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on the topic: «**DEVELOPMENT OF COMPOSITION OF COMBINED
VAGINAL SUPPOSITORIES FOR APPLICATION IN GYNAECOLOGY**»

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ANNOTATION

Literary data on the treatment of inflammatory diseases in gynecology are considered and summarized. The study of the pharmaceutical market of Ukraine antiseptic and anti-inflammatory dosage forms of industrial and external production.

The composition and technology of pessaries with essential oils and water aloe extract on a hydrophobic basis is substantiated. The physicochemical and organoleptic indicators of quality of samples of vaginal suppositories in accordance with SPU methods were performed. A further set of experimental studies was aimed at choosing a rational type of suppository basis, as well as emulsifiers in the dosage form (LF) in order to improve the release of active substances. Thus, the basis of Witepsol combined with the emulsifier tween-80 and cetostearyl alcohol (CSA) was chosen by us as a promising for further research and development of the composition

The work is presented on 46 pages. Includes 9 tables, 2 pictures, 50 sources of literature and 2 additions.

Keywords: gynecological diseases, pessaries, Witepsol, essential oils, water extract of Aloe.

АНОТАЦІЯ

Розглянуті та узагальнені літературні дані щодо лікування запальних захворювань в гінекології. Проведено вивчення фармацевтичного ринку України антисептичних та протизапальних лікарських форм промислового та екстемпорального виробництва.

Обґрунтовано склад комбінованих песаріїв з ефірними оліями та екстрактом алое водним на гідрофобній основі Вітепсол. Проведено вивчення фізико-хімічних і органолептичних показників якості зразків вагінальних супозиторіїв згідно методикам ДФУ. Подальший комплекс експериментальних досліджень був направлений на вибір раціонального типу супозиторної основи, а також емульгаторів у складі лікарської форми (ЛФ) з метою покращення вивільнення діючих речовин. Таким чином, основа Вітепсол в поєднанні з емульгаторами твін-80 та ЦСС була обрана нами як перспективна для подальших досліджень та розробки складу

Робота представлена на 46 сторінках. Включає 9 таблиць, 2 малюнки, 50 літературних джерел і 2 доповнення.

Ключові слова; гінекологічні захворювання, песарії, Вітепсол, водний екстракт алое, ефірні олії.

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LIST OF ABBREVIATIONS

API – active pharmaceutical ingredients

WHO – World health organization

BV – bacterial vaginosis

EO – essential oils

MS – medicinal substance

MF – medicinal form

PEO – polyethylenoxides

SMS– solid medicinal substances

CSA – cetostearyl alcohol;

SPU – State Pharmacopeia of Ukraine;

USP – United States Pharmacopeia

INTRODUCTION

Nowadays, the protection of reproductive health of the population in economic and demographic crisis is relevant. Serious medical and the social problem in obstetrics and gynecology is represented by infectious-inflammatory diseases of the female genitals, which are caused by various pathogens, sexually transmitted, or caused by nonspecific microflora.

The main inflammatory gynecological diseases include colpitis, vulvovaginitis, cervical erosion, trichomoniasis colpitis, bacterial vaginosis, etc. In the future, these inflammations lead to severe consequences: violation of the menstrual cycle, even to its complete termination, infertility, miscarriage of pregnancy. Treatment consists in eliminating the cause of inflammation, as well as maintaining the body's natural protection system. Nowadays, in the pharmaceutical market, a very small percentage are drugs of natural origin. For their treatment, such essential oils as chamomile, lavender, tea tree, sage, geranium, pine, eucalyptus are used. These chemical compounds exhibit disinfectant, anti-inflammatory, wound-healing and reparative effects. Their use is possible only after consulting a doctor and prescribing the main treatment, since with improper use they can have a negative effect on the woman's body. They exhibit a smaller spectrum of side effects compared to synthetic ones. Essential oils are not only such, but also exhibit a complex therapeutic effect. Abroad, vaginal suppositories with essential oils are popular.

These data confirm the prospect of using essential oils as effective components of drugs for the treatment of various inflammatory gynecological diseases.

Currently, one of the most common obstetric and gynecological diseases are vulvovaginal infections, among which 30 - 50% occupies bacterial vaginosis.

According to the well-known definition, bacterial vaginosis is a vaginal microecology dysbiosis caused by increased growth of mainly obligate-anaerobic bacteria and a sharp decrease in lactobacteria concentration.

Indicators of incidence of bacterial vaginosis remain high both in our country and abroad. In this regard, the issues of diagnosis, treatment and

prevention of this disease are of considerable interest to doctors. Patients with bacterial vaginosis are at risk for infectious complications during pregnancy, childbirth, as well as after surgical interventions on the pelvic organs.

The etiology of bacterial vaginosis has not been fully studied. It is known that the main anaerobic and optional anaerobic microorganisms (*Mobiluncus spr*; *Gardnerella vaginalis*, *Ureaplasma urealitycum*, *Mycoplasma hominis*, etc.) in various associations.

Thus, the need for further study of the problem of bacterial vaginosis is relevant. A consistent solution to this problem will contribute to improvement reproductive health and quality of life of women. Vaginal medicines are of paramount importance and widespread use in the complex treatment of mixed urogenital infections.

Increasing the local impact on the lesion is achieved by using dosage forms of local action. Of these, the most effective in gynecological practice are pessaries (vaginal suppositories).

The main reason is a violation of normal vaginal microflora. At the same time, normal microflora acquires pathogenic properties, and its representatives become causative agents of a number of diseases.

According to the literature, there is an expansion of schemes and methods of treatment of inflammatory gynecological diseases through the wide study and use of medicinal substances of synthetic origin and of biologically active substances of essential oils and medicinal raw materials.

Among the medicinal forms used in the treatment of inflammatory diseases in gynecology, certain advantages are vaginal suppositories (pessaries), that is, external medications that reduce clinical manifestations and improve the epithelization of the affected tissues.

The main reason is a violation of normal vaginal microflora. At the same time, normal microflora acquires pathogenic properties, and its representatives become causative agents of a number of diseases.

Nowadays, the extemporal technology of medicines in pharmacies does not lose its importance. Extemporal production of drugs makes it possible to individual approach to the patient, which allows you to take into account the features the body, the course of the disease, symptoms, disease and its stage. This is the main principle and advantage of the of drugs "ex tempore."

The purpose of our work is to develop the composition and technology of pessaries for the treatment of inflammatory gynecological diseases.

To achieve this purpose, you need to solve the following tasks:

- summarize the literary data on the current state of treatment of bacterial vaginosis;
- analyze the range of dosage forms for vaginal use and vaginal dosage forms;
- conduct research in order to substantiate the basis - the carrier;
- develop the composition and technology of vaginal suppositories for the treatment of bacterial vaginosis.

PART I. QUESTIONS OF THERAPY OF INFECTIOUS GYNECOLOGICAL DISEASES

1.1. Causes of infectious gynecological diseases

Inflammatory diseases of the internal genitals are the most common gynecological pathology in women.

Inflammatory diseases differ in the antiquity of occurrence and acute clinical manifestations (acute and chronic), causative factor (bacteria, viruses, fungi, protozoa, etc.), at the place of formation of the pathological process. In a separate group allocated postpartum, post-abortion, postoperative inflammatory processes. Classification of some inflammatory diseases at the location of the inflammatory process is given in Table. 1.1.

Table 1.1

Classification of gynaecological inflammatory diseases

Name	Localization	Explanation
Vulvitis	External genitals	Vulva - external sexual organ (lat.)
Bartolinitis	Large glands of vaginal walls (bartolin glands)	The glands are named after the anatomist who described them
Colpitis, vaginitis	Vagina	Kolpos - sheath (Greek.) Vagina - sheath (lat.)
Endocervicitis	Mucous membrane of the cervical canal	Cervix - cervix (lat.) Endocervix - cervical mucosa (endo - internally)
Endometritis	Mucous membrane of the uterus	Meters - uterus (Greek.) Endometrium - uterine mucosa
Metroendometritis	Uterus (of course - after childbirth or abortion)	Look above
Salpingoophoritis, adnexitis (synonyms)	Uterine appendages (fallopian tube + ovary)	Adnexa - appendages (lat.) Salpinks - pipe (Greek.) Oophorum - ovary (Greek.)

Often, inflammatory diseases of the genitals lead to infertility, menstrual disorders, reproductive health, disability [4.5].

Among the most common gynecological diseases are vaginal infections, among which one of the first places is bacterial vaginosis (BV). According to A.S. Ankirskaya [2002], 20 to 60% of all vulvovaginal infections of the lower genital tract [28, 29] account for this pathology.

1.2. Etiology, clinic and pathogenesis of bacterial vaginosis, colpitis, and cervical erosion

Bacterial vaginosis (BV) - inflammatory changes caused by violation of microbiocenosis in the vagina. BV has many synonyms that remain in the past, for example, vaginitis, gardnerellous vaginitis, non-gonorrhoea or nonspecific vaginitis, aminocolpitis, corneobacterial vaginitis or anaerobic vaginosis, a common feature of which was a false notion of the inflammatory nature of the process [9, 11, 13].

Etiology and pathogenesis

With the destabilization of the ecosystem due to hormonal disorders, prolonged antibiotic therapy, immunological disorders, etc., there is a sharp decrease in lactobacillus strains, as a result of which conditions are created for massive reproduction of gardnerellas, obligate anaerobic bacteria and stimulation of growth of other conditionally pathogenic bacteria.

The microecosystem of the vagina in women of reproductive age is a strictly estrogen-dependent system. The function of the ovaries determines the cyclicity of maturation pithelial vaginal cells and their contents glycogen, which is a substrate for the growth and reproduction of the dominant component of the vaginal microflora - lactobacillus. The number of these bacteria at the level of 6-8 lg COE/ml allows to inhibit the reproduction of the transient part of microcenosis, to keep it at the minimum level (3-4 lg COE/ml), but in this part of microcenosis there are more than 30 species of different conditionally pathogenic bacteria [23,24, 28].

The reasons for the development of imbalance in the microflora of the vaginal ecosystem and the development of BV are discounted. Most authors try to associate the development of BV with hormonal imbalance, microbial antagonism, impaired immunocompetence (mainly local immunity). Preliminary treatment with antibiotics, smoking, vaginal syringes, the use of intrauterine contraceptives increase the risk of BV development.

Especially it should be noted the role of sexual behavior in the sexual transmission of BV. Even N. Gardner and co-author managed to recreate the picture of BV only in one of 13 women who were introduced to the sheath pure culture *G. Vaginalis*, in 11 out of 15 women who were infected with vaginal discharge of patients with BV. Further numerous studies have not confirmed the point of view of the sexual path of BV transmission. But the main argument against the sexual transmission of BV is the lack of influence of treatment of sexual partners and the frequency of recurrence of BV.

Although about 50% of women with BV are asymptomatic, common symptoms include increased vaginal discharge. The discharge is often white or gray in color. There may be burning with urination. Occasionally, there may be no symptoms. The discharge coats the walls of the vagina, and is usually without significant irritation, pain, or erythema (redness), although mild itching can sometimes occur. The recommended treatment for Bacterial Vaginitis in Morocco is usually metronidazole or clindamycin. Metronidazole is available in the form of oral tablets or capsules, as well as vaginal suppositories and creams. Clindamycin is available in the form of vaginal creams. The following are some of the commonly available trade names of metronidazole and clindamycin in Morocco:

- Metronidazole: Flagyl, Metrazol, Rozex
- Clindamycin: Clindac, Dalacin, Evoclin

In addition to these medications, there are also some topical medications available for the treatment of Bacterial Vaginitis in Morocco. The following are some of the commonly available trade names of topical medications for Bacterial Vaginitis:

- Clindamycin: Clindac, Dalacin { The usual dose of clindamycin vaginal cream is 5 grams (1 applicatorful) inserted vaginally once daily, preferably at bedtime, for 7 days }
- Metronidazole: Anabact, Metroso, Rosiced

Suppositories allow for direct delivery of medication to the affected area, which can improve treatment outcomes and reduce the risk of systemic side effects.

To use a suppository for bacterial vaginosis, the patient typically inserts the suppository into the vagina once or twice daily for a specified period of time, as directed by their healthcare provider. It is important to follow the instructions carefully and complete the full course of treatment, even if symptoms improve before the medication is finished.

In addition to medication, other self-care measures can also be helpful in managing BV. These may include avoiding irritants such as scented products and douches, wearing cotton underwear, and practicing good hygiene.

It is important to seek medical attention if you suspect you have bacterial vaginosis, as untreated infections can lead to complications. Your healthcare provider can diagnose the underlying cause of your symptoms and recommend appropriate treatment options, which may include the use of suppositories.

Clinic

A feature of bacterial vaginosis is the absence of edema, hyperemia (signs of inflammation) of the vaginal mucosa. The leading symptoms of BV are abundant white with an unpleasant odor. The amount of them is about 20 ml per day (about 10 times higher than normal).

The diagnosis of bacterial vaginosis is based on the data of clinical and special laboratory methods of research. It can be put in the presence of three of the four following criteria:

- homogeneous discharge from the vagina;
- increase of pH level of sheath separated;
- positive amine test;

- key cells in strokes painted with gram

BV is a risk factor for the development of such obstetric pathology as premature childbirth, miscarriage. There is an opinion that the state of vaginal microecology can be a kind of "diagnostic mirror," which reflects the state of the upper part of the internal genitals [2, 14, 17].

Episodes of BV are accompanied by a decrease in the redox potential of tissues, the development of tissue hypoxia and high pH of vaginal secretions. This may result in the activation of viral infections (especially during pregnancy) and an increase in the risk of sexually transmitted infections, including HIV.

Treatment

For the treatment of BV, mainly local and antibacterial drugs are used:

- local drugs (vagilak - 1 candle intravaginally, within 10-20 days; clindamycin cream (dalacin C) - intravaginally, 5 g 1 time per day, better for the night, for 7 days; betadine - 1 candle per vagina per night for 10-14 days; Terzhinan - 1 candle per vagina per night for 6-10 days;
- antibacterial drugs (metronidazole - orally 0.5 g 2 times a day for 7 days or 2 g once; ornidazole - orally 0.5 g 2 times a day for 5 days; tinidazole - oral 2 g once

The purpose of the treatment of bacterial vaginosis is to restore the normal microflora vagina, restrain the growth of microorganisms, not inherent in this microecology.

Occasionally, there may be no symptoms. The discharge coats the walls of the vagina, and is usually without significant irritation, pain, or erythema (redness), although mild itching can sometimes occur. The recommended treatment for Bacterial Vaginosis in Morocco is usually metronidazole or clindamycin. Metronidazole is available in the form of oral tablets or capsules, as well as vaginal suppositories and creams. Clindamycin is available in the form of vaginal creams. The following are some of the commonly available trade names of metronidazole and clindamycin in Morocco:

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Studies have shown that the use of antibiotics such as tetracycline, ampicillin, erythromycin is effective only in 14-54% of cases. With the use of ofloxacin only in 43% of cases, recovery occurred. For the treatment of women with bacterial vaginosis, the use of β -лактамних antibiotics is also proposed, for example, a complex of amoxicillin and clavulonic acid, where the latter plays the role of an inhibitor β -лактамаз resistant strains of bacteria (for example, *Vasteroides fragilis*) [12,].

Widespread use in the treatment of infectious diseases of sexual systems also found synthetic antibacterial agents metronidazole and clindamycin.

Practically, for the treatment of bacterial vaginosis, this the main pharmacological groups: antiseptics and disinfectants, synthetic antibacterial agents, immunomodulators, antibiotics, antifungal agents, regenerants and reparants (tabl. 1.2 [23])

Table 1.2.

Pharmacological groups of medicines used for treatment bacterial vaginosis

№	Pharmacological group	Active substances
1.	Antiseptics and disinfectants	Miramistine
		Povidone-Iodum (betadine)
		Chlorhexidine (hexicone)
		Polycreulene
		Tea tree essential oil
2.	Synthetic antibacterial	Metronidazole
		Pifuratel
		Ornidazole
		Fursolidone
3.	Immunomodulators	Interferon F-2 (viferon)
		Polyoxidonium
		Meglumine acridonacetate (cycloferon)
4.	Antibiotics:	
	Macrolides	Rozytromycine
	Lincozamides	Clindamycin, lincomycin
	Penicillines	Amoxicillin and clavulonic acid
	Fluoroquinolones	Ofloxacin
	Cephalosporins	Cefalexime
5.	Antifungal remedies	Miconazol
		Econazole, Fluconazole
6.	Regenerants and reparants	Pumpkin oil
		Sea buckthorn oil

Etiology, clinic and pathogenesis of colpitis

Recently, there has been an increase in sexually transmitted infections among the adult population and adolescents. The incidence of chlamydia and trichomoniasis increases [15].

Consider the etiology, pathogenesis and pharmacotherapy of infectious and inflammatory diseases in gynecology, namely: colpitis and cervical erosion.

Colpitis is an infectious and inflammatory lesion of the vaginal mucosa.

Etiology and pathogenesis

The occurrence of colpitis is caused by an infection caused by trichomonas, candida fungi, intestinal flora, conditionally pathogenic pathogens (proteus, escherichia, hemophilic stick). Inflammation occurs due to trophic disorders of vaginal tissues caused by general (infectious diseases, diseases of metabolism, disorders of the menstrual cycle, etc.) and local (disorders of personal hygiene, lowering the walls of the uterus and vagina, harmful conditions in production, etc.) factors [1, 4,17].

Clinic

In the acute stage of colpitis, patients complain of contamination of laundry with vaginal discharge. The latter differ from the usual in color, smell and quantity. If the white notes impurities of gas bubbles, then in this case the discharge is foamy, with an unpleasant fish odor - this is typical for trichomonade colpite. With mycotic lesions, the vaginal discharge has a white color and a curly appearance. Discharge is often accompanied by a itch, sometimes swelling and redness of the external genitals. Quite often, dysuric disorders and pain in the lower abdomen or back join colpitis. The temperature with acute colpitis does not rise, it can reach subfebrile figures with colpitis with a deep lesion of the vaginal walls.

Treatment

A number of authors recommend such approaches to the treatment of colpitis, as a focus on the treatment of concomitant and functional disorders. Treatment of colpitis consists of local and general taking into account the nature of the pathogen. Local treatment consists in prescribing sedentary warm baths with chamomile infusion. With thick purulent or mucous secretions, vaginal syringe is

carried out with a solution of bicarbonate soda (2 tsp per 1 glass of water), and after 20-25 minutes, douching with manganese acid potassium is carried out.

Antibiotics and sulfonamides are prescribed after determining the sensitivity of the pathogen to them. They are used locally in the form of solutions and emulsions and for general treatment. WHO experts recommend schemes for specific treatment of colpitis, taking into account the sensitivity of microbes to antibiotics.

In the complex therapy of colpites, the following groups of drugs are used:

- antibacterial drugs of choice (metronidazole orally 2 g once; tetracycline g/h orally 4 times a day in a dose of 500 mg for 7days; with tetracycline intolerance an alternative drug is erythromycin - orally at a dose of 500 mg 4 times a day for 7 days);
- antifungal drugs (clotrimazole - intravaginally 100 mg each evening during the week; nystatin -by 100000-1000000 ME intravaginally daily for 14 days; miconazole 100 mg intravaginally for 7 days or 200 mg daily for 3 days)

In recent years, a promising direction is the development of new highly effective drugs based on substances of natural origin for the treatment of infectious and inflammatory gynecological diseases.

Etiology, clinic and pathogenesis of cervical erosion

Under erosion or true erosion of the cervix, the rejection (defect) of the epithelium is understood as a result of inflammation, datermocoagulation, radiation therapy, trophic tissue disorders, injuries [15, 20, 21, 36].

Etiology and pathogenesis

According to the etiological characteristics, the following types of erosions can be distinguished:

- inflammatory (as a result of maceration and rejection of the epithelium);
- traumatic (injury, for example, vaginal mirrors);
- post-fire;
- trophic (for example, in case of loss of the uterus, after radiation therapy);

- cancer;
- syphilitic.

In recent years, the number of women with erosive injuries has increased, 1/3 of which accounts for the proportion of young women who have not yet given birth. The group of diseases is characterized by a violation of the differentiation of the cells of the vaginal epithelium and cervix and their replacement with pathological ones not inherent in these organs and cells. The disease belongs to the group of precancerous processes and requires surgical methods of treatment and dispensary supervision, without excluding traditional therapy with medication and invasive drugs [18, 19].

Treatment

1. Treatment of the underlying disease that led to the formation of erosion, vitamin therapy, regulation of immune and endocrine homeostasis.
2. Therapy of concomitant diseases of inflammatory processes of the cervix and vagina.
3. Stimulation of reparative processes (strictly according to indications!).

To stimulate reparative processes in cervical erosion, helium-neon laser radiation is used (up to 10 sessions of 5-10 minutes), some authors (Krasnopolsky V.I., 1997) recommend the use of an action on the cervix with a microwave centimeter range by a vaginal emitter. Widespread use to enhance reparative processes found ointment swabs (with sea buckthorn oil, fish oil, siphon oil, etc.), well proven aerosol preparation "Olazol." It should be emphasized that stimulation of reparative processes is not included in the complex of treatment of cancerous and syphilitic junction, and is never prescribed for cervical ectopies.

1.3. Medicines for vaginal use

Today suppositories and pessaries are still present among the most promising solid dosage forms due to their advantages, such as as fast delivery of medicinal substances, reducing the risk of side effects, etc.

Suppositories are prescribed for the purpose of local action (antiseptic, analgesic, etc.) and general, resorptive action for patients with cardiovascular disorders, neuro-mental disorders as протизапальні, antipyretic, cardiotonic, analgesic, etc.

Medicines for vaginal use (vaginal drugs) can be liquid, soft or solid and intended for use in the vagina in order to ensure local action. They contain one or more active substances in an appropriate basis.

Medicines for vaginal use can be classified as:

- pessaries;
- vaginal tablets;
- vaginal capsules;
- vaginal solutions, emulsions and suspensions;
- tablets for the preparation of vaginal solutions and suspensions;
- soft medicines for vaginal use;
- vaginal foams;
- vaginal medical swabs

Pessaries

Pessaries are solid single-dose drugs. They can be of different shapes, of course egg-like; by volume and consistency should meet the vaginal application.

They contain one or more active substances dispersed or dissolved in the base, which can dissolve or disperse in water or melt at body temperature. The composition of pessaries, if necessary, may include excipients, such as diluents, adsorbents, surfactants and lubricants, antimicrobial preservatives, as well as dyes permitted for medical use.

1.4. Assortment of vaginal medicinal forms at the pharmaceutical market of Ukraine

Nowadays, there is a wide range of drugs in different dosage forms for the treatment of vulvovaginal infections. The most rational form of medicine is the means of local action, which act directly in the center of infection.

We analyzed the range of vaginal dosage forms antibacterial and atyseptic action in the pharmaceutical market of Ukraine (table 1.3).

Table 1.3.

Antibacterial and antiseptic vaginal medicinal forms at the pharmaceutical market of Ukraine in 2019/2020 yy.

№	Trade name	Active substance	Country, manufacturer
1	2	3	4
Vaginal suppositories (pessaries)			
1.	Betadine®	Povidone Iodine	"EGIS" Pharmaceuticals PLC for the licence of company «MUNDIFARMA A.G», Hungary/Switzerland
2.	Betadin	Povidone Iodine	"Alkaloid AD-Skopje", Macedonia Republic
3.	Vokadin	Povidone Iodine	"Wockhardt Ltd", India
4.	Ginazol-7	Econazolum	"Sagmel Inc"; "IDA (Istituto De Angeli;)", USA/Italy
5.	Gino-Pevaril	Econazolum	"Cilag AG", Switzerland
6.	Gino-Travogen	Econazolum	"Intendis Manufacturing S.p.A." and "Schering S.p.A." departments of company "Schering AG" for "Intendis GmbH", Italy/Germany
7.	Gerksikon®	Chlorhaxidine	LTD "Niwpharm", t. Nuwnyi Novgorod , Russian Federation
8.	Gravagin	Metrinidazole	AT "Sperko Ukraine", t. Vinnutsya, Ukraine
9.	Evcolec	Chlorophylliptus thick extract	LTD "Lekhim-Kharkiv", t. Kharkiv, Ukraine
10.	Evkalin	Econazolum	"Jaka 80 Radovis Macedonija"AD, Macedonia
12.	Iodoxidum®	Povidone-Iodine	LTD "Niwpharm", t. Nuwnyi Novgorod , Russian Federation
13.	Ketodine	Ketoconazole	LT "Sperko Ukraine", t. Vinnutsja, Ukraine
14.	Zalain Ovules	Sertoconazole nitratis	"Theramex" for"Egis" Pharmaceutical Ltd, Monaco/

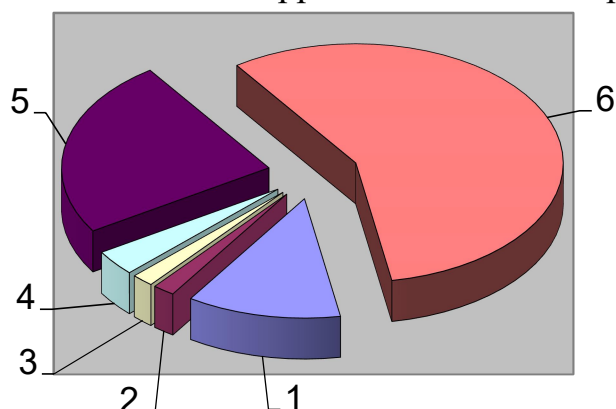
1	2	3	4
15.	Econazol-LX	Econazolum	LTD "Lekhim-Kharkiv", t. Kharkiv, Ukraine
16.	Ketoconazole-LX	Ketoconazole	LTD "Lekhim-Kharkiv", t. Kharkiv, Ukraine
17.	Livarol®	Ketoconazole	LTD "Niwpharm", t. Nuwnyi Novgorod , Russian Federation
18.	Mico-Penotran	Myconazole nitratis	"Embil Pharmaceutical Co.Ltd" for "Schering AG", Turkey/Germany
19.	Mycofel	Omoconazole	"TEVA Pharmaceutical Industries Ltd" на заводі "TEVA Pharmaceutica Works Co.Ltd" Israel/Hungary
20.	Mylagin	Clyndamycine	LT"Sperco Ukraine", t. Vinnutsya, Ukraine
21.	Macmiror complex	Nifuratel Nistatine	"Doppel Farmaceutici S.r.L." for "Poli Industria Chimica S.p.A.", Italy
22.	Metronidazole	Metronidazole	LT "Monfarm", t. Monasturyshe, Cherkassky reg., Ukraine
23.	Metronidazole	Metronidazole	"Farmaprim SRL", Moldova Republic
24.	Metronidazole - Darnitsa	Metronidazole	LTD "Pharmaceutical firm "Darnytsa", t. Kyiv, Ukraine
25.	Neo-penetrane forte	Metronidazole Myconazole nitratis	"Embil Pharmaceutical Co.Ltd" for "Schering AG", Turkey/Germany
26.	Neo-penotrane®	MetronidazoleMiconazole nitratis	"Embil Pharmaceutical Co.Ltd" for: "Schering AG", Turkey/Germany
27.	Pimafulcine®	Natamycine	"Astelas Pharma S.p.A"; "Temmler Italia S.r.l" для " Astelas Pharma Europe B.V.", Italy/ The Nethaerlands

1	2	3	4
Vaginal tablets			
1.	Ginalgin	Metronidazol Chlorkhinaldine Limonen oil	"ICN Polfa Rzeszow" S.A., Poland
2.	Candibene	Clotrimazole	"Merckle GmbH"/"ratiopharm GmbH", Germany
3.	Candid-B6	Clotrimazole	"Glenmark Pharmaceuticals Ltd", Індія
4.	Clion-D 100	Metronidazole Miconazole	"Richter Gedeon Ltd", Hungary
5.	Clotrimazol	Clotrimazole	LTD "Borshagivskiy CFP", t.Kyiv, Ukraine
6.	Clotrimazol л	Clotrimazole	"Synmedic Laboratories", India
7.	Clotrimazol	Clotrimazole л	LTD" Borshagivskiy CFP", t.Kyiv, Ukraine
8.	Clotrimazol	Clotrimazole	"GlaxoSmithKline Pharmaceuticals S.A." для " GlaxoSmithKline Export
9.	Clotrimazol	Clotrimazole	"Elegant India", Індія
10.	Micowynax	Metronidazole Myconazole	"Mekophar Chemical Pharmaceutical Joint-Stok Comhany", Vietnam
Vaginal capsules			
1.	Lomexin	Fentakonazole	"Recordati Chemical and Pharmaceutical Company S.p.A", Italy
2.	Polygynax	Neomycine Polymixine Nistatine	"Laboratories Innotech Internacional" at the plant "Innothera Shuzy", France
Soft vaginal medicinal forms (gels, creams)			
1.	Vagicin- Zdorovje	Clindamycin	LTD "Pharmaceutical "Zdorovje", t. Kharkiv, Ukraine
2.	Ginofort	Butoconazole nitrtatis	"KV Pharmaceutical Co ." for "Richter Gedeon Ltd", USA/Hungary
3.	Dalacin™ vaginal cream	Clindamycine	"Pharmacia & Upjohn Company" for " Pfizer Inc.", USA

Domestic assortment of vaginal suppositories is represented by Drugs of 5 pharmaceutical enterprises: CJSC "Lekhim-Kharkiv," Kharkiv; JV "Sperko Ukraine," Vinnytsia; OJSC "Monfarm," Monastyrysche, Cherkasy region; CJSC "Pharmaceutical Company" Darnitsa, "Kyiv, Ukraine, Fitolek.

After analyzing the data, it was found that the largest number of vaginal dosage forms are vaginal suppositories (pessaries) almost 54%, vaginal tablets - about 27%, creams and gels - 11.5%, capsules - less than 4%, and solutions for vaginal use and tablets for the preparation of solutions - 1.80% (pis. 1.1.). [4,37,40].

Pessaries make up the largest share of all medicinal vaginal forms, as they are the most convenient form of application and have a pronounced local effect.



Pic. 1.1. Assortment of antibacterial and antiseptic vaginal medicinal forms on the Ukrainian market in 2020/2021 yy.

The basis of the investigational nomenclature of drugs - 77.6%, forming preparations of pharmaceutical companies in Western Europe and India, only 23.4% - vaginal dosage forms manufactured in Ukraine:

- 1 - Soft medicines for vaginal use - 11.5%;
- 2 - Powders for preparation of vaginal solution - 1,80%;
- 3 - Vaginal solutions - 1,80%;
- 4 - Vaginal capsules - 3.50%;
- 5 - Vaginal tablets - 27.20%;
- 6 - Pessaries - 53.80%.

The main part of this nomenclature are drugs of synthetic origin that have a significant number of undesirable effects. For example, allergic reactions,

abdominal pain, nausea, decreased appetite, nonspecific diarrhea, and dyspeptic disorders, ototoxicity, candidiasis, suppression of blood creation, suppression of the immune system, inhibition of the growth of connective tissue, suppression of the blood clotting system, neurotoxicity, etc [39, 42,].

Instead, herbal drugs, a much smaller number of undesirable effects and much more positive qualities: they are close in composition to the human body, a complex effect on the body due to the presence of biologically active substances, a large number of plants with a similar effect, low cost compared to synthetic drugs.

It can also be noted that in the production of the drug of synthetic origin, various preservatives and stabilizers are used, thanks to which the shelf life is 2 years.

Therefore, the medicine of choice for the treatment of bacterial vaginosis are herbal preparations, namely: aloe extract and tea tree oil, chamomile essential oils.

1.5. Application of essential oils in medicine

Due to the fact that essential oils are very complex chemically mixtures of substances of different biological effects, it is not surprising that the action of essential oils is manifested by a very complex complex of pharmacological and clinical action. This action is due to the peculiarities of the simultaneous long-term chemical evolution of fragrant plant substances and human evolution.

Surface effect.

Application of essential oils on the skin leads to rapid sorption and their penetration into the blood. Different oils are sorted differently by the skin. This depends on the lipophilicity of the components included in the essential oils.

In addition, the penetration rate greatly depends on the skin temperature and humidity conditions. For example, in a warm bath, the rate of penetration of essential oil is 100 times higher than just at room temperature.

Hyperemical effect.

It is explained by increased local circulation. In this case, redness of the skin occurs. Local exposure to essential oil can cause the appearance of mediators in the body, leading to the phenomena of vasodilation (relaxing muscles in the walls of blood vessels) with the subsequent effect on the internal organs (calming pain, the effect of "heart ointment"). The initial violation can cause humoral reactions, as a result of which there is an anti-inflammatory effect. The following oils and their liniments, tinctures and alcohol solutions have the following properties: eucalyptus, gaultherium, juniper berries, rosemary, rectified turpentine, as well as a number of substances isolated from these essential oils (camphor and methylsalicylate).

Some oils have a sufficiently strong effect, which leads to burns. Such oils can be used only with great caution and chronic diseases: mustard oil, kantaridin, capsaicin and croton oil.

Anti-inflammatory effect. Some essential oils cause secondary biochemical reactions, through which humoral mechanisms stimulate a number of leukocyte

reactions that lead to the resorption of inflammation. Such oils include: chamomile, yarrow, some wormwood oils and other oils containing matricine, hamazulene and (-) - α -бисаболол, arnica oil, other oils containing lactone gelenaline and gelenalinacetate, as well as terpene oil and some oils, containing thymol. In some cases, chamomile essential oils are falsified: they do not have any anti-inflammatory action with semi-synthetic guayazulene, (\pm) -Bisabolol or (+) - α -Bisabolol isolated from *Populus balsamifera* (balsamic poplar), which have a significantly less anti-inflammatory action than hamazulene, α - Bisabolo or Chamomnille mathricine.

Antiseptic and antimicrobial action is often accompanied by anti-inflammatory action. Penetrating into the cells, the oil begins to affect the metabolism of microorganisms. It has been observed that the antiseptic activity of many compounds entering the essential oils, as well as the essential oils themselves, depends on their ability to dissolve in fats and thus penetrate the cell through lipid membranes. Bacteriostatic activity of essential oils partially depends on their surface activity.

For a simplified assessment of antiseptic activity, a phenolic coefficient is used, which shows how many times the bactericidal activity of the essential oil is stronger than the bactericidal activity of phenol, an indicator of which is taken per unit.

Of course, such a coefficient gives only an approximate estimate, since phenol can act on other bacteria and affect those microorganisms that are not affected by essential oil and vice versa.

Healing effect. The anti-inflammatory and hyperemical effect is accompanied by the healing effect. This effect is largely inherent in the essential oil of chamomile, both in the form of alcohol, and in the form of ointments and gels. Japanese rectified mint oil activates the healing of the epithelium with scratches and does not act on burns. Ordinary St. John's wort oil (obtained by extraction of *Hypericum perforatum* flowers with olive oil), containing hypericin and pseudohypericine (diantrons), is used for wound healing.

Deodorizing effect. Many essential oils destroy bad odors. Among them, rectified citrus oil (without terpene), rectified terpene oil, thyme oil, coniferous oils.

Insecticidal and repellent effect. Many oils have the property not only to scare away insects, but also to destroy them. Essential oils and their components have such properties as citronella oil, eucalyptus oil, clove oil, cinnamon oil, as well as citral, carvon, brown aldehyde, camphor contained in some essential oils. Essential oil of tetraploid lepecha species (the so-called Indian Jammu oil), containing more than 90% β -азарона, acts on insects as a chemical sterilizer.

Internal application.

The main method of internal use of essential oils is inhalation, and inhalation is a more effective way to get essential oils into the blood than oral use.

Expectorant action is caused mainly by secretolytic, secretomotor and to a lesser extent bronchospasmolytic effect. With the joint action of oils of coniferous and eucalyptus, menthol and camphor, induced bronchospasm decreases. Anise and fennel increase mucociliary activity (fennel is stronger than anise), and thyme reduces this activity. The obstructive effect of thyme preparations allows them to be used as effective expectorants. When inhaling essential oils there is increased secretion under the influence of mucous trachea and bronchi. In addition, there is a secondary stimulation of sensitive endings of the mucous membrane of the stomach surface. Expectorant effect also have chamomile oil, flowers and orange peel, peppermint, sage and cinnamon. The anti-acid effect of essential oils has a different mechanism than the codeine effect and is in a sense a "positive" side effect.

Stimulation of digestion. A number of essential oils have the ability to stimulate appetite and cause choleric, cholekinetic and carminative (wind) effect. Some essential oils enhance the secretion of the stomach and intestines, stimulate the liver (anise, angelica, fennel, orange, peppermint and cinnamon) and gallbladder (turmeric containing sesquiterpene phenol xanthorizol and paratolylmethylcarbinol, calamus, cumin, Choleric effect (increased secretion of bile)

causes peppermint, which contains menthol, and turmeric (*Curcuma xanthorrhiza*), containing curcumin. Substances capable of enhancing the secretion of bile include borneol, camphor, 1,8-cineol, α -i β -pinen, menthol and menthon contained in various essential oils. Carminative action has dill, anise, basil, fennel, chamomile, coriander, cumin and peppermint.

Antispasmodic effect. It is found in the relaxation of muscle tissues (intestines, bronchi). This effect has varying degrees of chamomile oil, cumin, fennel, orange, peppermint, lemon balm and cinnamon.

Anti-inflammatory and antiseptic action. Very strong anti-inflammatory effect has chamomile oil, containing matricine. It is used to treat stomatitis. Antiseptic effect is very important for colds. In this case, inhalation and rinsing with essential oils of sage, eucalyptus, thyme and cinnamon are used.

Diuretic effect. Essential oils do not have a true diuretic effect, but only provoke the kidneys to release certain substances contained in essential oils from the body. This property has terpinen-4-ol, contained in some essential oils (majorana, tea tree).

Sedative effect. The most famous extractive essential oil with sedative (sedative) action is valerian, containing valepotriates associated with active tranquilizers. *Valeriana officinalis* contains small amounts of these compounds 0.8 - 1.7%, *Valeriana wallichii* and *V. edulis* contains 2.8-3.5% and 8-12%, respectively. Melissa, hops and St. John's wort also have some sedative effect, but this information is contradictory. Only for the components of melissa (citronellal and minerals) this information is confirmed experimentally. St. John's wort oil has a mild antidepressant effect.

Strengthening of circulations. Some essential oils in high doses can stimulate respiratory brain centers, heart and circulation activity. In the latter case, this effect is used in the form of so-called snuff (fragrant) salts. The action of camphor as a central analeptic is not always reliable. In addition, she has many side effects. Camphor has a stimulating effect on the respiratory, circulation and vegetative centers, stimulating the heart and blood vessels. Rosemary oil due to the

high content of borneol, bornilacetate, 1,8-cineol and camphor also has a circulating effect. This is true for avalanche and peppermint, especially with inhalations.

Thus, oils have: hyperemical and anti-inflammatory effects, antiseptic and antimicrobial actions, healing, deodorizing, insecticidal and repellent, diuretic sedative effects. They also have expectorant, anti-inflammatory actions, stimulate digestion and increase circulation.

Side effects.

Side effects of essential oils are manifested in various allergic reactions, some oils have phototoxic effects, a number of oils exhibit necrotic properties. Many oils act as narcotic substances, nephrotoxins, hepatotoxins and carcinogens. In many cases, side effects occur when abused or misused essential oils. It should be noted that many types of exposure to essential oils are individual.

CONCLUSIONS

1. Modern information on etiology, pathogenesis and pharmacotherapy of inflammatory gynecological diseases is summarized (according to the literature bacterial vaginosis is detected in 64-80% of cases).
2. In the treatment of this pathology, an important role is paid to traditional antibacterial and local therapy. Given the etiology, pathogenesis and existing treatment regimens of this disease, it is advisable to create multicomponent combined drugs based on synthetic and natural substances.
3. Anaerobic and optional anaerobic microorganisms (*Mobiluncus* spp., *Gardnerella vaginalis*, *Ureaplasma urealitycum*, *Mycoplasma homis*, etc.) play a major role in the occurrence of the disease in various associations.
4. The purpose of the treatment of bacterial vaginosis is to restore the normal microflora vagina, restrain the growth of microorganisms, not inherent in this microocenosis.
5. The main pharmacological groups for the treatment of bacterial vaginosis are: antiseptics and disipifiers, synthetic antibacterial agents, immunomodulators, antibiotics, antifungal agents, regenerants and reparants.
6. When determining a mixed infection, drugs that act on concomitant pathogens are prescribed. In this regard, it is advisable to create combined dosage forms based on natural and synthetic substances.
7. Domestic assortment of vaginal suppositories is presented 5 pharmaceutical enterprises: CJSC "Lekhim-Kharkiv," Kharkiv; JV "Sperko Ukraine," Vinnytsia; JSC "Monfarm," Monastyryshche, Cherkasy region; CJSC "Pharmaceutical Company" Darnitsa, "Kyiv, Ukraine, Fitolek 8. As a result of the analysis of the range of vaginal dosage forms of antibacterial and antiseptic action on the pharmaceutical market of Ukraine, it is established that the preparations of domestic production make up 23.4% of Western Europe and India - 77.6%.
9. Studies have shown the prospect of creating a domestic antibacterial and antiseptic medicone for the treatment of bacterial vaginosis in the form of pessaries.

PART II. OBJECTS AND METHODS OF RESEARCH

When developing the composition of extemporal prescription of combined vaginal pessaries, medicinal substances that are allowed for use in pharmaceutical and medical practice were used.

The development of the composition of this dosage form is based on various physico-chemical and structural-mechanical studies.

2.1. Objects of research

2.1.1. Characteristics of active substances

Melaleuca aetheroleum

Tea tree oil

Tea tree oil described in SPU 1.2, p.591, Pharmacopoeia of Europe 4.1, pp. 2541 and Pharmacopoeia of Britain [5, 35].

Tea tree essential oil is a transparent, moving liquid from colorless to pale yellow with a characteristic odor derived from the leaves and apical shoots of *Melaleuca aetheroleum* (Maide Betchn and) Cheel, M. *Linariifolia* Smith, M.*dissii*. Mueller and/or other *Melaleuca* types by distilling with dropsy steam.

- α - pinen (from 1 % till 6 %),
- sabinen (less then 3,5 %),
- α -terpinen (from 5 % till 13 %),
- limonen (from 0,5% till 4%),
- cyneol (less then 15 %),
- γ -terpinen (from 0,5 % till 28 %),
- p -cymen (from 0,5 % till 12 %),
- terpinolen (from 1,5 % till 5 %),
- terpinen - 4 -ol (not less then 30 %),
- aromadendren (less then 7 %),

- a – terpineol (from 1,5 % till 8 %).

The most important active component is considered natural terpinen-4-ol, which provides antiseptic effect of oil.

Quality indicators of tea tree oil presented in Table. 2.1.

Table 2.1.

Quality indicators of Tea tree essential oil

Indexes	State Pharmacopeia of Ukraine 1.2, p. 591	European Pharmacopoeia 4.1
Description	transparent, moving liquid from colorless to pale yellow color with a characteristic odor	transparent, moving liquid from colorless to pale yellow color with a characteristic odor
Identification	thin-layer chromatography	thin-layer chromatography
Cleanliness Tests:		
relative density	from 0,885 till 0,906	from 0,885 till 0,906
refractive indicator	from 1,475 till 1,482	from 1,475 till 1,482
optical rotation	from + 5 till + 15	from + 5 till + 15
chromatographic profile	gas chromatography: internal normalization method	gas chromatography: internal normalization method

Aloes extractum

Aloe vera extract is derived from the leaves of the aloe vera plant and is known for its anti-inflammatory and wound-healing properties. It has been used topically to treat skin conditions such as burns, cuts, and eczema.

In suppository form, aloe vera extract may have potential as a soothing and healing agent for conditions such as vaginal irritation or inflammation.

Aloe Vera is a succulent plant that has been used for centuries for its medicinal properties. It contains over 200 active compounds, including vitamins,

minerals, amino acids, and polysaccharides. Some of the main active compounds found in Aloe Vera include:

- Acemannan: a polysaccharide that has been shown to have immunomodulatory properties
- Aloin: a compound with laxative effects
- Anthraquinones: compounds with laxative and anti-inflammatory properties
- Barbaloin: a compound with laxative effects
- Polysaccharides: compounds with wound-healing and anti-inflammatory properties.

Aloe extract for injection described in the book "Medicinal substances" 2 part M.D. Mashkovsky, p 150.

Water extract from canned (aged at low temperatures in a dark place) fresh or dried aloe leaves (*Aloe aborescens*).

Aloe extract - liquid (sterile) from light yellow to brown-red color with a weak fruit odor; pH 5.0 - 6.8.

Aloe extract quality indicators are presented in Table. 2.2.

Table 2.2.

Indicator name	Permissible limits	Control methods
1	2	3
<u>Description</u>	Liquid from light yellow to yellow-brown with a specific smell. Note. It is allowed to have a hang, which during storage falls into precipitation, which when shaking the ampoule passes into a uniform curl.	Ac to p. 1
<u>Identification</u> <u>Barbaloine,</u> <u>Aloesin derivatives</u>	A. When viewed in UV light at a wavelength of 365 nm on the chromatogram of the test solution, a yellow spot should be found at the level of the yellow spot of the comparison solution (barbaloin), and a spot with bright blue fluorescence (aloesin derivatives) below the yellow spot.	Ac. p. 2A, SPU, 2.2.27
Anthracenopausal Aloe-emodine Natrium	<u>B.</u> When viewing the resulting solution in UV light at 365 nm appears yellow-green fluorescence. <u>C.</u> When viewed in UV light at a wavelength of 365 nm, a spot with red fluorescence should be detected on the chromatogram of the test solution. <u>D.</u> The drug gives a characteristic reaction to sodium.	Ac. p 2B For p 2C, SPU, 2.2.27 For p. 2D, SPU, 2.3.1.N
Indicator name	Permissible limits	Control methods
Anthracenopausal Aloe-emodine Natrium	<u>B.</u> When viewing the resulting solution in UV light at 365 nm appears yellow-green fluorescence. <u>C.</u> When viewed in UV light at a wavelength of 365 nm, a spot with red fluorescence should be detected on the chromatogram of the test solution. <u>D.</u> The drug gives a characteristic reaction to sodium.	Ac. p 2B Ac. p 2C, SPU, 2.2.27 Ac. p. 2D, SPU, 2.3.1.N
<u>Transparency</u>	The preparation diluted with water in a ratio of 1:5, the degree of turbidity should not exceed the reference solution IV.	Ac. p. 3, SPU, 2.2.1
<u>Optical density</u>	The optical density of the alcohol solution at a wavelength of 460 nm should not exceed 0.600.	Ac. p 4, SPU, 2.2.25

1	2	3
Indicator name	Permissible limits	Control methods
<u>Mechanical inclusions</u>	Must withstand tests.	Ac. p. 5, SPU, 2.9.20, KD 42Y-001-93
<u>pH</u>	From 0,5 till 6,8	Ac. p. 6, SPU, 2.2.3
<u>Volume extracted</u>	Not less than the amount of nominal volumes taken for testing.	Ac. p. 7, SPU, 2.9.17
<u>Sterility</u>	The drug should be sterile	Ac. p. 9, SPU, 2.6.1
<u>Bacterial endotoxins</u>	Less then 350 MO/ml.	Ac. p. 10, SPU, 2.6.14
<u>Abnormal toxicity</u>	The drug should be non-toxic	Ac. p. 11, SPU, 2.6.9
<u>Quantitative determination</u>	Not less than 0,0012% of the amount of gadroxyanthracene derivatives in the drug, in terms of barbaloin.	Ac. p. 12, SPU, 2.2.25

2.1.2. Characteristics of excipients

In order to substantiate the rational composition of vaginal suppositories used various bases and auxiliaries that are allowed apply in medical practice.

Witepsol H 32 (Witepsol H 32) - is a basis consisting of triglycerides of lauric and stearic acids.

In appearance - a brittle wax flakes. Witepsol is described in pharmacopeia of Europe and the USA. It is analyzed by the following indicators: saponification number, non-washable residue, iodine and acid numbers, hydroxide number, melting point, peroxide number.

The number of saponification of Witepsol H 32 is about 249. The content of the unaltered part does not exceed 0,3%.

Iodine and acid numbers, according to pharmacopoeia of Europe and the USA, are 3.0 and 0.07 respectively.

- The hydroxide number is 2,4, and the peroxide number is 0,1.

The number of saponification of Witepsol H 32 is about 249. The content of the unaltered part does not exceed 0,3%.

Iodine and acid numbers, according to pharmacopoeia of Europe and the USA, are 3.0 and 0.07 respectively.

- The hydroxide number is 2,4, and the peroxide number is 0,1.
- The melting point is determined according to the methodology described in the Pharmacopoeia of Europe, and it is 32.1 ° C.

Store Witepsol H 32 in well-packed cans, at a temperature of 15 to 25 ° C, in a place protected from light.

Tween-80 (TPA 42-1676-80) is a synthetic emulsifier that is a complex ester of oleic acid and polyoxyethylated sorbitane. Transparent oily liquid of yellow or brown-yellow color with a weak characteristic odor. Easy soluble in water, 96% alcohol, ethyl acetate, methyl alcohol, dissolved in corn and peach oils, almost insoluble in vaseline oil.

Density - from 1,060 to 1,100 г/см³, p H from 6,0 to 8,0.

2.2. Physical and chemical methods of research

Medicines for vaginal use are usually controlled by such quality indicators as are given in DFU 1.1 and DFU 1.2: description, identification, average mass and homogeneity of the mass, homogeneity of the content, decay, dissolution, melting point or time of complete deformation, accompanying impurities, microbiological purity, quantitative determination.

Description

Pessaries can have different shapes, usually egg-shaped with maximum diameter is not more than 1,5 cm. The weight of one pessary is usually within the range of 1.5 to 6.0 g [36]..

Appearance.

Before examination, rectal suppositories and pessaries should be taken out from packaging. They have by a smell, colour match the properties of the ingredients included in their composition. With unsatisfactory storage, rectal suppositories and pessaries may spread, solidify, dry or soften. These are signs of instability of medicinal form. Such dosage forms are not dispensed to the patient.

Average weight (2.9.5.)

Determination of the average mass is carried out according to article SFU 1.1 (2.9.5)

"Uniformity of mass for a unit of dosed drug." Twenty suppositories are weighed separately and the average mass is calculated. Medicinal product withstood the test, if not more than two individual masses deviate from an average mass of more than 5%.

Mass Uniformity (2.9.5)

Solid drugs in single-dose containers must withstand testing the uniformity of the mass for a unit of the dosed drug.

Mass uniformity test is not required if test homogeneity of the content is provided for all active substances.

Homogeneity of content (2.9.6)

If there are no other indications in a separate article, solid medicines in single dose containers with active ingredient content less than 2 mg or less 2% of the total mass must withstand tests for homogeneity content active substance in units of the dosed drug. If the drug contains more than one active substance, requirements applies only to those substances whose content meets the above conditions.

Melting Point (2.2.15)

For suppositories made on a lipohilic basis, determine melting point, which should not exceed 37 ° C, if there are no indications in a separate article.

Resistance to Destruction (2.9.24)

The test allows to determine the stability of suppositories and pessaries to destruction under certain conditions by measuring the mass necessary for their destruction by crushing.

This test is carried out for suppositories and pessaries on a fatty basis. The test is not applicable for hydrophilic-based preparations of the mixture type gelatin-glycerin. Tests are carried out for 10 suppositories or 10 pessaries.

CONCLUSIONS

1. In the development of the composition and technology of combined pessaries for the treatment of inflammatory gynecological diseases, active and auxiliary substances that are allowed for medical use in Ukraine were used.

2. The methods used for the analysis and quality control of pessaries are given in accordance with the current pharmacopoeia.

PART III. DEVELOPMENT OF COMPOSITION AND TECHNOLOGY OF PESSARIES WITH ALOE EXTRACT, ETHER OILS OF CHAMOMILLA AND TEA TREE,

Based on the study of the therapeutic activity of drugs for the treatment of BB, the following components were chosen: aloe extract, tea tree oil, chamomile oil [5,6, 7,10].

Aloe extract is a well-known biostimulant that promotes immunity, has also expressed antiseptic, bactericidal and reparative properties [12].

Chamomile oil essential, used by us as an object of study, is also often used in medical practice due to its pharmacological properties, namely: anti-allergic, antiseptic, analgesic, antipyretic, anti-inflammatory, antispasmodic, tonic and antidote. Chamomile oil is useful in solving female problems (cystitis, colpitis, vulvitis), especially associated with premenstrual and menopause syndromes.

Tea tree oil inhibits the growth of bacteria such as staphylococci, streptococci, pneumococci, gonococci, E. coli. Unlike antibiotics, it does not kill bacteria and viruses, but limits their growth and brings the amount to a limited-permissible norm, while simultaneously stimulating the human immune system. It is equally effective against gram-positive and gram-negative bacteria, yeast and fungi [10].

Taking into account the pharmacological properties of essential oils and their use in medical practice, we have carried out studies on the development of the composition of a complex preparation based on the essential oils of wormwood, chamomile, tea tree and aloe extract for the treatment of infectious and inflammatory diseases in gynecology [11, 12].

3.1. Research on the choice of suppository base

Samples of pessaries were prepared on the bases of different types (Table. 3.1).

The quality assessment of pessaries was carried out according to the following criteria: homogeneity, deviation from the average mass, melting point, hardening temperature, time of complete deformation for pessaries prepared on diphilic and hydrophobic bases, and dissolution time - using hydrophilic bases. In addition, the resistance of pessaries to destruction, prepared on all these types of bases, was studied. Research results are presented in Table. 3.2.

Table 3.1

Composition of bases for preparing of pessaries

Name of the ingredient	Quantity of the ingredients in base, g %									
	1	2	3	4	5	6	7	8	9	10
Witepsol H 15	50									
Witepsol W 35	50							74	90	90
Masupol		90								
Novata			100							
Hard fat type A				90						
Palm oil					60					
Rikemal SV-65					30					
PEG 400						10	20			
PEG 1500						90	80			
Cetostearyl alcohol								21		
Tween-80								10		
Emulsifier T ₁									10	
Emulsifier T ₂										10
Lanoline		10		10	10					

These pessaries are intended for long-term treatment, so the hydrophilic base (PEO 1500 and PEO 400) is not recommended due to significant osmotic properties.

According to the indicator of "homogeneity" pessaries based on № 1, 2, 3, 5, 6 and 7 (Table 6) showed unsatisfactory estimates, so further studies were not conducted for them. According to the "resistance to destruction" pessaries on the bases of № 2, 5, 9 and 10 do not withstand loads greater than 1.5 kg.

In accordance with the results of the research (Table. 3.2) pessaries, obtained using 4 and 8 bases, met the basic requirements for this dosage form.

Deviation from the average mass of all samples of pessaries did not exceed the allowable values.

On the samples of pessaries were determined quality indicators (Table. 3.2)

Table 3.2

Quality indicators of pessaries

Indicators	Suppository base									
	1	2	3	4	5	6	7	8	9	10
Homogeneity	–	–	–	+	–	–	–	+	+	+
Temp. float, °C	37,0	35,4	37,2	36,6	–	–	–	37,5	38,2	37,5
Temp. frozen., °C	28,3	26,5	27,6	29,3	–	–	–	28,0	29,5	29,8
Full time deformation, min.	12,0	8,5	9,0	10,5	–	–	–	8,0	10,0	9,0
Time solution., min.	–	–	–	–	–	35,0	25,0	–	–	–
Resistance to destruction *	+	–	+	+	–	+	+	+	–	–

Notice - * no lower than 1.5 kg

The most optimal in terms of physico-chemical and technological properties is the composition of the base № 8, which was chosen by us for further research. Pessaries based on № 8 have a light green color, the average mass is about 2.6 g, the cut is allowed air rod.

3.2. Basement of technology of pessaries

To study the influence of technological factors on the quality of the suppository mass, samples of pessaries were obtained according to the following scheme: cetostearyl alcohol (CSS) was melted and mixed with vitepsol; a given amount of essential oils were braved, then added to a semi-cooled molten base; last of all, aloe extract with tween-80 was introduced and mixed; the resulting mass was added to the molten semi-cooled suppository base; if they received a homogeneous suppository mass, it was poured into contour packaging from polyvinyl chloride film. As a basis used supercycle HAS, Vitepsol W 35 and Hard fat.

The procedure for the introduction of active substances into suppository bases was determined by their technological characteristics. For the choice of rational pessaria technology was obtained in the specified way, the difference was in the ratio of the components of the base -CSS and tween-80.

The temperature regime was chosen taking into account the melting point of the base of dairy substances and derivatographic studies of pesarium samples.

The mass uniformity and melting point according to the requirements and methods according to the State Fiscal Service of Ukraine 1.0, p. 2.15 were determined for the obtained pesarians.

The rate and time of mixing suppository mass was studied at the selected temperature ($38,0 \pm 1,0$) °C. Thermostatting was carried out using a thermostat UV-10 with an accuracy of ± 0.5 °C after 20 minutes from the start of the test, and then every 10 minutes. The appearance of the suppository mass was evaluated visually.

Organoleptic and physical characteristics of the studied samples of pesarii obtained on different bases are given in Table. 3.3.

Table 3.3.

Organoleptic and physical characteristics of pesarians obtained on different bases

№	Composition of base, %	Appearance		Homogeneity	Resilience, kg
		colour	odour		
1	Witepsol W 35 – 93; CSA – 4; tween-80 – 3	Greenish -blue	Specific	homogeneous	1,1
	Witepsol W 35 – 86; CSA – 8; tween-80 – 6	same	same	homogeneous	1,5
	Witepsol W 35 – 72; CSA – 16; tween-80 – 12	-//-	-//-	homogeneous	2,2
2	Supocir HAS –93; CSA – 4; tween -80 – 3	-//-	-//-	inhomogeneous (stratification)	_____
	Supocir AS –86; CSA – 8; tween -80 – 6	-//-	-//-	inhomogeneous statification)	_____
	Supocir HAS – 72; CSA – 16; tween -80 – 12	-//-	-//-	inhomogeneous (stratification)	_____
3	Hard fat - 93; CSA – 4, tween-80 – 3	-//-	-//-	inhomogeneous (stratification)	_____
	Hard fat – 86; ЦСС – 8; ТВІН -80 – 6	-//-	-//-	inhomogeneous (stratification)	_____
	Hard fat – 72; CSA – 16; tween -80 – 12	-//-	-//-	inhomogeneous (stratification)	_____

As can be seen from the data of Table. 3.3, pessaries made on the basis of supocyre and hard fat had a deformed shape, the separation of aloe extract and base was observed. Pessaries based on Witepsol had satisfactory organoleptic and physical properties, but suitable for further study were pessaries containing Witepsol, CSS and tween-80 in a ratio of 72:16:12, which determined the melting point (Table. 3.4).

Table 3.4.

Results of definition of melting temperature of pessaries

Base	Pure base (liter. ate), °C	Base + ether oils, °C	Base+ water extract of Aloe, tween-80 CSA, °C	Developed samples of pessaries, °C
Witepsol W 35 (Germany) + CSA+ tween-80 <i>in ratio -72:16:12</i>	35,5 ± 0,2	34,0 ± 0,2	37,0 ± 0,2	36,0 ± 0,2

Note: n = 5

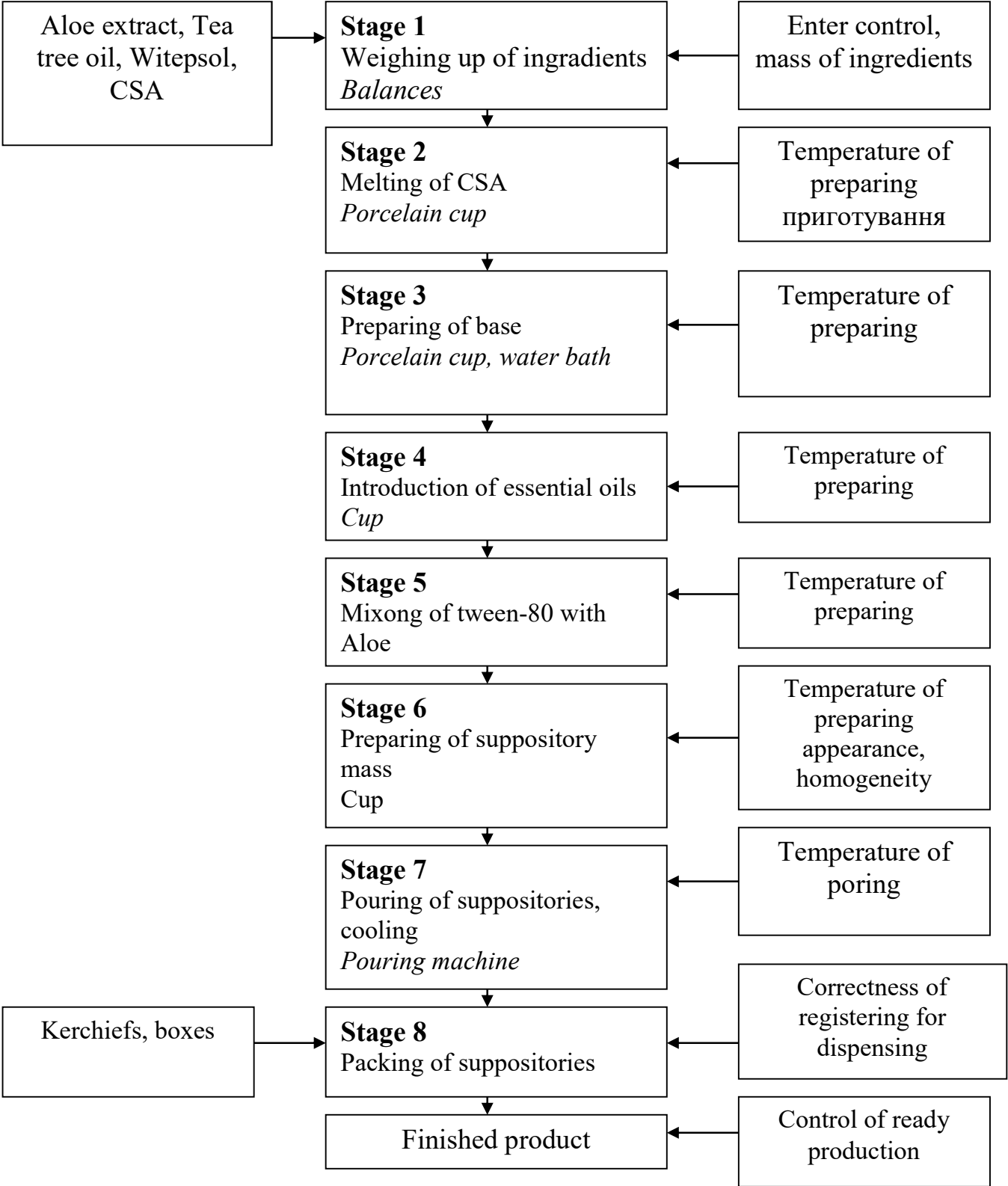
The obtained data indicate that the melting point of pessaries depends on the composition of components (essential oils, CSS), and especially on their number.

Taking into account the complex of research, we have developed a rational technology of pessaries (pic. 3.1).

Raw material, side products, materials

Preparing of pessaries

Quality control during preparing



Pic. 3.1. Technological scheme of pessaries with aloe extract, tea tree and chamomile oils on a hydrophobic basis i.

CONCLUSIONS

1. Experimentally grounded composition of pessaries based on a combination of natural substances (tea tree oil, chamomile oil and aloe extract) for the treatment of infectious gynecological diseases.
2. Based on physical and chemical studies, the rational basis of pessaries was chosen: vitepsol with the addition of cetostearyl alcohol and tween-80.
3. The optimal parameters of preparation of suppository mass of pessaries are substantiated.
4. The technology of pessaries has been developed, which ensures the production of the finished product of proper quality.

GENERAL CONCLUSIONS

1. According to the literature, bacterial vaginosis is detected in 64-80% of cases (modern information on etiology, pathogenesis and pharmacotherapy of inflammatory gynecological diseases is generalized).

2. According to the treatment regimen of infectious and inflammatory diseases (BV, colpitis, trichomoniasis), pharmacotherapy should be etiotropic, pathogenetic and symptomatic. When determining a mixed infection, medicines that act on concomitant pathogens are prescribed. In this regard, it is advisable to create combined dosage forms based on natural and synthetic substances.

3. The assortment of vaginal dosage forms of antibacterial and antiseptic action on the pharmaceutical market of Ukraine was analyzed.

4. Based on the research, the optimal composition and technology of extemporal pessaries production for the treatment of bacterial vaginosis was developed.

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APPENDIX

National University of Pharmacy

Faculty for foreign citizens' education
Department Drug technology

Level of higher education master

Specialty 226 Pharmacy, industrial pharmacy
Educational program Pharmacy

APPROVED
The Head of Department
Tatjana YARNYKH
“_28_” September 2022

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

Kabbaj ABDELMOUNAAIM

1. Topic of qualification work: «Development of composition of combined vaginal suppositories for application in gynaecology», supervisor of qualification work: Yuliia LEVACHKOVA, DSc, professor,

approved by order of NUPh from “28th” of April 2023 № 11

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

3. Outgoing data for qualification work: the work is devoted to the development of composition and technology of combined vaginal suppositories for application in gynaecology.

4. Contents of the settlement and explanatory note (list of questions that need to be developed): analyze and summarize the data of modern literary sources concerning the treatment of cough; to analyze the pharmaceutical market of Ukraine and establish the feasibility of creating medicinal products for the treatment of the corresponding pathology; on the basis of a complex of physicochemical and biopharmaceutical studies, to theoretically substantiate and experimentally develop a rational technology for obtaining a pesarii with essential oils and water aloe extract on a hydrophobic basis is substantiated; study the stability, conditions and shelf life of the study drug.

5. List of graphic material (with exact indication of the required drawings): Tables 9, pictures 2

6. Consultants of chapters of qualification work

Chapters	Name, SURNAME, position of consultant	Signature, date	
		assignment was issued	assignment was received
1.	Yuliia LEVACHKOVA, professor of higher education institution of department of drug technology	28.09.2022	28.09.2022
2.	Yuliia LEVACHKOVA professor of higher education institution of department of drug technology	17.11.2022	17.11.2022
3.	Yuliia LEVACHKOVA, professor of higher education institution of department of drug technology	19.12.2022	19.12.2022

7. Date of issue of the assignment: "28" of September 2023

CALENDAR PLAN

№ з/п	Name of stages of qualification work	Deadline for the stages of qualification work	Notes
1.	Choice of topic	september 2022 p.	done
2.	Analysis of literature resources	october 2022 p.	done
3.	Conducting experimental research	october-december 2022 p.	done
4.	Preparation and registration of master's work	january-march 2023 p.	done
5.	Submission of material	april 2023 p.	done

An applicant of higher education

_____ Kabbaj ABDELMOUNAAIM

Supervisor of qualification work

_____ Yuliia LEVACHKOVA

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 технології ліків			
Каббаж Абделмунаїм	Розробка складу комбінованих вагінальних супозиторіїв для використання в гінекології	Development of composition of combined vaginal suppositories for application in gynaecology	проф. Левачкова Ю.В. доц. Семченко К.В.

Підстава: подання Декана згоди 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**

№ 112720 від « 28 » квітня 2023 р.

Проаналізувавши випускну кваліфікаційну роботу за магістерським рівнем здобувача вищої освіти денної форми навчання Каббаж Абделмунаїм, 5 курсу, _____ групи, спеціальності 226 Фармація, промислова фармація, на тему: «Розробка складу комбінованих вагінальних супозиторіїв для використання в гінекології / Development of composition of combined vaginal suppositories for application in gynaecology», 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%****31%**

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ВИТЯГ З ПРОТОКОЛУ № 11

«28» квітня 2023 року

м. Харків

засідання кафедри технології ліків

Голова: завідувачка кафедри, доктор фарм. наук, професор
Тетяна ЯРНИХ

Секретар: канд. фарм. наук, асистент Світлана ОЛІЙНИК

ПРИСУТНІ: професор Тетяна ЯРНИХ, професор Олександр
КОТЕНКО, професор Юлія ЛЕВАЧКОВА, професор Ріта САГАЙДАК-
НІКІТЮК, доцент Марина БУРЯК, доцент Володимир КОВАЛЬОВ, доцент
Наталія ЖИВОРА, асистент Світлана ОЛІЙНИК, асистент Єлизавета
ЗУЙКІНА

ПОРЯДОК ДЕННИЙ

1. Про представлення до захисту до Екзаменаційної комісії кваліфікаційних робіт здобувачів вищої освіти.


СЛУХАЛИ: проф. Тетяну ЯРНИХ – про представлення до захисту до Екзаменаційної комісії кваліфікаційних робіт здобувачів вищої освіти.

ВИСТУПИЛИ: Здобувач вищої освіти 5 курсу групи Фм18(5,0д)-English 05 спеціальності 226 Фармація, промислова фармація Каббаз АБДЕЛМУНАІМ з доповіддю на тему «Розробка складу комбінованих вагінальних супозиторіїв для використання в гінекології» (науковий керівник: професор Юлія ЛЕВАЧКОВА).

УХВАЛИЛИ: Рекомендувати до захисту кваліфікаційну роботу.

Голова

Завідувачка кафедри, проф.



(підпис)

Тетяна ЯРНИХ

Секретар

асистент



(підпис)

Світлана ОЛІЙНИК

НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ**ПОДАННЯ
ГОЛОВІ ЕКЗАМЕНАЦІЙНОЇ КОМІСІЇ
ЩОДО ЗАХИСТУ КВАЛІФІКАЦІЙНОЇ РОБОТИ**

Направляється здобувач вищої освіти Абделмунаїм Каббаж до захисту кваліфікаційної роботи за галузю знань 22 Охорона здоров'я спеціальністю 226 Фармація, промислова фармація освітньою програмою Фармація на тему: «Розробка складу комбінованих вагінальних супозиторіїв для використання в гінекології»

Кваліфікаційна робота і рецензія додаються.

Декан факультету _____ / Світлана КАЛАЙЧЕВА /

Висновок керівника кваліфікаційної роботи

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

Керівник кваліфікаційної роботи

Юлія ЛЕВАЧКОВА

«12» квітня 2023 р.

Висновок кафедри про кваліфікаційну роботу

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

Завідувачка кафедри
аптечної технології ліків

Тетяна ЯРНИХ

«26» квітня 2023 року

Qualification work was defended
of Examination commission on

« » June 2023

With the grade _____

Head of the State Examination commission,

DPharmSc, Professor

_____ / Oleh SHPYCHAK /