

## DEVELOPMENT OF THE COMPOSITION AND TECHNOLOGY OF EXTEMPORANEOUS SUPPOSITORIES WITH CLINDAMYCIN AND SEA BUCKTHORN OIL

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### Introduction

At the Eastern European Congress of Young Doctors in Obstetrics and Gynecology (held April 26-27, Riga), it was emphasized that the treatment of infectious-inflammatory gynecological diseases is an important problem at the present stage of development of the healthcare sector. Colpitis, bacterial vaginosis, vaginal candidiasis, trichomoniasis tend to increase. The main cause of inflammatory diseases is infection. Mixed infections are now at least 30 % in the structure of infectious diseases of the lower genital tract [1].

Antibacterial therapy certainly plays an important role in the treatment of these pathologies, although in most cases it causes allergic states, antibiotic resistance of various types of microorganism strains, and also a disfunction of normal vaginal biocoenosis [2,3].

Anti-protozoal, antibacterial and antifungal agents are preferred, namely, ternidazole, metronidazole, fluconazole, clindamycin, miconazole, clotrimazole, nystatin, isoconazole etc. among the synthetic drugs used in gynecological practice [3].

Prospective plant medicines for solving this problem are essential oils (tea tree, sea buckthorn, wormwood, chamomile), which provide inhibition of the development of pathogenic anaerobes. The main mechanisms of their action are the ability to reduce vascular permeability, stabilize the membrane of cells,

suppress the exudative complement in infectious inflammation, activate a reparative process [4, 5].

Analyzed the data of 2017-2018 years, it was found that medicines for vaginal application are presented in different dosage forms, which distributed in percentage value as following: pessaries – about 54 %, vaginal tablets – 25 %, creams and gels – 12 %, etc. [6].

Vaginal medicines, namely, vaginal suppositories (pessaries) that act directly in the cell of infection and have high intensity of penetration of active substances into surrounding tissues, are of great importance and widespread use in the complex therapy of candida infection, trichomonal vaginitis, and various mixed urogenital infections. At the same time, the range of industrial production of pessaries (vaginal suppositories) of anti-inflammatory, antimicrobial, antispasmodic effects is insignificant. Extemporal production of vaginal suppositories in Ukraine is undeveloped practically [7].

Based on the data obtained and taking into account the etiology, pathogenesis and existing schemes for the treatment of infectious-inflammatory gynecological diseases, it is expedient to create a multicomponent pessaries based on the combination of synthetic and natural substances. As a synthetic substance, clindamycin is proposed, as a natural - sea buckthorn oil [8, 9, 10].

**The aim of the work** was to substantiate the composition and development of technology of combined vaginal suppositories (pessaries) with clindamycin phosphate and sea buckthorn oil for the treatment of infectious-inflammatory gynecological diseases.

Clotrimazole, metronidazole and clindamycin are most commonly used in the study of the range of active pharmaceutical ingredients (API) that are part of the medicines for the treatment of infectious-inflammatory diseases in gynecology. (Fig. 1).

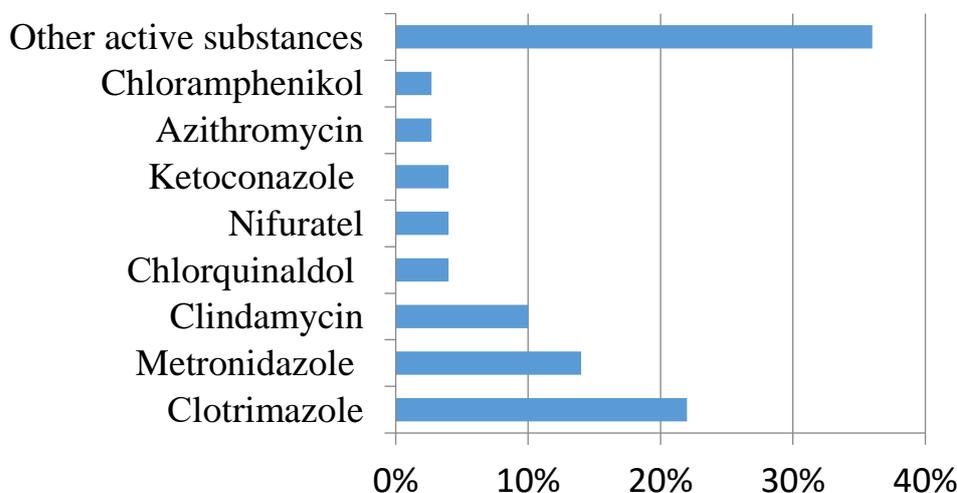


Fig.1. Assortment of active pharmaceutical ingredients, which contain a medicines for the treatment of infectious-inflammatory gynecological diseases.

The monograph for Clindamycin phosphate is given in the Europe Pharmacopoeia and the United States Pharmacopoeia [11, 12]. Clindamycin belongs to the lincosamides group. It discontinues the intracellular biosynthesis of bacterial protein, thus causing bacteriostatic action. In high concentrations of relatively highly-sensitive microorganisms may exhibit a bactericidal effect. Clindamycin treats severe infections caused by microorganisms which are sensitive to the medicine (including *Staphylococcus aureus*) in patients who have an allergic state to penicillin. For aerobic infections, clindamycin phosphate is an alternative when other antimicrobial medicines are not effective or contraindicated. In the case of anaerobic infections, clindamycin phosphate is a first choice medicine.

In order to increase the antibacterial action of suppositories, we propose the combination of essential oil with clindamycin, namely sea buckthorn oil. Sea buckthorn oil is a rich in carotenoids, useful in solving female problems (cystitis, colpitis, vulvitis), especially those associated with premenstrual and climacteric syndromes. Oil inhibits the activity of pathogenic microorganisms and promotes the penetration of antibiotics in a body cell, and, thus, it is possible to reduce the dose of antibiotics. The sea buckthorn oil, which is proposed to be included in the pessaries, is described in Europe Pharmacopoeia 5 and VFS 42U-218-1082-99. This is an oily liquid of orange-red color, with a specific odour. The content of carotenoids should be at least 180 mg %.

Today, the manufacture of medicines in pharmacies does not lose its significance. Extemporaneous production of medicines makes it possible for an individual approach to the patient

taking into account the peculiarities of the organism, the course and symptoms of the disease, its stage. This is the main principle and advantage of "ex tempore" manufacture of medicines [6]. Therefore, the creation of extemporaneous combined medicines for vaginal application on the basis of substances of synthetic and natural origin cause to solve the problem of infectious-inflammatory gynecological diseases of patients and improve their life quality.

In Ukraine PJSC "Lekhim-Kharkiv" produces suppositories with a sea buckthorn oil (0.5 g per one suppository), as well as in Russia, the company "Nizhpharm" produces "Suppositories with sea buckthorn oil" for 0.5 g of sea buckthorn oil.

"Dalacin" suppositories containing 0.17 mg of clindamycin phosphate are produce by "Pharmacia & Upjohn Company LLC" (USA) for "Pfizer Inc.". Suppositories "Milagin" containing clindamycin phosphate in a dose of 0.100 mg are produce by "Sperco Ukraine" (Ukraine).

### Materials and Methods

Model samples of suppositories were prepared with 0.100 g of clindamycin phosphate and 0.500 g of sea buckthorn oil. The above medicines ("Dalacin" and "Suppositories with sea buckthorn oil") were used as a comparative medicine. The composition of the model sample of pessaries is presented in Table. 1.

In some infectious-inflammatory diseases, a numerously secretions in the form of a liquid is released into the vagina. Polyethylene oxide (PEO) base (Macrogol) has osmotic properties and removes the excess moisture, therefore, according to medical indications, suppositories were prepared on the polyethylene oxide base.

**Table 1. The composition of model sample of suppositories with clindamycin and sea buckthorn oil**

API	Model sample of suppositories	Suppositories "Dalacin"	"Suppositories with sea buckthorn oil"
	Quantity, g		
Clindamycin phosphate	0.100	0.100	--
Sea buckthorn oil	0.500	--	0.500

The effects of emulsifiers on the pharmacotechnological parameters of suppositories have been studied. Emulsifiers were added for mixing of the hydrophilic and hydrophobic suppository phases. Disperse system of suppositories with clindamycin and sea buckthorn oil is an emulsion of 1<sup>st</sup> type, therefore it is possible to use as emulsifiers the following substances: polysorbate-80, emulsion wax or alkaline soaps.

The researches have shown that only samples of suppositories with polysorbate-80 become homogeneous and meet the requirements of the SPhU 2.0 [13].

The study of antibacterial properties of model samples of suppositories with clindamycin and sea buckthorn oil was carried out in the laboratory of Biochemistry and Biotechnology of the Mechnikov

Institute of Microbiology and Immunology (NAMS of Ukraine) under the direction of associate professor T.P. Osolodchenko (Table 2). A model sample of pessaries reveals a more pronounced antimicrobial effect for all investigated strains of microorganisms in comparison with the medicine "Dalacin" and "Suppositories with sea buckthorn oil". The combination of active substances in the model sample of suppositories with clindamycin phosphate and sea buckthorn oil increases the antimicrobial action of clindamycin phosphate to the resulted strains of microorganisms in 1.5 times. Sea buckthorn oil in the studied sample not only does not interfere with manifestation of antibacterial properties, but also strengthens them. The maximum diameters of bacteriostasis zones of microorganisms are noted for the model sample of suppositories (Table 2).

**Table 2. Antimicrobial activity of a model sample of suppositories with clindamycin and sea buckthorn oil**

Microorganisms	Diameters of bacteriostasis zones, mm		
	Model sample	Suppositories "Dalacin"	"Suppositories with sea buckthorn oil"
Staphylococcus aureus ATCC 25923	22.7±0.3	21.3±0.4	15.0±0.5
Escherichia coli ATCC 25922	16.7±0.4	16.7±0.5	14.3±0.5
Pseudomonas aeruginosa ATCC 27853	14.3±0.5	growth	growth
Proteus vulgaris ATCC 4636	16.7±0.5	growth	growth
Bacillus subtilis ATCC 6633	23.7±0.3	18.7±1.4	16.7±0.5
Peptococcus niger 19	25.3±0.3	16.0±0.5	12.7±0.3
Peptostreptococcus anaerobius 36	26.7±0.4	17.3±0.4	13.3±0.3
Fusobacterium sp 55	22.3±0.4	17.0±0.5	14.7±0.3

Note: n = 5; P = 95 %

Model samples of suppositories with clindamycin phosphate and sea buckthorn oil were checked by pharmaco-technological parameters (Table 3).

### Results and discussion

The results of the conducted researches shown that model samples of suppositories with clindamycin phosphate and sea buckthorn oil meet the requirements of the SPhU 2.0 for the following pharmaco-technological parameters: description, homogeneity, disintegration time, pH.

**Table 3. Pharmaco-technological parameters of a model sample of suppositories**

Parameters	Permissible limits	Results of analysis
Description	Suppositories of light-brown colour	Satisfy
Homogeneity	There should be no inclusions on the cut. The presence of an air rod is allowed	Satisfy
Disintegration time, min	Not more than 60	32
pH	4.00 – 6.00	4.95

The technology of suppositories is developed taking into account the physical and chemical properties of the API and excipients, their mass and technological equipment.

From a physical and chemical viewpoint, suppositories are a combined heterogeneous system, which consists of a disperse phase and a dispersive medium. Clindamycin phosphate is pre-grounded about 3 minutes and dissolved in a liquid corresponding to the base - polyethylene oxide-400, forming a solution. Polyethylene oxide base (mixture of PEO-400 and PEO-1500) are molten and successively add a solution of clindamycin phosphate, and then add a pre-mixed polysorbate-80 with a sea buckthorn oil, mix. The obtained homogeneous mass is pour into prepared forms. Cool for 10-15 minutes at the room temperature, then place in the refrigerator.

On the model sample of the suppositories, quality parameters were checked. A sample of vaginal suppositories manufactured according to the above technology, meets all requirements of SPhU 2.0.

### Conclusions

1. Based on the conducted research, the composition and technology of suppositories with clindamycin

phosphate and sea buckthorn oil for pharmacy preparation was developed.

2. A technological instruction for the pharmacy preparation of suppositories with clindamycin phosphate and sea buckthorn oil has been developed and tested in the conditions of pharmacy "Pharmacy No 9", Kharkiv.

### References

1. Podolskyi V.V. Modern possibilities of treating inflammatory diseases of the genital organs in women of childbearing age / V.V. Podolskyi, V.V. Podolskyi // Women's health. – 2017. – №5 (121). – P. 132-136.
2. Pharmacological research of Loravit suppositories / I.V. Herasymova, O.I. Tykhonov, O.S. Shpychak et al. // Asian Journal of Pharmaceutics – 2018. – N 12(1). – P. 106-110.
3. Yarnykh T.G. Study of antibacterial activity of combined vaginal pessaries with fluconazole and amaranth oil / T.G. Yarnykh, Yu.V. Levachkova, V.M. Chushenko et al. // Pharmaceutical Journal. – 2016. – № 2. – P. 60-64.
4. A complete book on aromatherapy. Prevention and treatment of diseases by essential oils / S. S. Soldatchenko et al. // 2<sup>nd</sup> ed., add. and recycled. – Symferopol: Tavryda., 2007. – 529 p.

5. Shapovalova N. V. Application of aromatherapy procedures for treatment of inflammatory processes of female genital organs / N. V. Shapovalova, A. P. Onishchuk, S. P. Ivaniuk // Pharmaceutical magazine. – 2008. – № 4. – P. 53-56.
6. Yarnykh T.G. Study of the stability of the combined pessaries "Klimedeks" / T.G. Yarnykh, Yu.V. Levachkova, V.M. Chushenko et al. // Pharmacy of Kazakhstan. – 2013. – № 6. – P. 54-57.
7. The problem of scientific substantiation of technologies of extemporaneous formulation and ways of its solution. Message 2. Comparative analysis of modern pharmacopoeial requirements for technology and quality control of extemporaneous drugs / O. S. Soloviov et al. // Pharmaceutical Journal – 2014. – № 2. – P. 3-12.
8. Burt S. Essential oils: their antibacterial properties and potential applications in foods – a review / S. Burt // Int. J. Food Microbiol. – 2004. – Vol. 94, Is. 6. – P. 223–253.
9. Carson C. F. Melaleuca alternifolia (Tea Tree) oil: a review of anti-microbial and other medicinal properties / C. F. Carson, K. A. Hammer, T. V. Riley // Clin. Microbiol. Rev. – 2006. – Vol. 19, Is. 7. – P. 50–62.
10. Melissa officinalis oil affects infectivity of enveloped herpesviruses / P. Chnitzler, A. Schuhmacher, A. Astani et al. / Phytomedicine. – 2008. – Vol. 15, Is. 9. – P. 734–740.
11. European Pharmacopoeia. 9<sup>th</sup> ed. Strasbourg: Council of Europe, 2017.
12. The United States Pharmacopoeia 40: The National Formulary 35. – New York, 2017. – 2569 p.
13. Governmental Pharmacopoeia of Ukraine: Suppositories and pessaries made in pharmacies / «Scientific Pharmacopoeia center». – 2 App. – Kh. : RIREG, 2014. – P. 716-723.

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**Introduction.** Antibacterial therapy certainly plays an important role in the treatment of these pathologies, although in most cases it causes allergic states, antibiotic resistance of various types of microorganism strains, and also a disfunction of normal vaginal biocoenosis. Anti-protozoal, antibacterial and antifungal agents are preferred, namely, ternidazole, metronidazole, fluconazole, clindamycin, miconazole, clotrimazole, nystatin, isoconazole etc. among the synthetic drugs used in gynecological practice. Prospective plant medicines for solving this problem are essential oils (tea tree, sea buckthorn, wormwood, chamomile), which provide inhibition of the development of pathogenic anaerobes. The aim of the work was to substantiate the composition and development of technology of combined vaginal suppositories (pessaries) with clindamycin phosphate and sea buckthorn oil for the treatment of infectious-

inflammatory gynecological diseases. **Materials and methods.** Model samples of suppositories were prepared with 0.100 g of clindamycin phosphate and 0.500 g of sea buckthorn oil. Disperse system of suppositories with clindamycin and sea buckthorn oil is an emulsion of 1<sup>st</sup> type, therefore it is possible to use as emulsifiers the following substances: polysorbate-80, emulsion wax or alkaline soaps. Model samples of suppositories with clindamycin phosphate and sea buckthorn oil were checked by pharmaco-technological parameters (description, homogeneity, disintegration time, pH). The study of antibacterial properties of suppository model samples with clindamycin and sea buckthorn oil was carried out. **Results and discussion.** Samples of suppositories with polysorbate-80 become homogeneous and meet the requirements of the SPhU 2.0. The results of the conducted researches of pharmaco-technological parameters shown that model samples of suppositories with clindamycin phosphate and sea buckthorn oil meet the requirements of the SPhU 2.0 for the following parameters: description, homogeneity, disintegration time, pH. **Conclusions.** The composition and technology of suppositories with clindamycin phosphate and sea buckthorn oil for pharmacy preparation was developed. A technological instruction for the pharmacy preparation of suppositories has been developed and tested in the conditions of pharmacy.

**Keywords:** suppositories, technology, suppository base, clindamycin phosphate, sea buckthorn oil.