**

**Секретар** **Володимир КОВАЛЬОВ**

*Ф А2.2.1-32-042*

# НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

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

Направляється здобувач вищої освіти Хажар БІКЕШ до захисту кваліфікаційної роботи за галуззю знань 22 Охорона здоров'я
спеціальністю 226 Фармація, промислова фармація
освітньою програмою Фармація
на тему: «Розробка складу супозиторіїв для лікування кандидозів».

Кваліфікаційна робота і рецензія додаються.

Декан факультету _____ / Світлана КАЛАЙЧЕВА /

### Висновок керівника кваліфікаційної роботи

Здобувач вищої освіти Хажар БІКЕШ представив магістерську роботу, яка за об'ємом теоретичних та практичних досліджень повністю відповідає вимогам до оформлення магістерських робіт.

Керівник кваліфікаційної роботи

_____ Ганна ЮР'ЄВА

«12» квітня 2022 року

### Висновок кафедри про кваліфікаційну роботу

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

Завідувачка кафедри технології ліків

_____ Тетяна ЯРНИХ

«28» квітня 2022 року

Qualification work was defended

of Examination commission on

« ___ » of June 2022

With the grade _____

Head of the State Examination commission,

DPharmSc, Professor

_____ / Oleh SHPYCHAK /