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QUALIFICATION WORK

ON THE TOPIC: «RESEARCH ON THE DEVELOPMENT OF COMPOSITION AND TECHNOLOGY OF EXTEMPORAL SUPPOSITORIES WITH ANTIINFLAMMATORY ACTIVITY»

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ANNOTATION

Annalized and generalized literary data on the current state of pharmacotherapy of inflammatory gynaeciologigical diseases. Substantiated composition and technology of suppositories with , Doxicylcine hyclas, Liniment of synthomycine. 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. Testing of the indicators of the fragmented extemporaneous suppositories was carried out according to DFU methods.Developed and grounded rational technology for combined vaginal suppositories, containing doxycycline hyclate, syntomycin linen and a number of other APIs for use in the treatment of acute gynecological illnesses in gynecology

According to the obtained data, samples of suppositories preoared on Cacao butter in studies of quality indexes according to State Pharmacopoeia had sufficient indicators , so we selected this base as more rational.

The work is set up on 63 pages. Includes 11 tables, 6 pictures, 4 diagrams and 42 literature sources.

Key words: pessaries, Menthol, Doxicylcine hyclas, Liniment of synthomycine *, Bacterial Vaginitis, choice, suppository bases*

АНОТАЦІЯ

Узагальнено і проаналізовано дані щодо сучасного стану терапії запальних захворювань в гінекології.Обгрунтований склад і технологія супозиторіїв з Доксицикліну хіклат, лінімент синтоміцину та іншими АФІ на супозиторній основі гідрофобного типу з використанням емульгатора.. Проведено вивчення показників якості розроблених екстемпоральних супозиторіїв відповідно методикам ДФУ.

Розроблкно і обґрунтовано раціональну технологію комбінованих супо зиторіїв з доксицикліну хіклатом, лініментом синтоміцину та рядом інших АФІ для засто3ування в терапріі запальних гінекологічних захворювань в гінекологіію

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Робота представлена на 63 сторінках. Включає 11 таблицm, 6 малюнків, 4 діаграми та 42 літературних джерел.

Ключові слова:песарії, ментол, Доксицикліну хіклат, лінімент синтоміцину, бактеріальний вагіноз, вибір,супозиторні основи

CONTENT

LIST OF USED ABBREVIATIONS

BV – bacterial vaginitis

BAS – biologically active substances

CV – candida vulvovaginitis

GPP – Good Pharmaceutical Practice

SPU – State Pharmacopoeia of Ukraine

WHO – World Health Organisation

USP – United States Pharmacopoeia

INTRODUCTION

For today the more than half of patients that appealed to the gynaecologist suffers the used for setting fire diseases. It is illnesses of young sexually active women. Principal reason of origin of the used for setting inflammatory diseases are infections passed by a sexual way. A disease arises up at a sexual contact with the infected man [1].

Among the diseases of muliebrias inflammatory processes occupy the first place on frequency and meet in 60-65 % gynaecological patients. For the last decade among the women of many countries there is an increase of infections of vagina, that proof occupy the first place in the structure of obstetric-gynaecological practice. Bacillosiss of vagina are the most widespread diseases that meet in gynaecological practice. Their frequency in different populations hesitates scope from 30 % to 80 %. Among infectious diseases most widespread are disbiotic states (bacterial vafinitis, urogenital candidiasis), thrichomoniasis [1,2].

The infectiously-used for setting fire gynaecological diseases of muliebrias occupy the special place in the structure of general morbidity in the world. Their meaningfulness is predefined first of all by that all these diseases strike organs and tissues that touch a reproductive function and continuation of family on Earth [2].

Vaginal infections are a source of considerable morbidity among women.

Main reasons of infectious vaginitis are vaginal candidiasis, thrichomoniasis and bacterial vaginitis. Each of these disorders can cause unpleasant vaginal symptoms, and two the last are caused by complications from the side of overhead reproductive ways.

Thus, a necessity of further study of problem of vaginal infections is actual [2].

The successive decision of this problem will assist the improvement of reproductive health and quality of life of women.

Vaginal medicinal medicines have an important value and application in complex therapy of the mixed urogenital infections.

The increase of local influence on the hearth of defeat is reached by the use of medical forms of local action. From them most effective in gynaecological practice are pessaries (vaginal suppositories) [1,2].

For today, making of medicines in the conditions of pharmacies does not lose the value. The extemporal production of medicinal preparations does possible the individual going near patients, that allows to take into account the features of organism, flow of illness, symptomatology of disease and his stage. It is main principle and advantage of making of preparations of «ex tempore».

The aim of our work is development of composition and technology of extemporal combined suppositories for a treatment of bacterial vaginitis, thrichomoniasis and to the vulvovaginal candidiasis.

For the achievement of this aim it is necessary to solve next tasks:

- to generalize literary data in relation to the modern state of treatment of infectious vaginitis;
- to conduct the analysis of assortment of medical forms for vaginal application and vaginal medical forms ;
- to conduct research with the aim of ground of basis-transmitter;
- in theory and experimentally to ground composition and technology of vaginal suppositories for treatment of infectious vaginitis.

CHAPTER I

THE MODERN STATE OF PHARMACOTHERAPY OF INFECTIOUS VAGINITIS

1.1. Pecularities of biocenosis of vagina of woman

The normal microflora of vagina for the healthy women of reproductive age is characterized by the large variety of types of bacteria, the vital functions of that in a great deal depend on their capacity for adhesion (capabilities to stick) on the cages of vaginal epithelium of possibility of competition between them for residences and foodstuffs. The microflora of vagina of healthy women of reproductive age includes the wide spectrum of microaerofiles (what develop, in presence the small amount of oxygen), optional and obligate anaerobes(table. 1.1.)[2].

On a background all specific variety a leading place in a vaginal microcenosis is occupied by microaerofiles lactobacillus the number of that can reach at 109 KUO/of ml. Colomising of the mucous membrane of vagina, lactobacillus is taken participating in forming of ecological barrier and provide the same resistance of vaginal microcenosis [3,4].

The normal microflora of vagina provides so-called colonisation resistance of genital highway. Colonisation resistance is an aggregate of mechanisms that provide constancy of quantitative and specific composition of normal microflora. The same, a normal microflora prevents settling of vagina pathogenic microorganisms or excessive reproduction of conditionally-pathogenic microorganisms, that enter in the complement of normal microcenosis, and distribution of them outside the ecological niches.

A basic mechanism that provides colonisation resistance of vaginal biotope is a capacity of lactobacillus for acid formation.

Suckling acid appears in the process of destruction of hepatin of vaginal epithelium and determines the reaction of pH of vaginal content, that in a norm

presents 3,80 - 4,50 [5,6]. Lactobacillus product suckling acid in amounts sufficient for creation of the expressed sour environment of vaginal secret and, the same, hinder to reproduction of acidophobous bacteria [5].

Table 1.1.

Specific composition of microflora of vagina of women of reproductive age

Types of microorganisms		Frequency of secretions, %
Microaerofile bact eria	Lactobacillus of spp.	71-100
	Gardnerella of vaginalis	6-60
Obligate anaerobic gramme positive bacteria	Lactobacillus of spp.	5-30
	Peptococcus of spp.	30-70
	Mobiluncus of spp.	0-5
	Propionibacterium of spp.	To 25
	Clostridium of spp.	10-25
	Peptostreptococcus of spp.	80-88
	Bifidobacterium of spp.	12
Obligate anaerobic gram-negative bacteria	Bacteroidides of spp.	9-13
	Fusobacterium of spp.	14-40
	Prevotella of spp.	60
Optionally anaerobic gram-positive bacteria	Streptococcus of spp.	To 10
	Staphylococcus of spp.	To 10
	Enterobacteria of spp.	To 10
	Porphyromonas of spp.	31
	Corynebacterium of spp.	30-40
	E.coli	2-10
Genital mycoplasmes	U.urealyticum	2-15
	M.hominis	2-15
Yeast-like fungi	C.albicans	15-20

Bifid bacteria that enter in the complement of vaginal microcenosis as to the sort of Lactobacillus, belong to the flora of Doderlein. For the healthy women of reproductive age they appear with less frequency, in concentrations 103 - 107 КУО/of ml. As well as Lactobacillus, they belong to the oxyntic microorganisms and participate in maintenance in the vagina of subzero values of pH.

Bifid bacteria attach on the surface of ephithelial cages vaginas capable to product bacteriacines, lysocim, alcohols, that also provides to them participating in creation and support of colonisation resistance in a vagina in relation to conditionally-pathogenic and pathogenic microorganisms [5,7].

Peptostreptococcus is the third component part of flora of Doderlein. The amount of anaerobic cocci in vaginal separated presents 103-104 CUO/of ml. Without regard to that peptostreptococci fold part of normal flora of woman sexual path, it is often found out at septic abortions, endomethritis and all difficult flowing infections of female genitals. In an association with other anaerobic bacteria of peptostreptococci in great numbers cases distinguish at bacterial vaginitis.

Propionbacteria are commensals of human organism. Due to producting by them organic acids these bacteria can participate in support of colonisation resistance of vagina. Posess immunestimulating characteristics. Distinguished in amounts that in a norm does not exceed 104 CUO/of ml.

Pathogenic properties strictly anaerobic gram-negative bacteria related to their fermental systems. So in Bacterioidides fragilis found out hyluronidase, collagenase, fibrinolysines, proteases of immunoprotein and heparinase. B.fragilis own other factors of pathogenicity, for example, capsule polysaccharide. In addition, the bacteroids of group Fragili are able to product catalase, that allows them to resist to the action of peroxigen, that is produced by Lactobacillus. Different proteases and collagenases were found for the bacteria of sort of Porphyromonas. Proteases and fibrinolysine were found out also at the different types of sort of Provotella. Fusobacterium of necrophorum have ability to synthesize hemolisines and factors of aggregating of thrombocytes.

The amount of Gardnerel quite often arrives at 106 CUO/of ml in the investigated material. Gardnerels own the expressed capacity for adhesion on the surface of vaginal epitheolicites. G.vaginalis can product toxic biofoods, mucolytic enzymes and hemolisines that is also a leycotoxic factor [6].

In the vagina of healthy women of corinebacteria appear in an amount 104-105 КУО/of ml. Genital mycoplasmes, staphylococcuss meet in an amount not more than 104 CUO/of ml.

The amount of streptococci in vaginal separated considerably varies and from different data folds 104-105 CUO /of ml. Streptococci of type of S.agalactiae is able to cause the heavy diseases of breathing organs, meningitises, септицемії that quite often result in a lethal result.

Enterobacteria - E.coli, Proteus of spp., Klebsiella of spp., and also P.aeroginosa meet in an amount 103 - 104 CUO/of ml and can be reason of urogenital infectious diseases [7,8].

The fungi of sort of Candida are determined in an amount to 104 CUO/of ml, not causing pathological processes. The amount of yeast-like fungis can rise at pregnancy. It is bound to that at physiology suppression of cellular immunity that takes place for expectant mothers, that is sent to the exception of possibility of tearing away of fetus favourable terms are created for a height and reproduction of yeast-like fungis.

It is discovered that C.albicans has ability to register to vaginal epiteliocytes by means of the special surface structures, and also to produce a gliotoxin that is able to violate viability and function of human leucocytes [10,11].

Thus, bacteria are representatives of normal microflora of vagina closely co-operating inter se and with the cells of vaginal epithelium create and support high colonisation resistance of vaginal biotope, but sometimes can become reason of inflammatory processes of urogenital tract.

As a vaginal microflora except protective executes the row of other important functions - fermantal, vitaminizing, immunestimulating et al, it is usually examined as an indicator of the state of vagina [11,12,13].

1.2. Classification of vaginal infections, basic complications, symptoms and reasons of origin

For the last decade among the women of many countries there is an increase of infections of vagina, that persistently occupy the first place in the structure of obstetric-gynaecological diseases. Bacterial vaginal infections are the most widespread diseases that meet in gynaecological practice. Their frequency in different populations hesitates scope from 30 % to 80 %[11].

Among infectious diseases most widespread is disbiosis (bacterial vaginitis, urogenital candidiasis, chlamidiosis, trichomoniasis).

Such social processes, as urbanization of society, worsening of ecology, and also consequences of uncontrolled application of medications (first of all antibiotics) have a negative influence on a woman organism.

At general level of frequency of chlamidiosis, trichomoniasis, gonorrhoea and other sexual-transmission diseases an increase of infections of vagina is objected, that flows with participation of microorganisms from composition of normal microflora of vagina [13].

Infectious and inflammatory diseases of female genitals occupy the special place in the structure of general morbidity in the world. Their meaningfulness is predefined first of all by that all these diseases strike organs and tissues that touch a reproductive function and continuation of generation on the Earth.

About an infectious process in his modern understanding it is known from middle XIX of century of Him classic positions are set forth by Koch and L. Paster. Large payment in the study of these questions was done by I.F. Zemmelveis, D. Lister, and. A. Mechnikov [12].

In a practical venereology it is accepted to distinguish traditional "classic" venereal diseases: syphilis, gonorrhoea, lymphogranulomatosis venereal.

After classification of WHO in the second group the included diseases that is passed, mainly, by a sexual way, with the repressing defeat of genital organs: chlamydia infection, trichomoniasis, vulvovaginal candidiasis, mycoplasmosis, genital herpes, bacterial vaginitis [31].

It is known that the normal microflora of genital tracts at certain terms acquires pathogenic properties, and its representatives become the causative agents of row of diseases of bacterial etiology. The modern level of microbiology allowed to extend an idea about the state of microbiocenosis of genital tracts of woman and prove that oppression of normal microflora of vagina results in the origin of bacterial vaginitis (BV), urogenital candidiasis (UGC), heterospecific vaginitis [10].

The necessity of perfect study of this problem is predefined by not only wide distribution of BV and UGC, but also that they belong to the risk factors not only for a development of heavy infectious process of genitals, but also for foetus and new-born that gets a microflora in childbitrh.

Researches of the last years testify that 95 % all vaginal excretions related to such diseases: bacterial vaginitis, candida vulvovaginitis, cervicitis, Herpes simplex or Neisseria gonorrhoea. 3 groups of vaginal infections are for today known however, most widespread in the USA and Europe: bacterial vaginitis (BV), candida vulvovaginitis (CV) and trichomonas colpitus (TC) [11,12,13].

From official data, the symptoms of vaginitis meet in 10 million women. Modern data specify on the wide vibrations of indexes of morbidity of BV (from 20 % to 90 %), that, probably, predefined by the different populations of the inspected women, ambiguous interpretation of disease, application of various non-standard methods of diagnostics.

From data of E.F. Kira, BV meets for 24 % women in the structure of general gynaecological morbidity and in 87,7 % patients that apply concerning excretions.

The factors of origin of the used for setting fire diseases are declines of резистентності (to the resistibility) of organism of woman at somatic and infectious diseases, decline of endocrine function of glands to incretion (disease of ovaries of different nature, menopause, diabetes mellitus, obesity), violations of anatomic and physiological structure of vagina through the prolapsus of its walls [13].

An infectious defeat depending on localization causes inflammation:

- vaginas (colpitus);
- external paleceous of organs (vulvitis);
- large gland of vagina (bartolinitus);
- necks of uterus (cervicitis);
- internal shell of uterus (endomethritis);
- salpinxs (salpingitis);
- ovaries (oophoritis);
- walls of uterus (miomethritis);

Basic complications:

- ectopic pregnancy;
- chronoc pelvic pains;
- a sickliness is at sexual life;
- disfunction of ovaries;
- futility;
- usual unmaturing of pregnancy.

Reasons:

- infections passed by a sexual way (gonorrhoea, chlamydia infection, trichomoniasis, micoplasmosis, ureaplasmosis);
- paratherapeutic reasons (medical abortion, diagnostic curettement, introduction of BMC, gynaecological operations);
- chronic infectious diseases (tuberculosis, mycosis).

Basic symptoms (symptoms often become sharp under time or right after menstruation):

- pain is in the underbody of stomach;
- there is pain in area of appendages;
- fever;
- nausea and vomiting;
- acraturesis;
- plentful excretions are from a vagina (it can be with a smell);

- itch of external genital organs;
- there is tumoural education in area of appendages of uterus, external genitalia.
- hormonal contraceptives;
- local remedies (treatments of vagina, urethra.

1.3. Diagnostics of vaginitis

Adequate medicare at vaginal infections requires determination of specific, correct diagnosis. The most widespread types of medical errors are empiric diagnoses on the basis of anamnesis of patient or simple visualization of excretions and improper verification in the presence of infection, in particular on trichomoniasis, sexually active women without a clinical symptomatology.

Without regard to circumstance that bacterial vaginosis is the most frequent widespread infection empiric diagnosis that will be set by practicing doctors — zymic mycotic infection [13].

Although, to show out conformities to law in relation to appearance of the vaginal excretions bound by that or other infection, it is necessary to conduct a specific analysis, to confirm a diagnosis. The mixed infections happen.

For many women with bacterial vaginitis or trichomoniasis infection is asymptomatic and they can be diagnosed only by generally accepted screening.

A question of treatment of asymptomatic bacterial vaginosis is debatable, unlike the question of treatment of asymptomatic trichomoniasis, and that is why women with the diagnosis of trichomoniasis require advising and treatment. Clinical research of vaginitis is relatively rapid and inexpensive.

It foresees description of excretions, measuring of vaginal pH, realization of amic test and major — research of vaginal secret under a microscope [14].

It is important, that a test for measuring of pH was got from a vagina and, that it did not contain a cervical secret that usually more alkaline after the composition. Blood, sperm and recent syringing, also can influence on the result of this analysis. A test is inflicted on a pH-paper, and the got color is compared to the color table. The second vaginal stroke is used for a microscopy and amic test.

This test is conducted by solution and 10-percent solution of potassium, smell then, if to check in the presence of «fish» smell of amines, that, if it is, specifies in the presence of bacterial vaginitis or trichomoniasis [13,14].

Preparation from this solution is investigated at a 400-multiple increase in the presence of yeasts and/or pseudohyphals in the stage of reproduction, movable Trichomonade, leucocytes and «key cages» (flat ephithelial cages concealed by bacteria so that the outlines of cages become unclear).

An attentive researcher also will pay attention to amount and morphotype of vaginal bacteria. Leucocytes can be observed at vulvovaginal candidiasis or trichomoniasis. They also can be in a cervical secret that testifies to the presence of cervivitis.

In preparation and research of standard for a microscopy it is important to take the sufficient amount of material, namely such, that he was not too liquid at mixing with salt solution. Also it is sometimes needed to investigate one preparation more than, especially for the exposure of pseudohyphals of yeasts.

By the results of these simple analyses it is mostly possible to set a concrete diagnosis (table 1.2) [14].

Table 1.2

	Candida	Trichomonas	Bacterial vaginosis
pH of secretions	< 4.5	>4.5	>4.5
Smell of amine in mixture with a 10-percent KITTY	Negative	Often positive	Positive
Unfixed preparation with solution or 10-percent KOH	Leucocytes; fungi that propagate, and pseudohyphas	Leucocytes, movable trichomonade	«Key cages»
Colouring is after Gramme	Leucocytes, fungi and pseudohyphas	Leucocytes, it is possible to see unmovable Trichomonade	«Key cages», decreasing of lactobacillus, increase of – cocci and curved cocci (Mobiluncus), which have less changing colour by Gramm

1.4. Ethiology, pathogeny and clinical displays of vulvovaginal candidiasis

Vulvovaginal candidiasis is known from vaginal infections, especially among a population. Its prevalence, probably, caused by self-treatment antifungal preparations that are for sale without recipes, and advertisement, in the popular press. Many women assume an error, considering that their vaginal symptoms arise up through a zymic infection, or thinking of diagnostic error of doctor [14].

It is found out, that zymic infections present 20-30 % cases of vaginitis. The greatest prevalence of vulvovaginal candidiasis is on the third and fourth decade of life.

Yeasts can colonize a vagina approximately in 15 % women, and can also exist on a skin and in a gastrointestinal tract. Consider that the clinical symptoms of vulvovaginal candidiasis develop as a result of excessive reproduction of causative agents in reply to different starting mechanisms.

Terms that assist to development of vulvovaginal candidiasis include a diabetes mellitus, pregnancy, exogenous estrogenes, use of antimicrobial preparations of wide spectrum, immunosuppression and, maybe, sexual intercourse. Mostly a starting mechanism it is impossible to identify.

Candida of albicans is the variety of bacterium that causes a vulvovaginal candidiasis mostly, although this can be C. of glabrata or C. of tropicalis and rarely other varieties of Candida. A few different stamms of C. of albicans are able to cause an infection. For women with the repeated vulvovaginal candidiasis it usually the same stamm that remains in the organism of transmitter. Women with a vulvovaginal candidiasis do not have obvious changes of vaginal flora, Lactobacilla prevail in them [15].

The signs of vulvovaginal candidiasis are vaginal excretions and itch. Excretions are thick, white, «cheese like» and can stick to the mucous membrane, but such signs can prevail, as erythema, was swollen.

It is necessary to try to confirm a diagnosis the direct microscopy of vaginal excretions. The presence of pseudohyphals of Candida confirms a diagnosis [14].

They can be better detected at addition 10-percent KOH to the substance that destroys other cellular elements and bacteria. Maybe, it will be to investigate a few tests, to find out pseudohyphas, as a sensitiveness of these analyses is

suboptimal. Sometimes yeasts that propagate notice only, especially for patients from C. of glabrata. For patients with a vulvovaginal candidiasis vaginal pH < 4,5 and an amine test is negative, if there is not concomitant bacterial vaginosis or T.vaginalis [11].

As it is inflammation, often present leucocytes. The exposures of a few cages of yeasts on the unfixed preparation in default of clinical symptoms consider normal. The use of culture is necessary to be left for the special circumstances, for example for confirmation of clinical diagnosis in patients with a negative microscopy or with resistance to treatment of infection, when authentication and analysis can become in case on a sensitiveness.

The use of culture each time will result in hyperdiagnostics, as yeasts can colonize a vagina, not causing an infection [15].

Etiology, pathogeny and clinical displays of bacterial vaginosis

Bacterial vaginosis - is a disease quite was recently distinguished in a separate nosology form. It is determined as the infectious noninflammatory syndrome constrained from disbiosis of vaginal biotype, and characterized by massive reproduction of severely-anaerobic gram-negative bacteria and disappearance of H202-producing of lactobaccilli [7].

Simpy speaking there are dysbacteriosis vaginitises which are the states at that correlation of microorganisms is violated, that in a norm live in a vagina. Those that it must be anymore (lactobacilluss), becomes less than, and vice versa, those that in a norm it must be a bit propagate [7].

Gardnerella- one of those bacteria, that it must be less than, but not single. This pathological process is caused by the associations of anaerobic bacteria of Peptostreptococcus of spp., Bacteroides of spp., Mobiluncus of spp., Fusobacterium of spp., the debatable is remained by belonging of M. of hominis.

Thus, vaginosis is a not infection, as it is not possible to be infected, bacteria do not come from outside, it rebuilt but only. The feature of bacterioscopic picture at vaginosis is a small amount of leucocytes, as there is not a contagium and

inflammatory process. Absent and external signs of inflammation: turning of mucous membrane, edema, sanguifluousness red. Therefore this state is named vaginosis (disease of vagina), but not vaginitis (inflammation of vagina)[3,6,14]. It does not require treatment of partner. In a norm a sour, rich in oxygen environment friendly to reproduction of lactobacilluss is supported in a vagina. At the change of terms of environment (absence of oxygen and злужнення environment) lactobacilluss are ousted гарднерелами and by other bacteria that live in an alkaline environment [6,8].

From data of the Scientific center of Russian Academy of Medical Science, bacterial vaginosis appears in 24 % practically healthy women and for 61 % patients with the clinical displays of heterospecific colpitus, mainly in early reproductive age [1,3].

Different endogenous and exogenous factors can assist development of bacterial vaginosis.

Endogenous (internal):

• change of hormonal status;

• violation of menstrual cycle;

• decline of immunological reactivity;

• use of hormonal medicines, immunodepressants;

• violation of microflora of intestines, chronic diseases of intestines and other states that cause dysbacteriosis (a lactics come with a meal and live in intestines).

Exogenici (external):

• protracted reception of antibiotics;

• carried and concomitant inflammations of urogenital highway;

• carrying of densely adherent synthetic linen, fitting snugly synthetic trousers, id est creation of obstacle for penetration of oxygen, abuse of gaskets "on" every day and by tampons;

• the improper feeding is a defect in the ration of soul-milk foods that are a source milk - sour bacteria;

• frequent changing of sexual partner;

• the protracted use of VMC is with the aim of contraception (5 more than).

Clinical motion

Distinguish two variants of clinical motion of bacterial vaginosis: asymptomatic with clinical symptoms.

At asymptomatic motion the clinical displays of disease are absent at positive laboratory signs [2,14].

The second variant of motion is characterized: protracted (on the average 2-3), massive, thick, homogeneous, suckling or grey color by excretions, mainly with the odor nuisance of "rotten fish" (what arises up as a result of disintegration of amines that is produced by anaerobic bacteria).

The signs of inflammation are observed in the halves of patients, 50 % women grumble about a vulvovaginal irritation as an itch and heartburn, and also on the unpleasant feeling at sexual intercourse.

Possible complications at bacterial vaginosis: the recrudescent used for setting fire diseases of organs of the reproductive system and urinoexcretory ways; pathological fallopian bleeding; a height of complications is after operations on the organs of small pelvis and cescar section; a premature break of fruitful shells is at luing-ins; post-natal ендометрит; a decline of weight and appearance of pneumonia are in new-born

Etiology, pathogeny and clinical displays of trichomoniasis

On three principal reasons of infectious vaginitis of trichomoniasis is an only disease, it is well-proven in relation to that it is passed by a sexual way.

Trichomoniasis is not illness about that necessarily it follows to report, thus, the real amount of cases is unknown, but annually trichomoniasis diagnose in the United States at three million persons. Although given, got from doctors, testify that the amount of cases diminishes, some groups of population remain in earnest staggered.

For example, among the visitors of the specialized clinics from treatment of illnesses that is passed by a sexual way, prevalence of this disease arrives at over 25 %[16].

National research of indexes of morbidity and treatment witnessed that the cases of vaginal trichomoniasis met often, but higher indexes are observed on a south. Plenty of cases found out among Afroamerican women, however the almost two third of all visits of doctor from this problem are on white women. Infections are most widespread among young, sexually active women.

An infection is caused by a parasite Trichomonas vaginalis. Its survival is although registered on the articles of the general use, consider that a microorganism is passed exceptionally by a sexual way. The latent period of this infection is unknown, but research of in vitro shows latent period from 4 to 28 days. Trichomonas often discover at a gonorrhoea and bacterial vaginosis[17,18].

Women with the clinical displays of trichomoniasis grumble about vaginal excretions, itch and irritation. The signs of infection include a selection (42 %), smell (50 %) and edema or erythema (22-37 %). Excretions classic describe foamy, but actually foamy they are approximately in 10 % patients.

The color of excretions can change. Spotted colpitus («strawberry neck of uterus») is a specific clinical sign of this infection, but it is found out onlyby colposcopy, but not during an ordinary review. Other complaints can include a dysuria and pain down stomach, etiology last not clear [18].

Almost half of all women from T.vaginalis do not have symptoms. Thus, if not to inspect these women, a diagnosis will be skipped. The degree of the used for setting fire reaction on a parasite determines the seriousness of signs. Factors, that influence on the used for setting fire reaction owner-transmitter clear not enough, but this can be a concomitant vaginal flora, stamm and corresponding concentration of microorganisms present in a vagina. Asymptomatic infections can eventually grow into illness with a clinical symptomatology.

The most infected men do not have symptoms, but trichomoniasis can cause an ungonococcus urethritis [17,18].

1.5. Pharmacotherapy of vaginal infections. Assortment of medicines for treatment of vaginal infectious at the pharmaceutical market of Ukraine

Aim of treatment of vaginal infections - to pick up thread the normal microflora of vagina, restrain the height of microorganisms not peculiar to its microcenoisis.

Treatment of infectious vaginitis must be complex, etiotropic, nosotropic and symptomatic. At the exposure of the mixed infection appoint medicines that influence on concomitant causative agents.

Many methodologies are presently offered for the correction of vaginal microflora. Without regard to numerous methods, the searches of effective methodology of treatment are conducted and to this day.

Vaginal infections are brought together in a great deal after the external displays, all of them have different nature. And at all modern pharmacology of only medications it does not exist as yet from them. Each of vaginal infections requires a careful inspection, medical control and individual holiatry. These are, as a rule, antibiotics (for every infection is the group of antibiotics!). Local treatment: vaginal candles, creams, ointments. Physiotherapy is vaginal lasers with the special medicines[15,19,20].

Eubiotics are preparations that neutralize the indirect actions of antibiotics. And also immune correction for the increase of protective forces of organism, polyvitamines and prophylactic measures [20].

Having regard to the features of infections of woman paleceous of organs, it is possible to set forth requirements to ideal preparation for their treatment:

- The expressed operating is on vaginal Trichomonade and creation of high concentration of antimicrobial preparation in the centre of inflammation.
- Expressed operating on a gramme - and gramme + stick and coccal flora, anaerobes.

- Rapid clinical effect: liquidation of symptoms of inflammation is an itch, heartburn.
- Warning of height of fungi, including as a result of inefficient antibiotic therapy.
- Absence of influence is on a normal microflora and acidity of vagina.
- Absence of system adsorption that stipulates the indirect operating on organs and systems of organism of woman.
- Possibility of application for pregnant with the minimum operating on a fruit and on new-born in the period of feeding by a breast.
- Possibility of application for the women of the different age-related groups, and also at presence of concomitant pathology (disease of liver, blood, CNS, diabetes mellitus).

From the point of view of these requirements, the most expedient combination is composition: antiprotozoan + antibacterial antimicotic [21].

Vaginal infections mostly treat oneself medications that are entered in a vaginaThere are medical forms such as creams, suppositories, pessaries, tablets.

Practically, for treatment of vaginal infections are used such basic pharmacological groups: antiseptic and desinfectant remedies, synthetic anti-infectives, antibiotics, antimicotics, eubiotics and reparatives (table 1.3)[24,26,27].

Table 1.3

Pharmacological groups of medicines that are used for treatment of vaginal infections

№	*Pharmacological group*	*Active substances*
1.	Antiseptics medicines	Miramistine
		Chlorhexidine (Hexicone)
		Polycreulene
		Povidone-iodine (Betadine)
		Menthol
2.	Synthetic antibactial remedies	Metronidazole
		Ornidazole
		Furazolidone
		Chloramphenicole
		Ternidazole

3.	Immunomodulator	Polyoxydonium
		Interferonum F (Viferone)
		Meglumine acridonacetate(cycloferone)
		Sodium desoxyribonucleate
4.	Antibiotics:	
	Aminoglycosides	Neomycini sulfas
	Macrolides	Roxitromycine
	Lincosamides	Clindamycine
	Glucocorticosteroides	Prednisolone
	Penicillines	Amoxicilline and clavulone acid
	Tetracyclines	Doxycicline
	Phtorchinolones	Ophlocsacine
	Cefalosporines	Cephalexine
5.	Antimicotic remedies	Miconazolum

In practice presently most positively combinations of type of Metronidazole + showed oneself miconazole or ternidazole + Neomycinum + nystatine [27,28].

The use of 5-nitroimidazoles for treatment of infections of woman sexual sphere has old and well documented history and it is well-proven by the most corresponding profile of this group of antimicrobial remedies for the specific terms of their flowing. In particular, until now widely used in practice metronidasole became a founder it to the group of antimicrobial preparations as early as 1959. Its meaningful property is activity simultaneously in relation to microbes, fungi and more simple.

Having regard to high bioavailability (80-100 % at a peroral reception) there is not a wide necessity of the use of parenterally forms 5 - nitroimidazoles.

They are high-activity antimicrobic preparations that have the expressed operating on more simple, obligate anaerobe, some optional anaerobe [27].

In particular, active in a relation as грам-, so и gramme+: bacteroids (включая of B.fragilis), Clostidum (includingof C.difficile), Fusobacterium of spp.,Eubacterium of spp., Peptostreptococcus of spp., Peptococcus of niger, Gardnerela of vaginalis. Sensible also more simple (T.vaginalis, G.lamblia, L.intestinalis, Leishmania of spp.), and also E.coli, H.pilori.L

Local vaginal facilities conditionally can be divided on:

- combined and one-component.

- with a bactericidal or bacteriastatic action.
- antibiotics and antiseptics [27].

On the first stage, setting of the preparations with an antianaerobic action, sent to the decline of amount of anaerobic microorganisms, is recommended, on the second stage is setting of eubiotics with the aim of proceeding in a microbiocenosis of vagina. As known there are two basic ways of introduction of preparations :

- System, when preparation is entered per os, intravenously and intramuscular.
- Local (vaginal, rectal as creams, ointments, suppositories).

Advantages of local therapy: absence of system influence on an organism, minimal risk of by-reactions, simplicity and comfort of the use, absence of intra-indications (except individual unbearableness).

So at system application reliable:

- from the side of gastro-intestinal tract: unpleasant taste in to the mouth, pain in area of stomach, vomiting, diarrhea;
- from the side of the nervous system: main pain, dizziness, hypotaxia of motions, violation of consciousness, cramp, epileptic attacks;
- allergic reactions: сип, itch, photodermatitus;
- haematological reactions: лейкопенія, neutropenia;
- local reactions: itch, phlebitis then in/introduction, appearance or strengthening of excretions.

At local application frequency of side effects is less.

For today there is a wide assortment of preparations in different medical forms for treatment of vaginal infections. The most rational medical form are medicines of local action, that operate directly in the heart of infection.

By us the analysis of assortment of vaginal medical forms of antibacterial and antiseptic action was conducted at the pharmaceutical market of Ukraine (table 1.4).

Table 1.4.

Antibactial and antiseptic vaginal medicinal forms at the pharmaceutical market of Ukraine in 2023/ 2024 y.

№	Trade name	Active substance	Country, manufacturer
1	2	3	4
Vaginal suppositories (pessaries)			
1.	Betadine®	Povidone iodum	"EGIS" Pharmaceutical works Ltd (by the license of company "MUNDIPHARMA AG", Switzerland), Hungary
2.	Betadine	Povidone iodum	"Alkaloid AD - Skopje", Macedonia republic
3.	Vokadin	Povidone iodum	"Wockhardt Ltd", India
4.	Geksikon®	Chlorhexydine	LTD "Nischpharm", Russian Federation
5.	Ginezol 7	Econazolum	"Sagmel Inc."; "IDA (Instituto De Angeli)", USA/Italy
6.	Gino-pevaril®	Econazolum	Silag AG, Switzerland
7.	Gino-Travogen	Econazolum	"Intendis Manufacturing S.p.A." та "Schering S.p.A." department of company "Schering AG" for "Intendis GmbH", Italy/Germany
8.	Gravagin	Metronidasole	TD "Sperko Ukraine", t. Vinnutsja, Ukraine
9.	Dalacin	Clyndamycine	"Pharmacia & Upjohn Company" corporation "Pharmacia & Corporation", USA
10.	Ecaline	Econazolun	JAKA 80 Radovisch Macedonia, Macedonia
11.	Econasol-LH	Econazolun	LTD "Lekhim-Kharkiv", t. Kharkiv, Ukraine
12.	Zalain Ovules	Sertaconazoli nitratis	TERAMEX, Monaco
13.	Iodoxide®	Povidone iodum	LTD "Nischpharm", Russian Federation
14	Ketodine	Ketokonazole	TD "Sperko Ukraine", t. Vinnutsja, Ukraine
14.	Ketokonazole	Ketokonazole	Pharmaprim ,Republic Moldova
15.	Ketokonazole-LH	Ketokonazole	LTD "Lekhim-Kharkiv", t. Kharkiv, Ukraine

1	2	3	4
16.	Clindamycine	Clindamycine	Pharmaprim ,Republic Moldova
17.	Clotrimazol	Clotrimazole	Pharmaprim ,Republic Moldova
18.	Livarol®	Ketokonazole	LTD "Nischpharm", Russian Federation
19.	Macmiror Complex	Nifuratel Nystatine	"Doppel Farmaceutici S.r.L." for "Poli Industria Chimica S.p.A.", Italy
20.	Metromicon-neo	Metrinidasole Miconazole nitrtate	Pharmapri ,Republic Moldova
21.	Metrinidasole	Metrinidasole	LTD "Monpharm", t.Monastyrushe,Cherkass reg., Ukraine
22.	Metrinidasole	Metrinidasole	Pharmaprim,Republic Moldova
23.	Metronidasole– Darnitsa	Metronidasole	LTD "Pharmaceurical firm "Darnitsa", t.Kyiv, Ukraine
24.	Micogal	Omoconasole	"TEVA Pharmaceutical Industries Ltd" at the plant "TEVA Pharmaceutical Works Co. Ltd", Israel/Hungary
25.	Мікогал®	Omokonasole	JSC Pharmaceutical plant TEBA, Hungary
26.	Mico-penotranен	Miconazole nitrtate	"Embil Pharmaceutical Co.Ltd" for "Schering AG", Turkey/Germany
27.	Milagin	Clindamycine	TD "Sperko Ukraine", t. Vinnutsja, Ukraine
28.	Neo-penotrane	Metronidasole Miconazole nitrtate	"Embil Pharmaceutical Co.Ltd" for "Schering AG", Turkey/Germany
29.	Neo-penotrane forte	Metronidasole Miconazole nitrtate	"Embil Pharmaceutical Co.Ltd" for "Schering AG", Turkey/Germany
30.	Ovestine®	Estriol	"N.V.Organon" for "Organon Agencis B.V.", the Netherlands
31.	Osarbon	Osarsol Boric acid Dextrose	LTD "Nischpharm", Russian Federation

1	2	3	4
32.	Pimafucin®	Natamycine	"Yamanochi Pharma S.p.A." concern "Yamanouchi Europe B.V.", Italy/The Netherlands
33.	Povidine-LH™	Povidone-iodum	ЗАТ "Лекхім-Харків", м.Харків, Україна
34.	Povidone-iodum	Povidone-iodum	"Hemofarm", Сербія
35.	Primafungin	Natamycine	Pharmaprim,Republic Moldova
36.	Sinthomycine	Sinthomycine	LTD "Monpharm", t.Monastyrushe,Cherkass reg., Ukraine
37.	Flagil®	Metronidasole	"Haupt Pharma Livron" for "Laboratories Aventis", France
38.	Flureniside	Flureniside	LTD "Monpharm", t.Monastyrushe,Cherkass reg., Ukraine
39.	Chinofucine-LH	Chlorchinaldole	LTD "Lekhim-Kharkiv", t. Kharkiv, Ukraine
Vaginal tablets			
40.	Ginalgin	Metronidasole Chlorchinaldine Citric acid	"Merckle GmbH"/"ratiopharm GmbH", Germany
41.	Candibene	Clotrimasole	"Merckle GmbH"/"ratiopharm GmbH", ", Germany
42.	Candid-B6	Clotrimasole	"Glenmark Pharmaceuticals Ltd", India
43.	Кліон- Д 100	Metronidasole Miconasole	"Richter Gedeon Ltd", Hungary
44.	Clotrimasol	Clotrimasol	"Elegant India", India
45.	Clotrimasol	Clotrimasol	"Synmedic Laboratories", India
46.	Clotrimasol	Clotrimasol	ЗАТ НВЦ "Борщагівський ХФЗ", м. Київ, Україна
47.	Clotrimasol	Clotrimasol	"GlaxoSmithKline Pharmaceuticals S.A." for "GlaxoSmithKline Export Ltd", Poland/Great Britain
48.	Meratin Combi	Ornidazole Neomycine sulphas Nistatine Prednisolone	"XL Laboratories Private Limited";"Themis Medicare Limited";"Unimax Laboratories" for "Mili Healthcare Limited", India/India/India/Great Britain
49.	Metromisol	Metronidasole	"Elegant India",India

1	2	3	4
50.	Micowinax	Metronidasole Miconasol	"Mekophar Chemical Pharmaceutical Joint-Stok Comhany", Vietnam
51.	Pulsitexc	Tinidasole, Miconasol nitrate, Neomycine sulphas	Дженом Біотек Пвт. Лтд., Індія
52.	Trichopole®	Metronidasole	"Polpharma" Pharmaceutical Works S.A., Польща
53.	Fluomisine	Dequalinii chloride	Medinova LTD , Switzerland
Soft vaginal medicinal forms (gelsi, cremes)			
54.	Vagicin Zdorovja	Clindamycine	LTD "Pharmaceutical company "Zdorovja",t. Kharkiv, Ukraine
55.	Ginesol	Econazolum	"Sagmel Inc.", USA
56.	Ginofort	Butoconasole nitrate	"KV Pharmaceutical Co." for "Richter Gedeon Ltd", USA/Hungary
57.	Dalacine ™ Vaginal cream	Clindamycine	"Pharmacia & Upjohn Company" corporation "Pharmacia & Corporation", USA
58.	Candid	Metronidasole	"Glenmark Pharmaceuticals Ltd", India
59.	Macmiror Complex	Nifuratel Nistatine	"Doppel Farmaceutici S.r.L." для "Poli Industria Chimica S.p.A.", Italy
60.	Metrogil Vaginal cream	Metronidasole	"Unique Pharmaceutical Laboratories" (department of the firm "J.B.Chemicals & Pharmaceuticals Ltd"), India
61.	Septiclin	Chlorhexidine glucinate Cetrimide	"Pharma Synth Formulations Ltd.", India

Analysing the obtained data, it is set that the most of vaginal medical forms is folded by vaginal suppositories (pessaries) - almost 61 %, vaginal pills - 22 %, creams and gels - 12 %, capsules - approximately 3 %, and solution for vaginal

application and powders for preparation of solutions - for 1.00 % (pic. 1.1.). Pessaries fold a most fate from all medical vaginal forms, so as they are the most comfortable form of application and have the expressed local action.

Basis of the investigated nomenclature of preparations - 81 % form preparations of pharmaceutical companies of countries of Western Europe and India, only 19 % vaginal medical forms of production of Ukraine (pic. 1.2).

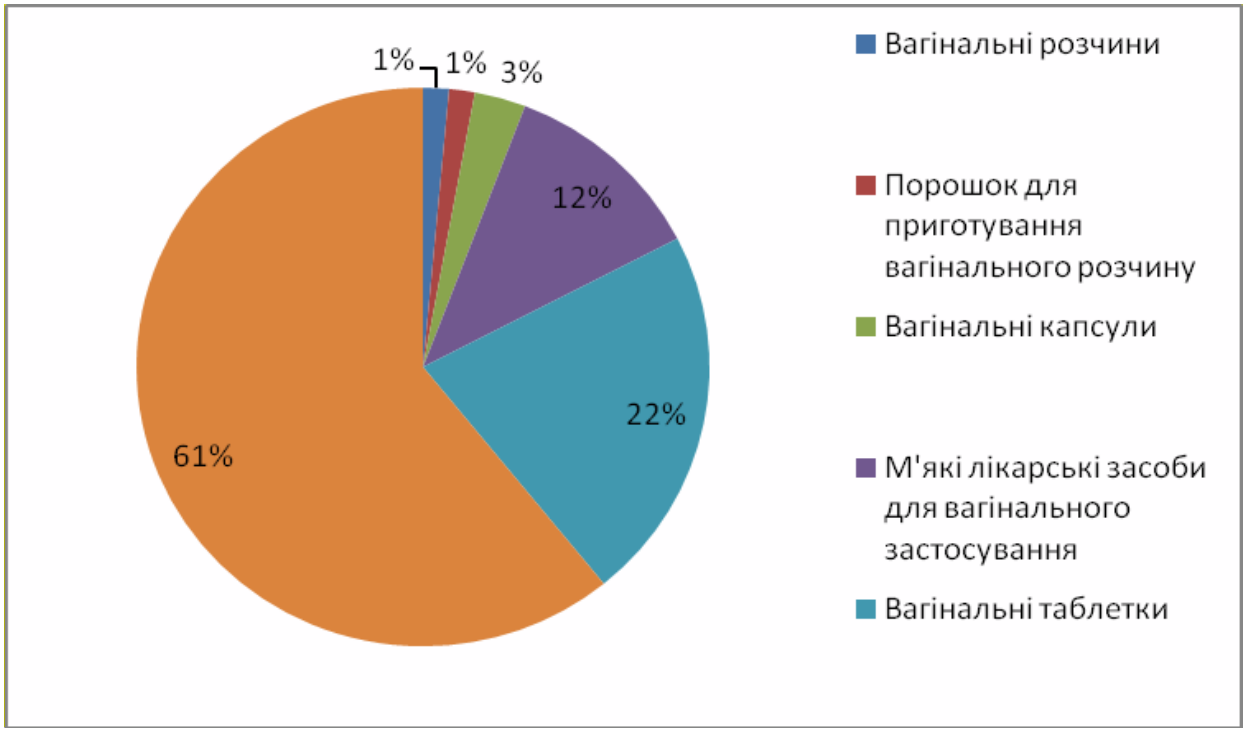


Рис. 1.1. Assortment of antibacterial vaginal medicinal forms at the pharmaceutical market of Ukraint 2022/2023 yy.

Preparation of choice for treatment of vaginal infections is metronidazole.

For today the assortment of medicines with metronidazole. is presented by mass of various medical forms : pills, capsules, vaginal suppositories, gel, cream, vaginal cream, and also solutions for injections and infusion solution.

Except metronidazole, for treatment of vaginal infections apply and other antibacterial preparations in dosages, corresponding to the height, mass of body. Antibacterial preparations or their combinations pick up taking into account a causative agent and its sensitiveness to antimicrobial medicines.

The unicity of antibiotics consists in that, unlike other most medicinal facilities, their target-receptor is not in tissues of human, but in the cell of microorganism [26].

Tetracyclines is one of early classes of antibiotics; the first from them were got at the end of 40-th of XX of century.

Classification of tetracyclines:

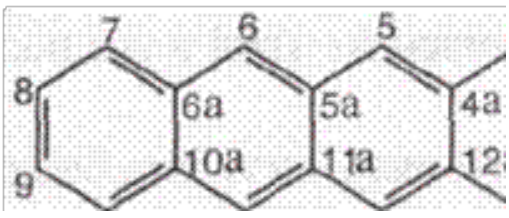
natural

- ✓ Dimethylchlortetracycline, Tetracyclinum, Oxytetracycline;

semisynthetic

- ✓ Metacycline (rondamycine), minocycline, doxycycline (vibramycine)
- ✓ Derivatives of minocyclines (glicylcycline).

In this group of preparations the incorporated preparations, in that basis of molecule is the fourcyclic condensed system that has the common name «tetracyclines».



Get the antibiotics of the Tetracyclinum row from the microorganisms of Streptomyces of aurofaciens Streptomyces of rimosus. In medical practice use natural Tetracyclines and their semisynthetic analogues. The antibiotics of this group own the general mechanism of action (oppression of biosynthesis is a

protein of microbal cage at the level of ribosomes), wide antimicrobial spectrum of activity [26,27].

Antimicrobial activity of Tetracyclin es

Gram-positive bacteria:

- S.aureus, S.epidirmidis, S.saprophyticus, S.pyogenes is a group And;
- S.pneumoniae, S.viridans;
- anaerobic cocci;
- spore-forming anaerobes - B.anthracis, C.perfringens, C.tetani, A.israelii;
- L.mono - cytogenes;
- other microorganisms.

Antimicrobial activity of Tetracyclines

Gram-negative bacteria:

- enterobacteria- E.coli, Enterobacter, Klebsiella, Salmonella, Yersinia spp., also Y.pestis, C.jejuni C.fetus, H.pylori;
- H.influenzae, H.ducreyi, M.catarrhalis;
- beta-lactamaforming stammes N.gonorrhoeae;
- B.pseudomallei, Stenotrophomonas maltophilia, Acinetobacter spp., Bartonella (Rochalimea) spp. (only Doxicycline);

Bacteroides (Prevotella spp., P.aknes, Fusobacterium spp).

Other microorganisms:

- Chlamidiya, Ureaplasma;
- Micoplasma (M.pneumoniae, M.hominis);
- Leptospirae spp., Borrelia byrgdotferi;
- Causative agents of typhus (R.prowazekii), Збудники туляремії (F.tularensis), plague (Y.pestis) [27].

Features of pharmakokinetics of Tetracyclines:

- Bioavailability of Doxicycline (93%) is higher, than Tetracyclinu's (70%);

- Tetracyclin are well distributed in tissues and liquids of organism (Doxicycline, having higherlipophylity, prevails Tetracyclinum on this index); [29].
- Distinguished from an organism with urine;

A place of Tetracyclines is in antimicrobial therapy

Testimony:

- ❖ Plague, rabbit-fever, anthrax, cholera, риккетсіози (spotted fever, turning typhus, and other),
- ❖ Leptospirosis;
- ❖ Chlamiduosis;
- ❖ Gynaecological infections (only Doxicycline).

They are active in relation to practically all gram-positive flora, gram-negative cocci (including gonococci), collibacillus, клебсієлли. To them highly sensitive chlamydiae, спірохети, лептоспіри, actinomycetess, and also very actual lately and mycoplasmes.

At the use they are well sucked in, thus Doxicycline is better than Tetracyclinum. Bioavailability of Doxicycline does not change, and to Tetracyclinum — in 2 times goes down during taking food. The maximal concentrations of preparations in the serum of blood are achieved in 1-3 hours after the use. At intravenous introduction most concentrations in blood are arrived at quicker than at a peroral reception [27].

Tetracyclines are distributed in many organs and environments of organism, thus Doxicycline (hydrochloride and monohydrate) forms the greatest tissue concentrations, than Tetracyclinum. A concentration in a neurolymph folds a 10-25 % level in the serum of blood, concentration in a bile — in 5-20 higher than in blood.

Important is circumstance that Tetracyclinum owns high ability to pass through a placenta, and also it is good to get to pectoral milk.

Application of preparations of group of Tetracyclinum not the uncommon causes indirect action:

- GST is stomach-aches or discomfort, nausea, vomiting, діарея;

- CNS is dizziness, at the protracted use is an increase of intracraneal pressure;
- a liver is a hepatotoxicity. Factors of risk: initial parafunctions of liver, pregnancy, rapid intravenous introduction, kidney insufficiency;
- allergic reactions are hives, anaphylactic shock.

Tetracyclines are forbidden for use for children of 8 yaers and till 8 (according to some dates — till 12 years), during pregnancy and lactation, at liver and kidney pathologies with expressed functional insufficiency[26].

However Doxicycline on occasion can be used and for patients with kidney insufficiency, as for these patients the basic way of his egestion is a gastrointestinal tract.

Taking into account a not uncommon presence also and non-sporecreated of anaerobic flora, expedient combination of Tetracyclinum with imidazoles (metronodazole) in corresponding doses [15].

Discussing the question of the use of preparations of group of Tetracyclinum in gynaecological practice, quite often it is possible to hear the idea of their insufficient efficiency, toxicness, not uncommon by-effects, presence of new, more effective and more safe antibiotics [27].

However on occasion however it will be for a number of reasons to give advantage to these old, but quite not forgotten and effective enough medicines that are the standard of WHO, to the receipt of results of bacteriologic examination with determination of sensitiveness to concrete antibacterial preparations, presence of sensitiveness of microflora only to Tetracyclinum, and also them not high cost.

At the careful study of contra-indications to the use and realization of the above-mentioned additional measures of the use of antibiotics of group of Tetracyclinum is rational and effective enough. In truth: «Novos of amicus dum paras, veteres cole» (Acquire «new friends, and old do not forget», lat.).

1.6. Extemporal medicines for the treatment of vaginal infections

For today suppositories and pessaries remain one of the most perspective hard medical forms due to the advantages, such as rapid delivery of medicinal substances, decline of risk of indirect action and others like that.

Medicines for vaginal application (vaginal medicinal forms) can be liquid, soft or solid and intended for application in a vagina with the aim of providing of local action. They contain one or more active substances in corresponding basis.

Containers for vaginal medicinal facilities must answer the requirements of the articles the «Materials used for the production of containers» (3.1. but subdivisions) and « Containers» (3.2. but subdivisions).

Medicinal facilities for vaginal application can be classified as:

- pessaries;
- vaginal tablets;
- vaginal capsules;
- vaginal solutions, emulsions and suspensions;
- tablets, for preparing vaginal solutions and suspensions;
- soft medicinal forms for vaginal application;
- vaginal foam;
- vaginal medicinal tampoos.

Vaginal suppositories can be spherical (marbles) - globuli;
egg-formed (ovules) - ovula or as a flat body with a rounding end (pessaries) - pessaria. Their mass must be from 1,5 to 6,0 g.

Pessaries are solid onedose medicinal forms. They can be of different form usually egg like; on volume and must correspond to vaginal application consistency.

They contain one or more operating substances, dispersed or cut-in into suitable basis that can dissolve in water or to melt at the temperature of body. In the complement of pessaries, if necessary, auxiliary substances can enter, such as adsorbents, surface-active substances, antimicrobial preservatives, and also dyes

settled to medical application [33]. At treatment of gynaecological diseases an important role is spared to traditional antibacterial therapy that in most negative cases causes the origin of allergic displays, resistency to antibiotics of different types of stamms of microorganisms, and also violation of normal vaginal biocenosis [13].

Therefore the choice of preparations for treatment of the used for setting fire gynaecological diseases remains a difficult task especially for expectant mothers.

Most rational for a treatment of sexual sphere are vaginal medical forms advantages of that are the direct operating on infestants and high intensity of penetration of operating substances to surrounding tissues.

Therefore in the world the nomenclature of suppositories and pessaries of extemporal preparation grows intensively, and their technology requires permanent perfection.

At the same time, an assortment of extemporal pessaries of antiinflammatory, antimicrobial, spasmolytic action for application in obstetrics and gynaecology is insignificant.

In Ukraine only every twentieth pharmacy makes preparations after the individual samples of prescriptions. This index of much more behind from the indexes of other countries of Europe and world. So, for example, in Germany, Australia and Great Britain, all pharmacies prepare medicinal remedies[13].

We conducted analyses of assortment of pessaries «ex tempore», which prepare in Kharkov (t. Kharkov, pharmacty № 9) and «Pharmacy of medicinal academy» t. Kruviji Rig for a treatment of inflammatory gynecological diseases.

In this division the extemporal compounding is presented for treatment of the used for setting fire gynaecological diseases (table 1.5) [42].

Table 1.5

Extemporal prescriptions

Prescription	**Application**
Sol. Methyleni coerulei 3 % (4 %) 100 ml	For smoothing vulva and vagina
Natrii tetraboratis 5.0 Glycerini 100.0	For smoothing vulva and vagina
Ac.borici 200.0	For sitting baths
Camphore 0.5 Zinci oxide 2.5 Talci 47.0	Powder for external use
Sol.Argenti nitratis 10 ml	For washing vulva
Cocaini hydrohloridi 1.0 Lanolini Vaselini aa 10.0	Ointment
Cocaini hydrohloridi 0.3 Mentholi 0.5 Phenilii salicylatis Ol. Olivarum aa 2.0 Lanolini	Ointment
Sol.Synoestroli oleosae 2% 1 ml Ol. Vaselini	For vaginal tampoos
Benzilpenicillini-natrii 200 000 ED Vaselini 60.0	For vaginal tampoos
Streptocidi subtilissimi 10.0 Ol. Jecoris Aselli 100.0	For vaginal tampoos
Tannini 5.0 Glycerini 100.0	For vaginal tampoo
Protargoli 7.5 Glicerini 50.0	For vaginal tampoo
Sol. Protargoli 3 % (5 %) 100ml	For vaginal bath
Osarsoli Streptocidi Glucosi Ac. Borici aa 0.3	For application into vagina
Furasolidoni 0.25 Sacchari 100.0	For application into vagina
Furasolidoni 0.004 Ol. Cacao 1.0	Rectal suppositories
Ac. lactici 100.	For syringing
Ac. Borici 50.0	For syringing

Aethacridini lactatis	For syringing
Tannini	For syringing
Natrii hidrocarbonatis	For syringing
Sol. Zinci sulfatis 25 %	For syringing
Sol. Kalii permanganatis 5 %	For syringing
Doxycyclini 0.100 Synthomicini liniment 10 % 0.25 PEO (9:1)	Pessaries
Doxycyclini 0.100 Dimexidi 0.02 Mentholi 0.01 Adeps solidus ad 3.00	Pessaries

The conducted researches showed that mostly in the complement of pessaries for treatment of vaginal infections enter:

- antibiotics (doxicycline, benzylpenicilline);
- antiseptics and desinfectant facilities (potassium permanganate, zinc sulfate, boric acid, aethacridine lactat, furazolidone, Protargolum, Collargolum);
- Sulfanilamidum preparations (streptocide);
- hormonal preparations (solution of synestrol).

The analysis of the extemporal compounding showed that most often doctors write recipes in the complement of that doxicycline hiclate, dimexidum, liniment of synthomycine, Mentholum.

Therefore the prescription of extemporal medicine, in the composition of which was doxicycline hyclate.draw our attention.

Select substances own next pharmacological properties (table 1.6) [26].

Table 1.6

Active substance	*Pharmacological activity*
Doxicylcine hyclas	A bacteriostatic activity is in the relation of gram-positive and gram-negative microorganisms
Liniment of synthomycine	Antiinflammatory, antimicrobial action
Dimexide	Antiinflammatory, analgetic, antimicrobial action, antiseptic
Menthol	Antiseptic action, analgetic

Doxicycline is an antibiotic from the group of Tetracyclinum. Preparation is well-known to each "Tetracyclinum" shows by itself natural substance, formed in the wild by the special type of fungi.

Active part of molecule of Tetracyclinum is distinguished and modified by means of difficult chemical synthesis, as a result appears fundamentally new biologically active substance, new antimicrobial preparation - it and there is Doxicycline.

Therapeutic activity excels activity of natural Tetracyclinum notedly, a chemical synthesis allows to obtain the high degree of cleaning of preparation and appearance for it new, very useful properties. As a result of it are new possibilities of the use and considerable diminishing of negative reactions toxic and allergic.

Amount of bacteria the height of that is actively repressed Doxicycline, very large - not for nothing it is attributed to the so-called antibiotics of wide spectrum by actions.

Value of such preparations in general and Doxicycline in particular, as one time and consists in that the same illness, for example fever of lungs, can be caused by hundreds of the most various bacteria.

In a situation, when a diagnosis is set, and causative agent the unknown, wide range of action of doxicycline acquires the special meaningfulness, repeatedly diminishing the risk of malpractice.

Probability of development of effects characteristic for Tetracyclinum, at the use of Doxicycline diminishes in several times.

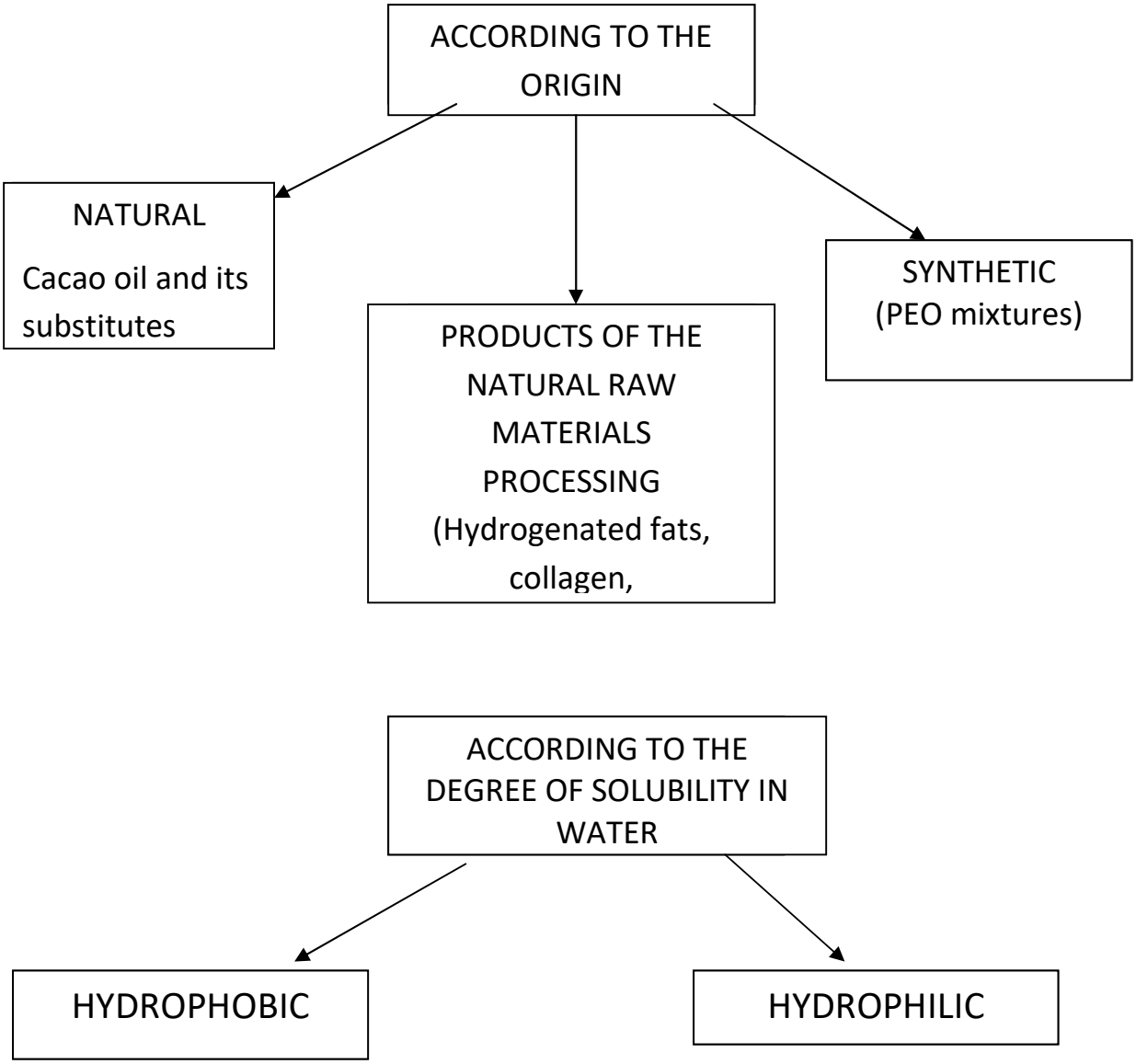
An allergy is possible, but risk of it, in comparison, for example, with the antibiotics of penicilline or cefalosporine groups, less than far.

Given the sample of prescribing of pessaries is prepared on hard fat by the method of pouring out.

1.7. Description of suppository bases and their classification

As main bases for preparing of soft medical forms in accordance with pointing of SPU X apply oil of cacao, animal, hydrogenated fat, lanole, alloys of

the hydrogenated fats with a beeswax, spermaceti, deresinated ozocerite, hard paraffin and different emulsifiers, gelatine-glycerine and soapily-glycerin gels, polyethyleneoxides and other substances.



Scheme 1. Classification of suppository bases

Medicinal substances, being therapeutically an active component, determine medical maintenance of setting of ointments, liniments and suppositories.

In a quantitative relation this group folds less part of medical forms usually.

Basic part of medical form is basis that provides a necessary volume and consistency.

Between medicamental part of medicines and its basis there is very difficult cooperation that forces to examine basis not as inert transmitter of medicinal

substances, but as important backer-up of maximal therapeutic action of medicinal substance.

Therapeutic efficiency is determined by various reasons.

It is set for certain, that a the same medicinal substance that is used in composition of soft medicinal form can do quite will cut on force of display a therapeutic action in dependence not only on that, how it is entered in medicines, but also from that, what basis it is applied with.

Next to active influence on the display of therapeutic action of medicinal substances of basis also influence on their stability during maintenance.

Receipt of proof forms that is well kept, maybe only at the use of bases, that own sufficient chemical indifference and firmness to influence of light, air, moisture, microorganisms, temperature factors and does not own the expressed ability of aging.

Between a medicinal substance and basis there are difficult mutual relations that does not allow to examine it as an inert transmitter.

The choice of ointment basis depends on physical and chemical properties of applied medicinal remedies.

For preparation of pessaries bases that have specific features must be used. To suppository bases are made next requirements [39]:

- sufficient hardness at a room temperature and ability to melt (whether to dissolve) at a temperature not higher than 37 °C, its ability sharply to go across from the hard state to the liquid, passing the stage of softening influence – ointment stage;
- to own sufficient viscidity, absence of smell, to provide a maximal contact between medicinal substances and mucous membrane;
- to be chemically and pharmacological indifferent;
- not to have an irritating action;
- not to change under the action of external factors (light, heat, moisture, oxygen, microorganisms);

- ability of easil acquiring a corresponding form, interfuse with the as possible greater amount of medicinal substances, not cooperate with them and be proof at storage;
- ability of easily free medicinal substances, to assist the display of them pharmacological action, that depends both on properties of bases and from the method of introduction of medicinal substances in basis;
- to own corresponding rheological indexes and optimal structurally - by mechanical properties.

At quality of fatty bases control determination of temperature of melting, acid and iodic numbers (they must not exceed the values set for these bases), test is foreseen on absence of extraneous admixtures.

Their hardness and plasticity have a very important value for quality of bases, the comfort of introduction of супозиторіїв prepared on these bases depends on that. Depending on the sources of receipt of ointment basis and their component subdivided into *natural and synthetic.* Bases, that are various synthetic or semisynthetic substances or their mixtures both one of one and with natural substances, are included in the last group.

After chemical composition bases are divided into *ethers of glycerin with higher fat acids, difficult ethers of these acids with high molecular monoatomic alcohols, high molecular hydrocarbons and their amines, inorganic connections, polysaccharidess* and other

The most characteristic sign must be fixed in basis of classification, that allows to unite substances in an only, organically constrained group. Such characteristic sign for all substances or compositions of bases is their ability to co-operate with water. For intensities of cooperating with water all bases divide into three groups: *hydrophobic, hydrophilic and diphilic.* Such classification is considered most rational. It is accepted in SP XI. *Hydrophobic* bases have brightly expressed lipophility, ability, as a rule, fully to interfuse with fats, by fatlike substances or to dissolve in them. Exceptions from this rule are liquids and behave to the digit of incompatibilities. So, for example, oil castor badly interfuses with hydrocarbons. Characteristic property of this group of bases - they are unmixed

with water and not emulsifying her, if not to count those small amounts of water or water solutions, what of them can retain due to the viscidity. *Hydrophilic* bases: gels of high molecular carbohydrates and albumens (ethers of cellulose, starch, gelatin, agar), gels of inorganics (bentonoites), gels of synthetic highly-molecular connections (polyethyleneoxide, polyvinilpirrolidone, polyadenitis) and etc. Characteristic property for this group of bases is the active cooperating with water: they or interfuse with it without restriction, or moisten or swell in her.

Diphilici (lipophilic-hydrophilic) base is waterless alloys of lipophilic bases with emulsifiers (alloy of vaseline with a lanolin or with other emulsifiers). Emulsive bases of type w/o (mixture of vaseline with an aquatic lanolin, consistency emulsion water/ vaseline and other) and o/w the natrium use as emulsifiers, potassium, twin-80 and others Offered classification gives an opportunity clearer to characterize properties of ointment bases, important in a technological relation, helps to do more correct choice of basis depending on physical and chemical properties of medicinal substance, to define the method of her introduction. In this time for making of suppositories the large assortment of bases that differentiate physical and chemical properties is used. they can be divided into two groups: hydrophobic and hydrophilic. At the international pharmaceutical market suppository bases of different character are presented. The most widely used suppository bases are witepsol, polyethyleneoxide basis and hard fat a pastry cook.

Hydrophobic suppository basis of synthetic origin of witepsol brands of H, W, S, E is more by the often used basis in modern technology. Basis is indifferent, well emulsifies hydrogens solutions, consonant with a number of medicinal substances. The lack of this basis is possible fragility of prepared suppositories.

Polyethyleneoxide basis belongs to hydrophilic synthetic bases. Suppository basis is got by combining of polyethyleneoxides (PEO) with different molecular mass that varies from 200 to 40000. These bases have such basic defects: large osmose, that results in dehydration of mucous membrane in the place of introduction, decline of speed of suction of medicinal substances, incompatibility with a number of medicinal substances.

Hard fat is a pastry cook types And, In, C, E is semisynthetic hydrophobic basis that is used for making of suppositories with hydrophobic substances. To the lacks of the indicated basis незмішуваність with hydrophilic medicinal substances and noticeable decline of temperature of melting of prepared супозиторіїв belong at addition of medicinal substances as water and oil-bearing solutions.

Suppository bases marked below have a semisynthetic or synthetic origin and can cause the unpleasant feeling at application or entail allergic reactions for patients, while suppository bases of natural origin do not have such consequences of application.

Oil of cacao belongs to natural hydrophobic bases and it is considered during many years the best basis of natural origin.

Basis is got from the toasted and cleared seed of chocolate tree (Theobroma Cacao, Streculeaceae) the method of the hot pressing.

Oil of cacao has certain advantages: well interfuses with different medicinal substances, quickly frees the entered medicinal substances, has the clearly expressed temperature of melting and high plasticity, and also has expressed reparative and oiling action.

A beeswax is the natural product of beekeeping, contains unique combination of active substances, including macro and microelements, vitamins, vegetable resins, polysaccharidess, amino acid, phenols of phytogenous, tannine substances and glycosides. Quality composition of beeswax stipulates its moderate antiinflammatory, reparative and anesthetizing properties. In composition of suppository basis beeswax also comes forward as compactor.

Conclusions

1. One of most widespread obstetric - gynaecological diseases there are vulvovaginal infections, among what 30 - 50 % occupies bacterial vaginitis, vulvovaginal candidiasis 20 - 30 %, thrichomoniasis over 25 %.
2. Basic pharmacological groups for a treatment of vaginal infections are: antiseptics and desinfectant remesdies, synthetic anti-infectives, immunomodulators, antibiotics, antimicotics, eubiotics and reparants.
3. As a result of analysis of assortment of vaginal medical forms of antibacterial and antiseptic action at the pharmaceutical market of Ukraine, it is set that preparations of native production fold 19 %, countries of Western Europe and India - 81 %.
4. The home assortment of vaginal medical forms is presented by preparations of 5th pharmaceutical enterprises: joint-stock company of «Lekhim-Kharkiv», Kharkiv; СП of «Sperko" Ukraine», Vinnytsya; BAT of «Monpharm»,, Tcherkasy region, Monastyrische; Joint-stock company is the «Pharmaceutical firm »Darnytsia«, Kyiv; LTD. is the Pharmaceutical company »Health«, Kharkiv, Ukraine.
5. On the basis of the got results, it is set that creation of native antibacterial and antiseptic means for treatment of bacterial vaginosis, candidiasis and trichomoniasis in a form of pessaries is perspective.

Chapter II

OBJECTS AND METHODS OF RESEARCH

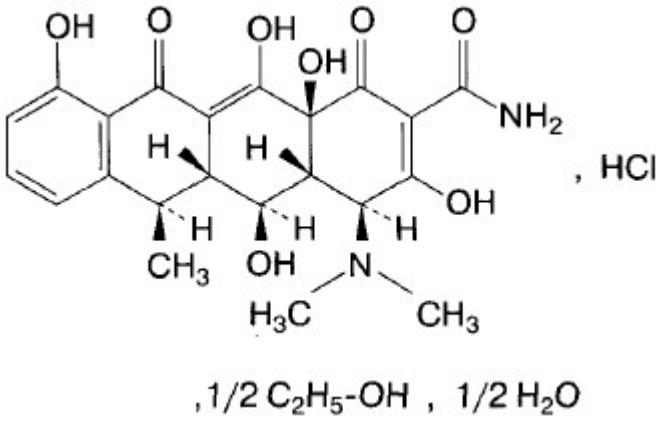
For the development of composition of extemporal prescription of combined vaginal pessaries medicinal substances that are permitted to application in pharmaceutical and medical practice were used.

Development of composition of this medical form is based on the study of physical and chemical properties and structural and mechanical researches.

2.1Objects of researches

2.1.1. Characteristics of active substances

Doxycyclini hyclas



Doxycycline is described in SPU 1.1 p. 329 [33], EP 4.1 [37] and other pharmacopeias.

Molecular mass 512.9 g/mole.

Substance of Doxycyclini hyclas analyse by the indexes, given in table 2.1

Table 2.1

Indexes of quality of Doxicycline hyklate

Indexes	State Pharmacopeia of Ukraine 1.2.	European Pharmacopoeia 4.1.
Description	Crystal yellow powder	Crystal yellow powder
Solubility	Easily soluble in water and metanol, slightly soluble in 96 % alcohol, practically insoluble in ether	Easily soluble in water and metanol, slightly soluble in 96 % alcohol, practically insoluble in ether
Identification:		
Maximum of absorbance at wave length, nm	365+2	365
Reaction with sulphuric acid	appearance of yellow colouring	appearance of yellow colouring
Reaction with chlorides	appearance of white sulphurous residue	appearance of white sulphurous residue
Tests for purity:		
Ethanol, %	4.3-6.0	4.3-6.0
Heavy metals, %	No more than 0.005	No more than 0.005
Water, %	From 1.4 till 2.8	From 1.4 till 2.8
Sulphate aches, %	No more than 0.4	No more than 0.4
Bacterial endotoxines, MO/mg	Less than 1.14	Less than 1.14
pH	From 2.0 till 3.0	From 2.0 till 3.0
Specific optical rotation, °C	From 105 till -120	From 105 till -120
Optical density, nm	From 300 till 335	From 300 till 335

Linimentum Synthomicini10 %

Liniment of Synthomycine has such composition for 100 g:

- Synthomycine 10,0
- Castor oil 20,0
- Emulsifier 7,0
- Thymole or 0,15
- Salicylic acid 0,125
- Distilled water till 100,0

Liniment of Synthomycine is thick, sour cream-like mass of white or slightly rather yellow color, with a weak specific smell.

Liniment of Synthomycine 10 % described in Pharmacopoeia of Europe of 01/2005:0071

The indexes of quality of liniment of Synthomycine are shown in a table 2.2 [37].

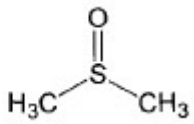
Table *2.2*

Quality indicators of liniment of Synthomycine

Indicators	European Pharmacopoeia 4.1
Description	Sour cream-like mass of white or slightly rather yellow colour, with a weak specific smell
Identification:	
ÏCaustic sodium Solution of nitric acid	Orange or red-orange colouring White curdled residue of silver chloride
Tests for purity:	
pH solution of bromcresol purple solution of brom thymole blue	5.3 – 7.0 (potentiometry) Should not be bright yellow colouring Should not be blue colouring
Heat stability	Should not be stratification during 6 hours in termostate under 45°, and during freezing in test tube till -20°
Quantitative definition:	
Synthomycine , % per 1 ml ofSodium nitritis	9.5 – 10.5

Dimethyl sulfoxide

Dimexidum



C_2H_6OS
[67-68-5]

Molecular mass 78.1 g/mole

Dimethyl sulfoxide is described in SPU 1.2 c.425 [35], European Pharmacopoeia 4.1 [37] and other pharmacopoeias.

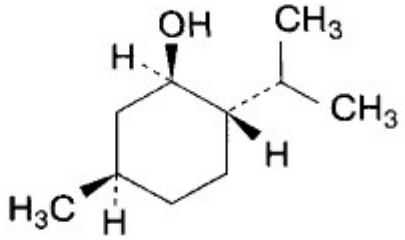
Substance of dimethyl sulfoxide is analysed by indicators given in table 2.3

Table *2.3*

Quality indicators of substance of dimethyl sulfoxide

Indicatora	State Pharmacopeia of Ukraine 1.2.	European Pharmacopoeia 4.1.
Description	Colourless liquid or colourless crystals. Hygroscopic	Colourless liquid or colourless crystals. Hygroscopic
Solubility	Miscible with water and 96 % alcohol	Miscible with water and 96 % alcohol
Identification:		
Relative density	From 1.100 till 1.104	From 1.100 till 1.104
Index of refraction	From 1.478 till 1.479	From 1.478 till 1.479
With nikel chloride	Green-yellow colour, after heating at the water bath till temperature 50°C should change from green till blue-green. After cooling colouring should be green-yellow	Green-yellow colour, after heating at the water bath till temperature 50°C should change from green till blue-green. After cooling colouring should be green-yellow
Tests for purity:		
Acidity	Pink colouring	Pink colouring
Relative density	From 1.100 till 1.104	From 1.100 till 1.104
Index of refraction	From 1.478 till 1.479	From 1.478 till 1.479
Temperature of solidity °C	No less 18.3	No less 18.3
Accompanying impurities	gas chromatography	gas chromatography
Watet, %	No more 0.2	No more 0.2
Quality of dimethyl sulfoxide, %	No less 98.5 and no more 101.0	No less 98.5 and no more 101.0

Mentholum racemicum



$C_{10}H_{20}O$

Molecular mass 156.3 g/mole

Mentholum racemicum is described in SPU 1.1 p. 395 [33], European Pharmacopeia 4.1 [37] and other pharmacopoeias.

Substance of menthol analyse by the indicators, given in table 2.4.

Table *2.4*

Quality indicators of menthol substance

Indicators	State Pharmacopeia of Ukraine 1.2.	European Pharmacopoeia 4.1.
Description	Crystal loose powder with a sight of aglomerates ot prysma or needle colourless bright crystalls	Crystal loose powder with a sight of aglomerates ot prysma or needle colourless bright crystalls
Solubility	Practically insoluble in water, slightly soluble in 96 % alcohol, ether. easy soluble in fat oils and vaseline oil, slightly soluble in glycerine. Melts under temperature till 34°C	Practically insoluble in water, slightly soluble in 96 % alcohol, ether. easy soluble in fat oils and vaseline oil, slightly soluble in glycerine. Melts under temperature till 34°C
Identification:		
Optical rotation, °	From + 0.2 till – 0.2	From + 0.2 till -0.2
Accompanying impurities	At chromatogram of tested solution (s) time of retention and square of main peak should response to chromatogram of comparison solution	
Tests for purity:		
Transparency of solution	Solution S should be transparent	Solution S should be transparent
Colouring of solution	Solution S should be colourless	Solution S should be colourless
Optical rotation, °	From +0.2 till -0.2	From +0.2 till -0.2
Acidity or alkalinity	During adding of 0.1 ml of phenolphthalein solution solution is colourless.Pink colour appears while adding no more than 0.5 ml 0.01 M solution of Sodium hydroxide	During adding of 0.1 ml of phenolphthalein solution solution is colourless.Pink colour appears while adding no more than 0.5 ml 0.01 M solution of Sodium hydroxide
Accompanying impurities	gas chromatography	gas chromatography
Dry residue, mg (%)	No more 1.0 (0.05)	No more 1.0 (0.05)
Quantitative contents of dimethylsulfoxide, %	Not less than 98.5 and no more 101.0	Not less than 98.5 and no more 101.0

2.1.2. Description of auxiliary substances

With the aim of ground of rational composition of vaginal suppositories are used different bases and auxiliary substances that are permitted for application in medical practice.

Products of directed ethrification of high molecular alcohols with fat acids obtained by a semisynthetic way relate to hydrophobic bases. From ethers of glycerin the most interesting are ether of glycerin of laurinos acid, ether of phtalic acid and high-atomic alcohols and other.

Cacao butter (Oleum Cacao) is fat oil that is got pressing of the cacaos of tropical chocolate tree toasted and released from the skin of seed - Theobroma of cacao of L., fam. Sterculiaceae. In a chemical relation basis is a mixture of glyceridess - difficult ethers of glycerin and higher fat acids. Cocoa butter is described in the pharmacopoeia of the USSR 10 th edition [29]. Oil is analysed for the next indexes: description, temperature of melting, presence of strangers fats, acid and iodic numbers. This basis by description shows by itself dense homogeneous mass of rather yellow color, weak fragrant smell of cacao and pleasant taste. A temperature of melting of cocoa butter is in limits from 30 to 34°C. Cocoa butter easily dissolves at shaking in ether and boiling waterless alcohol. Determination of strangers fats is conducted in obedience to the pharmacopoeia of the USSR [29]. The acid value of cocoa butter folds not more than 2,25 [29]. An iodic number, in obedience to Pharmacopoeia of the USSR, is from 32 to 38. Keep cocoa butter in well closedcans, in the cool, place protected from light.

Beeswax (Cera). A bee beeswax shows by itself hard, grainy, fragile mass from yellow to the brown color with the weak smell of honey. Melts at the temperature 63-65 °C. *The* Bee *beeswax* is well alloyed with fats, by hydrocarbons and other waxes. Due to the presence of higher alcohols a beeswax is able to emulgate some quantities of water. It adds to bases and ointments plasticity and promotes their closeness.

Emulsifier *of T-2* – is derivant polymerized glycerin. It is a mixture of incomplete difficult diethers of threeglycerine and stearin acid, refers to synthetic non-ionogenic surface - active substances, soluble in fats [36].

2.2. Physcal and chemical methods of research

Medicines for vaginal application usually control on such indexes according to SPU 1.1 [33] and SPU 1.2 [35]: description, authentication, middle mass and homogeneity of mass, homogeneity of content, disintegration, dissolution, temperature of melting or time of complete deformation, accompanying admixtures, microbiological cleanness, quantitative determination.

Description

Suppositories can have a different form usually egg-liked with a maximal diameter a not more than 1.5 cm.

Mass is usually in limits from 1.5 to 6.0 g of pessary.

Middle mass (2.9.5)

Determinations of middle mass conduct according to the article of ДФУ a 1.1 (2.9.5) «Homogeneity of mass for unit of the dosed medicinal means» [34].

Twenty suppositories weigh separately and expect middle mass.

Medicinal preparation passed test, if the not more than two individual masses deviate from middle mass more than on 5 %.

Homogeneity of mass (2.9.5)

Hard medicinal forms in one the dosed containers must maintain the test of homogeneity of mass for unit of the dosed medicinal means.

The test of homogeneity of mass is not required, if the test of homogeneity of content is foreseen for all active substances [34].

Disintegration (2.9.2)

If pessaries are not intended for the prolonged local action, they must maintain the test of disintegration. The state of pessaries is investigated through 30 min, if there is not other pointing in the separate article [34].

Temperature of melting (2.2.15)

For suppositories that were obtained on lipophilic basis, determine the temperature of melting, that must not exceed 37 °C, if there is not other indications in the separate article [34].

Chapter III

DEVELOPMENT OF TECHNOLOGY OF SUPPOSITORIES WITH DOXYCYCLINE «EX TEMPORE»

Development of vaginal pessaries for treatment of vaginal infections of здійснюється taking into account the special requirements of SPU and has the specific features.

Composition of pessary, that mostly write doctors are presented below

Composition for 1 pessary,g:

Doxycyclini hyclas	0.100
Linimentum synthomicini 10 %	0.250
Dimexidi	0.020
Mentholi	0.010
Adeps solidus	ad 3.0

These pessaries on the basis of hard fat are prepared by the method of pouring.

In the compo sition of pessaries next substances are included: doxycycline hyclate, liniment of synthomycine, dimexide and mentholum.

The aim of our work is substituting of synthetic base - hard fat by natural base – cacao butter.

3.1. Study of properties of active and auxiliary substances of substances, basis and to the emulsifier

- Doxicycline hyclate – crystal yellow powder, easy soluble in water, slightly soluble in alcohol, insoluble in ether;
- linimenum Synthomicini – liniment of Synthomycine 10 % of white colour, active substance – chloramphenicol, which is practically insoluble in water, easy soluble in alcohol;

- dimexidum – transparent liquid with specific odour, mixes up with water and alcohol;
- menthol – crystall loose powder in the form of aglomerates, or prysma, or neddle colourless bright crystalls, practically insoluble in water, too slightly soluble in glycerine, easy soluble in alcohol. ether, fat oils. [33,34,35].

Learning properties of medicinal substances, that enter in the complement of песаріїв set that such substances as diomexide and Menthol soluble in hydrophobic bases, that is why their introduction does not cause difficulties, and doxicycline hyclate insoluble in hydrophobic suppository bases, that is why necessary introduction in the complement of pessaries of auxiliary substances.

At creation of vaginal medicines, except the choice of corresponding active substances, the special value is spared to the variable pharmaceutical factors - nature of basis-transmitter, type of medical form.

At the international pharmaceutical market suppository bases of different character are presented. The most widely used suppository bases are Witepsol, polyethyleneoxide bases and hard fat a pastry cook.

Data of suppository bases have a semisynthetic or synthetic origin and can cause the unpleasant feeling at application or entail allergic reactions for patients, while супозиторні bases of natural origin do not have such consequences of application. With the aim of choice of rational transmitter by us different suppository bases were studied, namely basis of natural origin, that is worked out on the department of technology of medicens under the direction of professor Yarnykh T.G., Chushenko V.M., Tolochko K.V. and on that a patent is got for a useful model № 69000 (Base for suppositories). In the complement of base oil of cacao and beeswax.

Oil of cacao belongs to natural hydrophobic bases and it is examined during many years the best basis of natural origin. Oil of cacao has a row of advantages : well interfuses with different medicinal substances, quickly frees the entered medicinal substances, has enhanceable clear expressed temperature of melting and high plasticity, and also reparative and action of oiling was expressed.

Beeswax also enters in the complement of natural hydrophobic bases.

Quality composition of beeswax stipulates him moderate antiinflammatory, reparative and local anestetic properties.

Basis consists of oil of cacao and additionally of a beeswax, at next correlation of components (mass, %) :

Cacao butter- 92,5-99,0

Beeswax - up to 100,0

Base is prepared by the method of pouring, that occupies far fewer time and considerably improves quality of песаріїв, than rolling method.

We prepared model samples of bases in different correlations. The results of experiment are presented in a table 3.1

Table 3.1

Quality indexes of sample of sbases: cacao butter; beeswax in different ratios (pouring out method)

№/№	Cacao butter, %	Beeswax, %	Quality indexes		
			Description	Melting temperature, °C	Resistance to destruction, kg
1	92.5	7.5	Homogeneous base of white colour	36,8	2.3
2	95.0	5	Homogeneous base of white colour	34,5	2.1
3	97.5	2.5	Homogeneous base of white colour	32,1	1.6

Analysing the standards of basis drew conclusion, that basis in correlation oil a cacao-beeswax (97.5-2.5 %) does not suit to making of pessaries, in connection with the subzero temperature of melting - 32,1 °C.

Therefore for a further experiment stopped for basis oil a cacao-beeswax is a beeswax in correlation (92.5- 7.5 %) and (95.0-5.0 %.).

As doxicycline hyclate is a hydrophilic substance, for an improvement to quality of pessaries (basis is hydrophobic) added the emulsifier of T-2.

Emulsifier of T-2 is a lipophilic emulsifier, with HLB 3-6, because it is an emulsifier of type water-oil. At mixing with water solutions there is an emulsifier of T-2 forms emulsion of type w/o (water in oil).

Table 3.2

Results of quality of samples of pessaries with doxicycline hyclate, prepared on the base of: cacao butter: beeswax with addition of emulsifier T-2

№	Ration of cacao butter: beeswax, %	Quantity of emulsifier, %	Quality indexes			
			Description	Melting temperature, °C	Time of full deformation, min	Resistance to destruction, kg
1	92.5 : 7.5	1 2 3	Non-homogeneous Homogeneous Homogeneous	- 37,9 37,8	14.40	2.4
2	95.0 : 5.0	1 2 3	Non-homogeneous Homogeneous Homogeneous	- 36,2 36,3	10.46	2.2

Taking into account results of experiment it is obvious to make a conclusion,, that pessaries with doxicycline hyclate made on basis oil of cacao : a beeswax in correlation (92.5: 7.5) and by addition of emulsifier of T-2 in an amount 1, 2, 3 % and in correlation (95.5: 5.0) and amount of emulsifier 1 % does not meet the requirements of SPU on an index ″Temperature of melting″.

The conducted researches showed that standards of pessaries on basis of oil cacao in ratio (95.5: 5.0) with content of emulsifier of T-2 in an amount 2-3 % meet the requirements of SPU on an index "Homogeneity" and "Temperature of melting".

At the same time studied solubility of doxicycline hyclate in a number of auxiliary substances: liniment of синтоміцина 10 % and glycerin.

It is experimentally set that doxicycline hyclate easily dissolves in liniment of synthomycine that considerably facilitates its introduction into suppository base and improves quality of got pessaries (absent effect of settling).

3.2. Technology of making of extemporal pessaries with doxycycline hyclas

The technology of making of pessaries with doxycycline hyclate was. worked out on the basis of the conducted researches

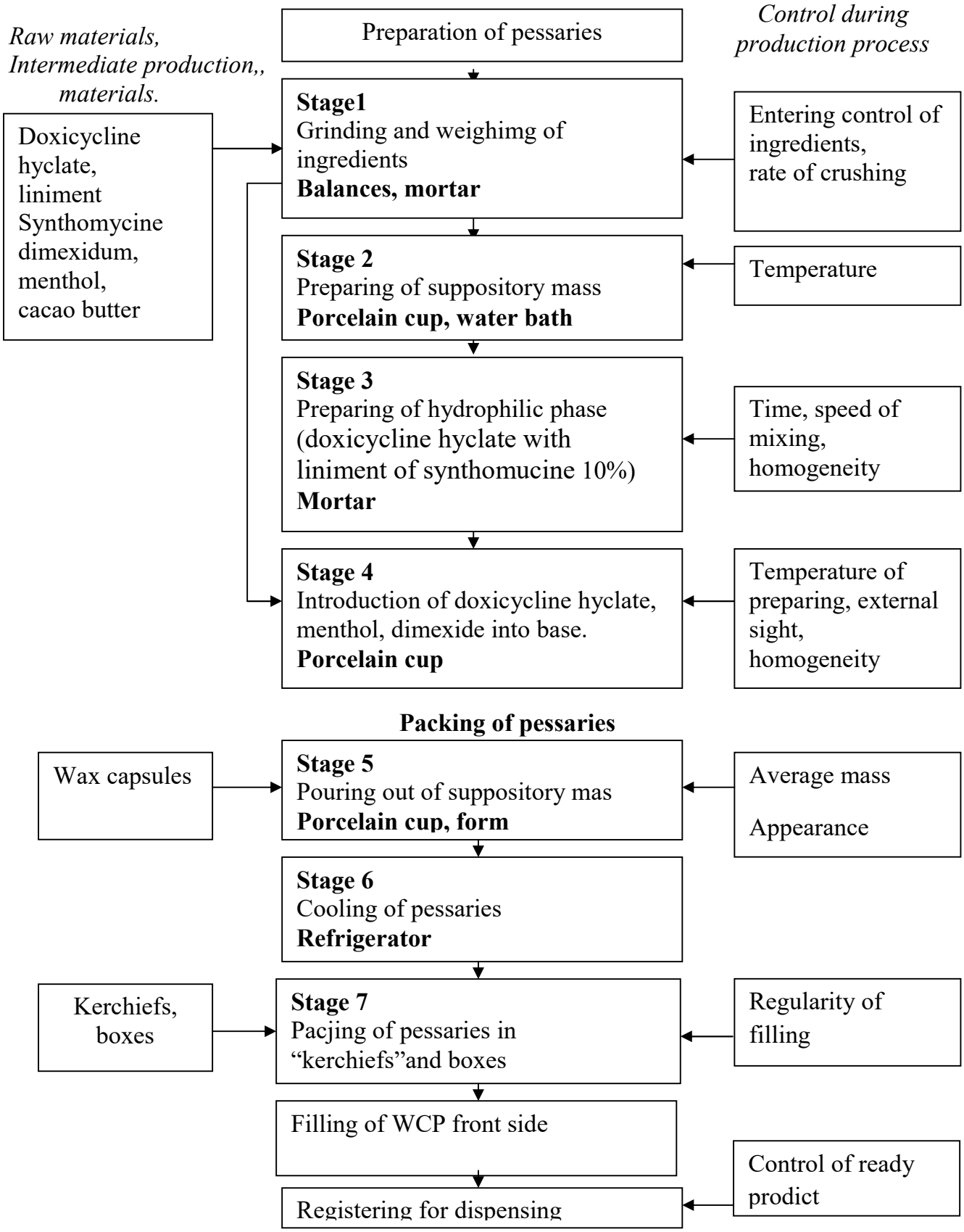
In a mortar weigh out doxycycline hyclate, grind 3 min, add liniment of synthomycine 10 %, grind till receipt homogeneous mixture.

In a porcelain cup on water bath melt a beeswax and emulsifier of T-2 (50,0±2,5) °C, in an amount 2 %, cool to (40,0± 2,5) °C, then add cacaos butter and take off from water bath.

In a porcelain cup to the chilled suppository base add the got mixture from a mortar, and then add dimexide and menthole.

Carefully mix semicooling mass. Quickly pour out in preliminary smeared a soap alcohol and the chilled form, put in a refrigerator for 20 - 30 min

Technological scheme of preparation of pessaries with doxycycline hyclate is given below at the scheme 3.1



Pic. 3.1.Stages of technological process of preparing of pessaries with doxicycline hyclate by pouring out method.

3.3. Estimation of quality of pessaries from doxycycline hyclas. Control of quality

Standards of pessaries with doxycycline hyclas is prepared on the basis of Witepsol were analysed for to the next indexes in accordance with the requirements of SPF 1.0 [34] but 1.2 [35], operating orders, instructions of Ministry Of Health of Ukraine and methodical recommendations:

Description

Standards of pessaries from doxycycline hyclate on basis oil of cacao of white color.

Authentication

At cooperation of doxycycline hyclas the yellow colouring appears with acid sulphuric.

Middle mass

Weigh 20 pessaries. Expect middle mass of one pessary.

According to counts middle mass to песарію folds 3,0 ± 0,15 and answers a possible rejection that folds ± 5 %.

Homogeneity

Homogeneity of mass was defined by sight: on the longitudinal cut of standards of pessaries from doxycycline hyclas has no disseminations.

Disintegration

On the standards of pessaries tested on disintegration in accordance to SPU. The standards of pessaries disintegrated in a device for determination of disintegration no more than in 30 minutes, that answers requirements.

Temperature of melting

On the standards of pessaries, defined the temperature of melting, in accordance with SPU that folds not more than 37 °C.

Table 3.3.

Results of estimation of quality of pessaries from doxicycline hyclas

Index of quality	Results of analysis
Description	White - coloured pessaries with smooth surface
Homogeneity	On a cut the homogeneous, mechanical including, cracks and stratifications are absent.
Authentification	A reaction is with acid sulphuric- appearance of the yellow colouring
Middle mass, g	2,85 ± 3,15
Temperature of melting	No more than 37 °C.
Disintegration, min	No more than 30

Conclusions

1. The study of physical and chemical descriptions of active components of pessaries is conducted.
2. As a result of the conducted experimental researches basis of natural origin is neat oil of cacao and beeswax bee and concentration of emulsifier of T-2.
3. Prescriptions of preparation of pessaries from doxicycline hyclate ″ex tempore″ are worked out.

GENERAL CONCLISIONS

1. A study and generalization of literary sources about varieties, etiology, pathogeny, clinical displays and basic directions of pharmacotherapy of infectious vaginitis are conducted.
2. For today there is an insufficient amount of extemporal preparations in the pharmacies of Ukraine for a treatment of infectious vaginitis. Reasonable expediency of creation of new medicinal preparation – pessaries with doxicycline hyclate.
3. The native market of medicinal preparations of industrial and extemporal production for treatment of infectious vaginitis is investigated. It is set that most medicines of industrial production (81 %) are of foreign origin. At the native pharmaceutical market there is an analogical tendency: pessaries - almost 61 %, vaginal tablets - 22 %, creams and gels - 12 %, capsules - approximately 3 %, and solutions for vaginal application and powders for preparation of solutions - for 1 %.
4. Theoretically and experimentally is grounded composition and technology of pessaries with doxicycline hyclate is woked out.

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Ф А 2.2.1–32-366

National University of Pharmacy

Faculty for foreign citizens' education
Department pharmaceutical drug technology

Level of higher education master

Specialty 226 Pharmacy, industrial pharmacy
Educational program Pharmacy

APPROVED
The Head of Department
Liliia VYSHNEVSKA

_____
"_06_" May 2024

ASSIGNMENT
FOR QUALIFICATION WORK
OF AN APPLICANT FOR HIGHER EDUCATION

Rachid AHMED-AYMAN

1. Topic of qualification work: «Research on the development of composition and technology of extemporal suppositories with anti-inflammatory activity, supervisor of qualification work: Yuliia LEVACHKOVA, DSc., prof.

approved by order of NUPh from "06" of February 2024 № 34

2. Deadline for submission of qualification work by the applicant for higher education: November 2024.

3. Outgoing data for qualification work: Research on the development of composition and technology of extemporal suppositories with anti-inflammatory activity.

4. Contents of the settlement and explanatory note (list of questions that need to be developed): analyze and summarize literature data about curing of inflammatory diseases in gynaecology;; conduct an analysis of the extemporaneous formulation of pessaries; theoretically and experimentally choose the composition and technology of extemporal suppositories, conduct theoretical and experimental choice of emulsifiers; to carry out analysis of pharmaceutical market of different types of vaginal medicinal forms, that are used in gynaeciology for the treatment of vaginal infections..

5. List of graphic material (with exact indication of the required drawings):
tables 7 , 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 Pharmaceutical drug technology	20.05.2024	20.05.2024
2	Yuliia LEVACHKOVA, professor of higher education institution of department Pharmaceutical drug technology	14.06.2024	14.06.2024
3	Yuliia LEVACHKOVA, professor of higher education institution of department Pharmaceutical drug technology	16.09.2024	16.09.2024

7. Date of issue of the assignment: "06" May 2024

CALENDAR PLAN

№ з/п	Name of stages of qualification work	Deadline for the stages of qualification work	Notes
1	The topic selection	May 2024	done
2	Analysis of literary sources	June 2024	done
3	Conducting experimental research in	September - October 2024	done
4	Designing the work	October 2024	done
5	Submission of finished work to the examination commission	October 2024	done

An applicant of higher education _____**Rachid AHMED-AYMAN**

Supervisor of qualification work _____ Yuliia LEVACHKOVA

ВИТЯГ З НАКАЗУ № 34
По Національному фармацевтичному університету
від 06 лютого 2024 року

1. Затвердити теми кваліфікаційних робіт здобувачам вищої освіти 5-го курсу 2 циклу Фм20*(4,10д) 2024-2025 навчального року, ступінь вищої освіти «магістр», галузь знань 22 Охорона здоров'я, спеціальність 226 – Фармація, промислова фармація, освітньо-професійна програма – Фармація, денна форма здобуття освіти (термін навчання 4 роки 10 місяців). Мова навчання англійська

№ з/п	Прізвище, ім'я здобувача вищої освіти	Тема кваліфікаційної роботи		Посада, прізвище та ініціали керівника	Рецензент кваліфікаційної роботи
• **по кафедрі аптечної технології ліків**					
3.	Рачід Ахмед-Айман	Дослідження з розробки складу песаріїв з протизапальною дією	Research on the development of composition of pessaries with anti-inflammatory activity	проф. ЗВО Левачкова Ю.В.	доцент ЗВО Солдатов Д.П.

Ректор

Вірно. Секретар

ФА2.8-03-317

ВИСНОВОК

експертної комісії про проведену експертизу
щодо академічного плагіату у кваліфікаційній роботі

здобувача вищої освіти

«22» листопада 2024 р. № 329648875

Проаналізувавши кваліфікаційну роботу здобувача вищої освіти Рачід Ахмед- Айман, Фм20*(4,10д)-англ-02, спеціальності 226 Фармація, промислова фармація, освітньої програми «Фармація» навчання на тему: «Дослідження з розробки складу песаріїв з протизапальною дією / Research on the development of composition of pessaries with antiinflammatory activity», експертна комісія дійшла висновку, що робота, представлена до Екзаменаційної комісії для захисту, виконана самостійно і не містить елементів академічного плагіату (компіляції).

Голова комісії,
проректор ЗВО з НПР,
професор **Інна ВЛАДИМИРОВА**

Ф А 2.2.1-25-353

RESPONSE

for the qualification work of the master's level of higher education of the specialty 226 Pharmacy, industrial pharmacy
Rachid AHMED-AYMAN

on the topic ««**Resaerch on the development of composition and technology of extemporal suppositories with antiinflammatory activity»**

Relevance of the topic. Therapy of inflammatory gynecological diseases remains an acute issue of modern health protection. The most common are inflammatory processes of the pelvic organs, viral and bacterial infections transmitted by halves. Especially relevant were the problems of bacterial vaginitis, trichomoniasis. Its frequency has more than doubled in recent years,
The market analysis showed that in the pharmaceutical market of Ukraine there are not enough extemporal drugs of anti-inflammatory and action of Ukrainian production. Thus, it is necessary to supplement the range of anti-inflammatory and antimicrobic preparations of local action,.

Author's suggestions on the research topic The author theoretically justified the composition of vaginal suppositories with Doxicycline hyclate, Linimenth of synthomycine, menthol and other API. Choice cof suppository base and optimal emulsifier has been conducted. Rational technology of combined vaginal suppositories has been developed.

Practical value of conclusions, recommendations and their validity. The practical value of the work is based on the theoretical and experimental justification of the concentration of Doxicylcine hyclas, Liniment of synthomycin and menthol, which allowed to obtain a significant antiinflammatory effect, which was taken into account in the development of the composition and technology of the dosage form. Higher education fellow also theoretically based on the advantages of producing this medicinal form by pouring, since the specified method allows you to get samples of good quality suppositories. The source of higher education is theoretically based on the composition and technology (choice of API and memorable substances) of vaginal suppositories antimicrobic and antiseptic substances for local therapy of vaginal infections in gynaecology.

Assessment of work. Qualification work on both theoretical and practical research fully responds to the requirements for the fulfilling of qualification works.

General conclusion and recommendations on admission to defend.. Rachid AHMED-AYMAN ualification work can be submitted to the National Pharmaceutical University Examination commission for the awarding of the obscure qualification level of Master..

Scientific supervisor _____ Yuliia LEVACHKOVA

«5» of October 2024

Ф А 2.2.1-32-356

REVIEW

of scientific supervisor for the qualification work of the master's level of higher education of the specialty 226 Pharmacy, industrial pharmacy
Rachid AHMED-AYMAN

on the topic: **«Research on the development of composition and technology of extemporal suppositories with anti-inflammatory activity»**

Relevance of the topic. The relevance of the development of the technology of extemporal suppositories based on antimicrobic substances and other API due to the rationality of the use of drugs, the pharmacological effect of which can eliminate the symptoms of the disease. The pharmaceutical market of antibacterial drugs in various forms in Ukraine is widely represented, but it is necessary to choose the most effective and less harmful substances that can be applied in gynecology. These drugs should have the maximum therapeutic effect and be less toxic.

Author's suggestions on the research topic The author theoretically justified the composition of suppositories with Doxicylcine hyclate, Liniment of synthomycine, Dimexide and menthol on the bases of hydrophobic type, so the introduction of it into the composition of pessaries containing some active pharmacological ingredients (API), which are hydrophylic by its properties was carried out, using an emulsifier. Quality indexes of samples of the developed dosage form (as melting temperature, time of full deformation, etc.) were studied; rational technology of vaginal suppositories has been developed.

Theoretical level of work. The work carried out by Rachid AHMED-AYMAN is devoted to analysis literature data on the market of drugs used in gynaecology, theoretically substantiated the composition and technology of the vaginal extemporal suppositories.

Assesment of work. The author while working learned to use the data of scientific literature, to search for the necessary information, proved to be a talented experimenter, able to draw sound conclusions from the result

Practical value of conclusions, recommendations and their validity.
Based on the author's organoleptic, physico-chemical, pharmacotechnological studies, the choice of suppository hydrophobic base in combination with an emulsifeier and the amount of this emulsifier in the composition of suppositories with active subsrtances prepared by the method of pouring out for use in gynecology as an anti-inflammatory and antimicrobic agent.

Disadvantages of work. According to the text of the work there are some typographical errors, bad expressions. However, this does not reduce the value of the work and does not call into question the results obtained

General conclusion and recommendations on admission to defend. The qualification work of Rachid AHMED-AYMAN can be submitted to the National Pharmaceutical University Examination Commission for the awarding of Master's Degree in Education and Qualification.

Reviewer _____ as.prof. Dmytro SOLDATOV

«10» October 2024 y.

Ф А2.2.1-91-287

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ВИТЯГ З ПРОТОКОЛУ № _2_
«_14_» _ жовтня _ 2024_
року м. Харків

засідання кафедри
аптечної технології ліків
(назва кафедри)

Голова: завідувачка кафедри, професор Вишневська Л. І.
Секретар: докт. філ., ас. Зуйкіна Є.В.

ПРИСУТНІ:

проф. Половко Н.П., проф. Семченко К.В., проф. Зуйкіна С.С., проф. Левачкова Ю.В., доц. Ковальова Т.М., доц. Буряк М.В., доц. Ковальов В.В., доц. Олійник С.В., доц. Марченко М.В., доц. Живора Н.В., ас. Іванюк О.І., асп. Бондар Л.А., асп. Паливода П.В.

ПОРЯДОК ДЕННИЙ:

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

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

ВИСТУПИЛИ: Здобувач вищої освіти групи Phm20*(4,10d) eng 02 спеціальності 226 «Фармація, промислова фармація» Rachid AHMED-AYMAN – з доповіддю на тему «Research on the development of composition and technology of extemporal suppositories with anti-inflammatory activity» (науковий керівник, проф. Юлія ЛЕВАЧКОВА).

УХВАЛИЛИ: Рекомендувати до захисту кваліфікаційну роботу.

Голова
Завідувачка кафедри, проф. _____ **Лілія ВИШНЕВСЬКА**
(підпис)

Секретар
асистент _____ **Єлизавета ЗУЙКІНА**
(підпис)

Ф А2.2.1-32-042

НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ПОДАННЯ
ГОЛОВІ ЕКЗАМЕНАЦІЙНОЇ КОМІСІЇ
ЩОДО ЗАХИСТУ КВАЛІФІКАЦІЙНОЇ РОБОТИ

Направляється здобувач вищої освіти Rachid AHMED-AYMAN до захисту кваліфікаційної роботи
за галуззю знань 22 Охорона здоров'я
спеціальністю 226 Фармація, промислова фармація
освітньою програмою Фармація
на тему: ««Investigations for the development of composition and technology of extemporal suppositories with antiinflammatory activity»

Кваліфікаційна робота і рецензія додаються.

Декан факультету _____/ Світлана КАЛАЙЧЕВА /

Висновок керівника кваліфікаційної роботи

Здобувач вищої освіти Rachid AHMED-AYMAN представила кваліфікаційну роботу, яка за об'ємом теоретичних та практичних досліджень повністю відповідає вимогам до оформлення кваліфікаційних робіт.

Керівник кваліфікаційної роботи

_____ Юлія ЛЕВАЧКОВА

«04» жовтня 2024 р.

Висновок кафедри про кваліфікаційну роботу

Кваліфікаційну роботу розглянуто. Здобувач вищої освіти Rachid AHMED-AYMAN допускається до захисту даної кваліфікаційної роботи в Екзаменаційній комісії.

Завідувачка кафедри
аптечної технології ліків

_____ Лілія Вишневська

«14» жовтня 2024 р.

Qualification work was defended

of Examination commission on

« 28 » of November 2024

With the grade _____

Head of the State Examination commission,

D.Pharm.Sc, Professor

_____ / Oleh SHPYCHAK