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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

DEVELOPMENT OF FORMULATION TECHNOLOGY OF VAGINAL DRUG DOSAGE FORMS BASED ON LICORICE *(GLYCYRRHIZA GLABRA)*

Specialty: 3400.01 – Drug technology, organization of pharmaceutical business

Field of science: Pharmacy

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GENERAL DESCRIPTION OF WORK

Relevance of the topic and degree of development. All activities of the Azerbaijani healthcare system are aimed at protecting and restoring the health of the population of our country, and highly effective medicines, including those of herbal origin, play an important role in the success of these measures.

Over the past decades, there has been an increase in the number of pathologies of the female genital area throughout the world, among which inflammatory diseases are considered the most common. In the general structure of gynecological diseases, pelvic inflammatory diseases (PID) account for 60-65% of outpatient cases and up to 30% of hospitalized cases. The causative agents of these pathologies, according to WHO, in 10-15% of cases are viruses, among which the herpes simplex virus, papillomaviruses, and cytomegaloviruses predominate[1,2,3].

The approaches to modern treatment of diseases of the female genital tract (FGT) are primarily etiotropic in nature, but they include drugs from many pharmacological groups (non-steroidal anti-inflammatory, antiseptic, antifungal, immunomodulators, etc. drugs). This is explained by the fact that with PID, all systems of the body are involved in the pathological process, including metabolic processes. However, even such multidirectional treatment does not always allow achieving complete rehabilitation of the patient and prevent relapses of the disease, therefore, it is recommended to combine PID therapy with herbal medicine. Herbal medicine in this case is of an auxiliary nature, but when taking herbal medicines, the

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[2] Gondwe, T. Novel bacterial vaginosis-associated organisms mediate the relationship between vaginal douching and pelvic inflammatory disease/ T.Gondwe, R.Ness, P.A.Totten [et. al.]// Sex Transm Infect. – 2020. Vol 96(6), - p.439-444.

[3] Romaguera, R. Foreword — Sexually Transmitted Disease Surveillance, 2019 // CDC. — 2021.

natural biological complex of active compounds of the medicinal plant has an effect on the body[4,5,6,7].

Numerous biopharmaceutical studies have confirmed the importance of the dosage form for delivering the active substance to the pathological focus. Depending on the type of pathology, stage and course of the disease, each dosage form performs its own set of tasks in the patient's body. Therefore, from the range of dosage forms prescribed in gynecology, due to their biopharmaceutical properties, vaginal suppositories and gels. Vaginal suppositories and gels melt at body temperature, are easy to use and widely available, in addition, they have unique properties – they ensure the absorption of the active substance into the blood, bypassing the liver barrier[8,9].

The developed clear trend of intensification of inflammatory and viral diseases of the FGT everywhere has contributed to the increase in the frequency of PID diseases in Azerbaijan. In the region, the level of these pathologies is 79.5% and the structure of morbidity is dominated by pathologies of polymicrobial etiology (43.5%), bacterial vaginosis (30-80%) and enteroviral infections. The causative agents of the noted urogenital infections are mainly

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[4] Алиева, Ф.А., Бабаева, С.Г. Оценка проблемы, повышение качества диагностики и ведения пациентов, совершенствование контроля, перспективы внедрения принципов общественного здравоохранения в профилактику и лечение инфекций, передаваемых половым путем в Азербайджане// -Баку, -2015. Т2, №2, - 12 с.

[5] Ботоева, Е.А., Решетникова, Н.С., Цибикова, М.В. Применение фитоэкстрактов в гинекологии // Вестник Бурятского Государственного Университета, - 2017. вып. 3, - с. 27-37.

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[7] Окунев А.А. Инфекции, передаваемые половым путём (ИППП) - симптомы и лечение/ электронный ресурс, 2022

[8] Панкрушина, Т.А. Суппозитории. Современный взгляд на лекарственную форму / Т.А.Панкрушина, Л.Н.Ерофеева, Т.В.Орлова [и др.]. Монография, Курск:- 2017. - 212 с

[9] Анурова, М.Н. Определение реологических оптимумов вагинальных гелей / М.Н Анурова., Е.О. Бахрушина, А.М.Подколзин, [и др.] // Разработка и регистрация лекарственных средств, - 2018. № 2(23), - с. 46-51.

morphotypes of Gardnerella (about 70.59%), gram-positive and gram-negative bacilli (64.71% and 32.14%)[10,11,12,13].

Providing Azerbaijan with plant resources contributed to the accumulation of rich experience in the development of technologies for various medicines from plant medicinal raw materials. Particular attention was paid to licorice as a source of a natural complex of biologically active substances that have lymphotropic, anti-inflammatory, antiviral, immunocorrective, antitumor and other effects. Being a unique source of many active substances, glycyrrhizic acid and phytoestrogens in particular, licorice has a wide range of uses, including in gynecological practice[14,15,16,17].

Thus, the development of the composition and technical parameters research of dosage forms containing components of licorice glabra for the use of its pharmacotherapeutic effects in the treatment and prevention of diseases of the FGT is a timely and relevant research area.

Objects and methods of the study: suppository bases (PEO, oil mixture,Witepsol), gelling agents (methylcellulose derivatives),

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[10] Heydərova, N.F. Hamiləliyin adəti pozulmaları və xronik enterovirus infeksiyaları olan qadınlarda hamiləliyin aparılma taktikası:/ tibb elmi doktoru dis.avtoreferatı. / - Bakı, 2014. - 40 s.

[11] Şıxlı, V.Ş.Uşaqlıq yolunun opportunist bakterial infeksiyalari ilə xəstələrdə hamiləliyin gedişi və nəticəsi: / tibb üzrə fəlsəfə doktoru dis.avtoreferatı. / - Bakı, 2014. - 22 s.

[12] Багирова, Л.У. Современные принципы диагностики и лечения бактериального вагиноза у женщин репродуктивного возраста в условиях г. Баку: / автореферат дис. доктора фармацевтических наук. / - Баку, 2013.–22с.

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[14] Vəliyeva, M. Biyan və onun təbabətdə tətbiqi /M.Vəliyeva. - Bakı: Elmvə təhsil, - 2012-224 s.

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[16] Аммосов, А.С., Литвиненко, В.И., Попова, Т.П. Солодка: применение в мировой практике “Государственный научный центр лекарственных средств и медицинской продукции”, - Харьков. (обзор по материалам охранных документов за период с 1901 по 2020 годы).

[17] Musayeva, S. Prospects for the development of drugs with antiviral activity based on licorice / S.Musayeva, M.Valiyeva, F.Madatli [et. al.] // Eurasian Chem.Commun., -2021. Vol 3, - p. 301-309.

auxiliary substances (polysorbate-80, Lanette®SX). The quality standards of vaginal suppositories and intimate-gel, rheological characteristics, and antimicrobial and antifungal activity of suppositories has been established. Modern analysis methods have been used (L. Kruvchinsky method, spectrophotometry, chromatography, disk diffusion test, etc.).

Research aim and objectives. Development of obtaining technology and quality standards determination for vaginal dosage forms based on licorice *(Glycyrrhiza glabra).*

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

- to develop a composition of vaginal suppositories with licorice root extract based on biopharmaceutical studies of auxiliary components;
- to develop a composition of an intimate gel based on a thick extract of licorice based on the results of an analysis of auxiliary components;
- to propose a model of the technological scheme for the production of vaginal suppositories and prophylactic vaginal intimate gel with a thick extract of licorice root;
- determine quality standards for developed vaginal dosage forms;
- to study the rheological characteristics, antimicrobial and antifungal effects of experimental vaginal suppositories.

The scientific novelty of the dissertation.

For the first time in Azerbaijan:

- a comparative analysis of phytoprophylactic and phytotherapeutic agents used in gynecological practice, including those based on licorice in particular, has been conducted;
- biopharmaceutical studies have been carried out to select excipients included in the composition of experimental vaginal suppositories with a thick extract of licorice;
- research to select auxiliary substances included in the composition of the prophylactic intimate gel with a thick extract of licorice has been conducted;

- the technological basis for the production of vaginal suppositories and intimate gel with a thick extract of licorice has been developed;
- for the developed vaginal dosage forms have been established quality standards, and have been studied the rheological characteristics, antimicrobial and antifungal effects of the experimental vaginal suppositories.

Scientific and practical significance and implementation of research results. Scientifically based material on the development of vaginal medicinal products based on a thick extract of licorice in the form of vaginal suppositories and phytopreventative intimate gel is introduced into the educational process of the Department of Pharmaceutical Technology and Management of the AMU for students of the Faculty of Pharmacy and is used in the subjects "Pharmaceutical Technology-1" and "Pharmaceutical Technology-2". Eurasian patent No. 033596 "Suppositories for the treatment of cervical erosion" dated 07.11.2019 has been received, which allows us to recommend the developed vaginal suppositories based on a thick extract of licorice for the production to the National Biyan Industrial Park of the Republic of Azerbaijan**.**

An industrial scheme for the production of vaginal suppositories and phytopreventative intimate gel based on a thick extract of licorice has been developed.

The following patents have been published in the bulletins of the Eurasian Patent Office: No. 201600339/26 dated 05/02/2016 "A product for the prevention and treatment of the genitourinary system in men based on medicinal plants"; No. 201800275 03/29/2018 "Medicine for the treatment of proctological diseases", No. 201800277/26 dated 04/30/2018. "A drug for the treatment and prevention of thyroid diseases."

Approval of work. The main points of the dissertation work have been presented at scientific conferences: Congress of Azerbaijan on Allergology, Immunology and Immunorehabilitation (Baku, October 19-20, 2012); III All-Russian scientific-practical conference with international participation in "Problems of Pharmaceutical Science and Practice" (Vladikavkaz, 2013), the final

conferences of AMU "Current problems of medicine" (Baku, 2013, 2014, 2015, 2018), "Development, research, and marketing of new pharmaceutical products" (Pyatigorsk, 2016), "Modern Problems of Pharmacy" 5th International Scientific Congress dedicated to the 90th anniversary of the establishment of AMU, and "Current problems of pharmacy in Azerbaijan " dedicated to 80th anniversary of higher pharmaceutical education (Baku, 2021), "Scientific advances and challenges in biology" (Baku, 2021). Karabakh II. International Congress of Applied Sciences (Baku, 2021).

Publications. Based on the results of the dissertation work, 20 articles and theses have been published, including 8 in the abroad, educational and methodological recommendations have been developed, 1 Eurasian Patent has been received, and 3 positive decisions on Eurasian Patents have been obtained.

Main provisions submitted for defense:

- biopharmaceutical study of excipients included in the composition of vaginal suppositories with thick extract of licorice root:
- results of the selection of excipients and development of the composition of a preventive intimate gel with a thick extract of licorice;
- technological principles of production of vaginal suppositories and prophylactic vaginal intimate gel with thick licorice root extract;
- results of quality standards establishing for developed vaginal dosage forms;
- study of the rheological characteristics, antimicrobial and antifungal effects of experimental vaginal suppositories.

Scope and structure of the dissertation. The dissertation consists of an introduction (10102 characters), 6 chapters - literature review (55201 characters), objects and methods of research (17334 characters), development of the composition of vaginal suppositories with a thick extract of licorice root (33899 characters), development of the composition of intimate gel based on a thick extract of licorice (18309 characters), modeling of technological processes for the production of vaginal suppositories and intimate gel containing a

thick extract of a licorice (7667 characters), setting up of quality standards and study of rheological characteristics and effects of experimental vaginal suppositories (24747 characters), conclusion (20540 characters), results (2264 characters), practical recommendations (737 characters) and a list of references. The number of characters in the dissertation is 197737. The dissertation materials in the form of computer text are presented on 171 pages, contain 33 tables, 6 figures and 13 diagrams. The bibliography includes 209 sources, including 13 in the national language and 196 in a foreign language.

CONTENTS OF THE STUDY

When developing the technology for obtaining vaginal dosage forms based on licorice, has been used, obtained in the industrial park of "Biyan Products" LLC from local raw materials, a ready-made thick licorice extract *(Extractum Glycyrrhizae spissum)*.

Objects and methods of research.

The objects of the study have been:

– suppository bases: hydrophilic - polyethylene oxides (PEO) with molecular weights of 1500 and 400 in various ratios (7:3; 8:2; 9:1) and gelatin-glycerin base; lipophilic - hydrofat, cocoa butter and a mixture of cocoa, sea buckthorn and milk thistle oils in a ratio of 6:3:1; diphilic - an alloy of hydrogenated cottonseed oil with 3% emulsifier T-2 (GHM-3T), Witepsol;
– Structural and mechanical properties of hydrophilic, lipophilic and amphiphilic bases, and the degree of release of the active substance from suppositories prepared on these bases;
– Excipients (polysorbate-80, pyrogenic silicon dioxide, and gelatose) used in the technology of vaginal suppositories with a thick extract of licorice in a mixture of cocoa, sea buckthorn and milk thistle oils (6:3:1); the priority excipient and its concentration were determined;
– Intimate gel prepared with 5 gelling agents - sodium alginate Protanal CR 8223 (FMCBioPolymer), methylcellulose MC,

hydroxypropylcellulose Klucel® (Ashland), hydroxyethylcellulose Natrosol® 250G (Ashland) and rare cross-linked acrylic polymer Carbopol ETD 2020 (Lubrizol));

– Excipient, emulsifier Lanette®SX (a mixture of cetearyl alcohol, sodium lauryl sulfate, and sodium cetearyl sulfate), as part of an intimate gel with a thick extract of licorice; determined its optimal concentration;
– Prepared vaginal suppositories and intimate gel with thick extract of licorice; identified quality standards for these products. Additionally, rheological characteristics, antimicrobial and antifungal effects of experimental vaginal suppositories and antioxidant activity of licorice thick extract were determined.

Research methods: The selection of the optimal suppository base for vaginal suppositories with a thick extract of licorice was carried out based on the results of studying the structural and mechanical characteristics of suppositories on these bases (solubility for suppositories on hydrophilic bases; melting temperature (t_p^0) and hardening temperature (t_z^0), hardness (h), time of complete deformation (t_d^') for suppositories on lipophilic and amphiphilic bases). The degree of release of glycyrrhizic acid from the analyzed vaginal suppositories was determined by L. Kruvchinsky's method, based on equilibrium dialysis of the active substance through a semi-permeable membrane into various media. Using a spectrophotometric method in the UV region at 258 nm, the priority suppository base was determined by the maximum degree of release of glycyrrhizic acid into aqueous and acidic environments. Acetate buffer solution (pH 3.7-4.0) imparted acidic properties to the medium.

We also determined the priority stabilizing auxiliary substance for suppositories with a thick extract of licorice and its required concentration using the method of equilibrium dialysis (according to L. Kruvchinsky) in aqueous and acidic environments.

The priority gelling agent and the required concentration of the Lanette®SX emulsifier for intimate gel were determined through a comparative assessment of the kinetic stability coefficients of

intimate gel samples prepared using test gelling agents with the addition of various concentrations of Lanette®SX (1.0, 2.0 and 3 .0%). The correctness of the choice of the priority gelling agent (methylcellulose (MC)) was confirmed by comparing the osmotic activity of MC with other cellulose derivatives.

The quality standards of prepared vaginal suppositories have been assessed by General Pharmacopeial Article (No. 91500.05.001-00 “Quality Standard for Medicines. Basic Provisions”) and General Pharmacopoeia Monograph (1.4.1.0008, “Semisolid drug dosage forms” of State Pharmacopoeia of the Russian Federation XV). Rheological parameters, microbiological purity, antimicrobial and antifungal activities have been also assessed. The antioxidant activity of different concentrations of thick licorice extract have been assessed.The quality standards of the prepared intimate gel have been determined potentiometrically.

In the process of statistical processing, MS Excel, Statistika 6.0 and SPSS programs have been used.

DISCUSSION OF RESEARCH RESULTS

Development of the composition of suppositories with licorice root extract. Determining the priority suppository base for simulated vaginal suppositories with a thick licorice extract begins by assessing the solubility of suppositories on hydrophilic bases (PEO and glycerol-gelatin base). The average solubility of suppositories on PEO bases has been 1.63±0.05 g/min. PEO (8:2) and PEO (9:1) have the best solubility. After 15, 30 and 45 minutes between the solubility of PEO (8:2) and PEO (9:1) according to the Wilcoxon test (W), there have been the statistical differences of varying degrees of significance (respectively $^{15}W=20.5$, $p=0.025$, pPEO (8:2)/PEO(9: 1)<0.050; $^{30}W=55.0$, $p=0.005$, pPEO (8:2) /PEO(9:1)<0.010; $^{45}W=0$, $p=0.005$, pPEO(8:2)/PEO(9: 1)<0.010), after 60 minutes there have been no differences ($^{60}W=6.0$, $p=0.102$, pPEO(8:2)/ PEO(9:1)>0.050). Consequently, after an hour these bases have been equally completely dissolved.

After 15, 30, 45, and 60 min, significant differences have been observed between the solubility of PEO (8:2) and glycerol-gelatin base (respectively, ^{15}T=-30,450, ^{30}T=-12,378, ^{45}T=11,901, ^{60}T=-18,277, p<0,001). After 15, 30 and 60 min, statistically significant differences were also observed between the solubility of PEO (9:1) and the glycerol-gelatin base (respectively, ^{15}T=-7,267, ^{30}T=-28,935, ^{45}T=-19,491, ^{60}T=-15,096, p<0,001).

However, the high solubility of PEO suppositories expresses their special hygroscopicity, which can lead to dehydration of the mucous membranes. The incomplete solubility of the glycerol-gelatin based suppository (residue 0.19±0.09) characterized its solubility with a slight swelling effect, which is undesirable for the mucous membranes. This base also has low mechanical strength and hardness, but most importantly prone to microbial contamination and molding.

Of the lipophilic bases, the structural and mechanical requirements put forward to vaginal suppository bases (melting point t_m^0≈37^{0}C, the difference between the melting point and solidification temperature t_m^0 and t_s^0±5^{0}C, the time of complete deformation no more than 15 min) have not been met by confectionery hard fat and cocoa butter. t_m^0 of hard fat was higher than 37^{0}C (respectively 38.4±0.30) and the difference between t_m^0 and t_s^0 was 8.2^{0}C (respectively 38.4±0.30 and 30.2±0.25).Cocoa butter, on the contrary, had t_m^0 below 37^{0}C (respectively 34,6±0,28) and the difference between t_m^0 and t_s^0 have been 9^{0}C (respectively 34,6±0,28 and 27,4±0,28). Suppositories based on a mixture of cocoa, sea buckthorn, and milk thistle oils had optimal t_m^0 (36,9^{0}C±0,17) and the difference between t_m^0 and t_s^0 (4,3^{0}C). Between t_m^0 mixtures of oils (m/o), solid fat (s/f), and cocoa butter (c/b) according to Student's t-test, statistically significant differences were observed (respectively $T_{m/o \text{ and } s/f}$ =11,115, $T_{m/o \text{ and } c/b}$ = -18,459, p<0,001). Between t_s^0 mixtures of oils, confectionery hard fat type A and cocoa butter also showed differences (respectively $T_{m/o \text{ and } s/f}$=-19,832, $T_{m/o \text{ and } c/b}$ = -32,263, p<0,001). Between hardness (h)of mixtures of oils, solid fat, and cocoa butter also showed statistical differences (respectively $T_{m/o \text{ and } s/f}$=5,348, $T_{m/o \text{ and } c/b}$ = 25,896, p<0,001). Full deformation timet_d'

oil mixtures (6,6±0,22) were statistically significantly different from t_d' solid fat (9,6±0,23) and cocoa butter (5,6±0,40) (respectively, $T_{m/o \text{ and } s/f}$ =-36,145, $T_{m/o \text{ and } c/b}$ = 5,815, p<0,001).

Of the amphiphilic bases, Witepsol had the most suitable structural and mechanical characteristics (correspondingly, the indicators $t_m^0$36,8±0,17; t_s^0 30,8±0,17; h 6,1±0,26 and t_d'6,4±0,21). Betweent_m^0 mixtures of oils and Hydrogenated Cottonseed Oil-3T (HCO-3T) statistically significant differences were observed ($T_{m/o \text{ and } hco}$=-4,269, p=0,002, p<0,010). Between t_m^0 mixtures of oils and Witepsol, no statistically significant differences have been observed ($T_{m/o \text{ and } w}$=0,742, p=0,477, p>0,050). Between t_m^0 mixtures of oils and Hydrogenated Cottonseed Oil-3T and Witepsol statistically significant differences were observed (respectively $T_{m/o \text{ and } hco}$=13,784, $T_{m/o \text{ and } w}$ =19,398, p<0,001). Between hardness (h) of oils mixtures and Hydrogenated Cottonseed Oil-3T statistically significant differences were observed ($T_{m/o \text{ and } hco}$ =4,528, p=0,001), no differences were noted between h mixture of oils and Witepsol ($T_{m/o \text{ and } w}$= 2,068, p=0,069, p<0,05). Full deformation time t_d' oil mixtures (6,6±0,22) and Hydrogenated Cottonseed Oil-3T were statistically significantly different ($T_{m/o \text{ and } hco}$ =2.786, p=0,021, p<0.050); t_d' mixtures of oils and Witepsol did not differ statistically significantly ($T_{m/o \text{ and } w}$ = 1.696, p=0.124, p<0.05).

Thus, according to the results of the study, the optimal ointment bases were a mixture of oils and Witepsol. Next, using the method of L. Kruvchinsky, we compared the level of kinetics of glycyrrhizic acid from vaginal suppositories on optimal bases in aqueous and acidic environments.

The average availability of glycyrrhizic acid from suppositories containing a mixture of oils and Witepsol into the aqueous environment was statistically significantly different (respectively:^{15}T=-5.605, p=0.005, p<0.05, ^{30}T=85.791, p<0.001, ^{45}T=55.223, ^{60}T=-41.097, ^{75}T= 20.083, p<0.010).

A comparison of the average concentrations of glycyrrhizic acid released from suppositories on a mixture of oils and Witepsol into an acidic buffer solution also showed the preferential kinetics of glycyrrhizic acid from suppositories on a mixture of oils. After 15

minutes, the following statistical differences were noted between the indicators: T=34.98 (p<0.001); in 30 minutes -T=59.70 (p<0.001); in 45 minutes - T=51,32 (p<0,001); in 60 minutes – T=21,13 (p<0.001); in 75 minutes - T=24.56 (p<0.001).

To improve the quality and, most importantly, increase the stability of experimental vaginal suppositories with a thick extract of licorice, we introduced an additional, stabilizing, auxiliary substance into the composition of the suppository.

We compared the completeness of the release of glycyrrhizic acid into an aqueous medium and an acetate buffer solution from suppositories prepared with a mixture of oils with the addition of polysorbate-80, pyrogenic silicon dioxide and gelato in an average amount (2%). The maximum kinetics of glycyrrhizic acid from suppositories prepared with a mixture of oils in an aqueous medium was observed when using polysorbate 80. After 15 minutes, statistical differences according to the ANOVA criterion were: A=21180,121(p<0.001), in 30 minutes - A=56931.909 (p<0.001), in 45 - A=17806.031(p<0.001), in 60- A=12778.169 (p<0.001), in 75- A=6848.563 (p<0.001).

At the next stage of the study, the concentration of polysorbate-80 was determined, which promotes the maximum release of glycyrrhizic acid from simulated suppositories into an acidic buffer solution. The minimum accessibility value was observed in the presence of 1% polysorbate, and the maximum – in the presence of 3% polysorbate. Accordingly, after 15 minutes the availability value –88.82±0.10 with the polysorbate 1% and 89.32±0.06 with the polysorbate 3% (A=22.878, p<0.001), in 30 minutes - 89.20±0.10 and 89.50±0.12 (A=6.814, p=0.012, p<0.050), in 45 minutes - 89.42±0.10 and 89.72±0.06 (A=9.722, p=0.003, p<0.05), in 60 minutes – 89.54±0.11 and 90.06±0.13 (A=21.148, p<0.001 in 75 minutes-89.56±0.17 and 90.58±0.06 (A=66.127, p<0.001). However, in the NTD the maximum permissible amount of introduction of polysorbate-80 into the dosage form is no more than 1%. Taking into account the conducted study, the proposed composition of simulated vaginal suppositories with a thick extract of licorice includes: thick extract of licorice 0.2 g; suppository base a mixture of cocoa butter,

sea buckthorn, and milk thistle (6:3:1) 4.0 g; polysorbate - 80 0.1 g.

The definition of a mixture of oils as a priority base gave us grounds to use the pouring method for preparing suppositories. The mass of the components included in the suppository (thick licorice extract - 0.2 g and polysorbate-80 - 0.1 g) exceeded the permissible 5% of the total mass of the suppository (4 g), so it was necessary to recalculate the amount of the suppository base taking into account the Dosage Replacement Factor (DF).

To calculate DF, 40 vaginal suppositories were experimentally prepared: 20 "placebo" suppositories without active ingredients and 20 containing active ingredients. The ratio of the difference between the weight of 20 suppositories with a thick licorice extract + polysorbate-80 g (85.80 g) and "placebo" (79.69 g) to the total weight of thick licorice root extract + polysorbate-80 contained in 20 suppositories (5.98 g) allowed us to determine DF (1.02). Next, the weight of the suppository base was calculated as the difference between the weight of 20 "placebo" suppositories and DF multiplied by the total weight of excipients (thick licorice extract + polysorbate-80) contained in 20 suppositories, which was 73.60 g.

Development of a composition of a prophylactic intimate gel with licorice root extract. In order to select the optimal type of gelling agent and concentration of emulsifier, the experimental intimate gel was prepared using five gelling agents, thick licorice extract, and emulsifier were added in various concentrations (1.0, 2.0, and 3.0%), and then the kinetic stability coefficient (K) values of the prepared gel samples were determined. The lowest K value is characteristic of cellulose derivatives, in particular, methylcellulose (MC) (respectively, after 24 hours with the addition of 1% emulsifier 0.07, 015, 0.21). Further calculations allowed us to establish a negative value (-0.05; -0.05; -0.06) of the deviation of K from the average value, which proves the presence of the truly lowest K values for MC (the average value of the K coefficient is ≈0.16). Homogeneity of deviations of the coefficient of K from the average value is noted after 7 days during the preparation of the intimate gel, with the addition of an emulsifier at a concentration of 1.0%; 2.0%; and 3.0%. As a result, we conclude that a kinetically stable intimate

gel with a thick extract of naked licorice can be obtained on the MC with the addition of an average amount (2.0%) of emulsifier.

To confirm the priority of MC as a gelling agent for the modulated prophylactic intimate gel, we additionally conducted a comparative study of the osmotic activity (OA) and other cellulose derivatives (hydroxypropyl cellulose and hydroxyethylene cellulose). According to the results of OA calculations, the most pronounced osmotic activity was possessed by the gel on MC, which absorbed up to 254% of water from the initial mass, retaining osmotic activity for up to 10 hours. Comparison of the degree of liquid adsorption through a semipermeable membrane in gel samples prepared on MC and other gelling agents at intervals showed that there were no statistical differences between the degree of liquid adsorption after 2 and 6 hours by gels on MC and hydroxypropyl cellulose. (respectively, $T=-0.557$, $p=0.591$, $T=-2.236$, $p=0.052$, $p>0.050$), after 4 hours, there were also no statistical differences between the absorption rates of gels on MC and hydroxyethylcellulose ($T=-1.627$, $p=0.138$, $p>0.050$).

Based on the above studies, the composition of the prophylactic intimate gel has been substantiated: thick extract of licorice 5.0 g; MC 6.0 g; Lanette®SX 2.0 g; nipagin/nipazole (1:3) 0.15-0.23 g; glycerin 20.0 g; purified water up to 100 g.

Technological process for the production of vaginal suppositories and intimate gel containing a thick extract of licorice.

We have proposed models of technological schemes for obtaining suppositories and intimate gel, consisting of auxiliary work (sanitary treatment of the premises, equipment, suppository form, and mixing reactor), necessary calculations, preparation of the base, gelling agent and medicinal substances, introduction of active and auxiliary substances, obtaining, formation and packaging of finished products.

The technology algorithm for producing an experimental intimate gel included: obtaining a gelling agent, adding a thick extract of licorice in glycerin, adding Lanette®SX emulsifier and

preservatives, mixing, homogenization, deaeration of the composition, packaging, packaging and labeling (chart 1).

At stage TP 4 (technological process), when preparing the suppository base, introducing auxiliary and active substances, the mass of the mixture of cocoa, sea buckthorn and milk thistle oils (6:3:1) was melted at a temperature not exceeding 37^0C, then filtered through a colatur with a two-layer gauze. Polysorbate 80 at 35^0 C has been introduced into 1/8 of the suppository base with intensive stirring in mixers. After 45 minutes of grinding, the remaining suppository base was added and mixed for a quarter of an hour at 45-50 revolutions per minute. A solution of thick extract of naked licorice at pre-mixed 35^0 C for 60 minutes with 1⁄4 of the suppository base, including polysorbate 80, then added to the remaining suppository base and mixed for another 25 minutes. The resulting mass has been tested for homogeneity, time of complete deformation, solidification, and melting temperatures, amount of glycyrrhizic acid and microbiological purity. The high-quality suppository mass has been sent to the stage of forming vaginal suppositories. At stage TP 5, the mold cells were filled with the melted mass obtained above (t_m36-37 ^{0} C), cooled for 20-25 minutes, then the appearance, weight, and quantitative content of the active substance in the finished product has been checked.

At the final packaging and labeling operation (PLO), vaginal suppositories with a thick extract of licorice were packed in 6 pcs. The finished suppositories were accompanied by instructions for use, and the boxes were provided with an inscription informing about the name of the drug in Azerbaijani, Russian, and Latin, the amount of thick licorice extract per suppository, and the expiration date. The finished suppositories have been subjected to quality control in batches. The proposed process flow chart has been used to obtain 4 batches of vaginal suppositories.

The algorithm for the technology of obtaining the experimental intimate gel included: obtaining a gelling agent, adding a thick extract of licorice in glycerin, adding the Lanette®SX emulsifier and preservatives, mixing, homogenizing, deaerating the composition, packaging, packing and labeling (Fig. 1).

At the stage of obtaining the gelling agent, ½ of the required amount of purified water was added to the reactor mixer at a speed of up to 80 rpm, and the contents of the reactor were heated to a temperature of 80-90 °C. Then the required amount of methylcellulose is loaded into the reactor. The contents have been mixed until homogeneity, then left at room temperature until cooled, poured in the remaining volume of water, and kept at a temperature of 4C and below until completely dissolved. Next, a measured amount of a mixture of thick licorice extract in glycerin, Lanette®SX emulsifier, and preservatives was added to the reactormixer, mixed and homogenized. Deaeration has been carried out by daily settling, and periodically stirring the mass. Upon completion of all technological stages, the gel products have been analyzed according to standard parameters by TR (marketable appearance, smell, color, acidity, water content, etc.). Having received positive analysis results, the reactor contents were sent to the packaging and labeling stage.

The establishment of quality standards and the study of the rheological characteristics and effects of experimental vaginal suppositories were carried out according to the pharmacopoeial article on suppositories prepared on a lipophilic base and containing plant raw materials: the appearance (shape, color), absence of impurities, time of complete deformation, average weight and deviation from it, uniformity of dosing, melting point, stability during storage, authenticity and quantitative content of glycyrrhizic acid, acid, iodine and peroxide numbers and microbiological purity were assessed.

The resulting suppositories were identical in appearance, torpedo-shaped, smooth, brown with a specific odor, and homogeneous (longitudinal section without inclusions). The authenticity of the vaginal suppositories was determined by qualitative reactions to glycyrrhizic acid. The purity of the product for the absence of possible impurities was assessed by TLC. The stability of the vaginal suppositories over time was determined using the "forced aging" method. The finished vaginal suppositories were stored in a cool, dark place at a temperature of +8-16 °C. After 24 months. After storage, the quality of the suppositories was re-evaluated. To justify

the regulation of the shelf life and storage conditions, 4 series of vaginal suppositories were prepared and stored in a dry, dark place at different temperature conditions. Two series -012016/1 and 012017/1 were stored for 24 months at room temperature (16.0 –22.00 C) and two series 012016/2 and 012017/2 were stored for 24 months at a temperature of 8.0 –15.00 C; all series were tested every 6 months. Glycyrrhizic acid in the analyzed series was quantitatively determined by spectrophotometry. Stability during storage was also assessed by the time of complete deformation. The results of the study made it possible to establish the conditions (store in a cool, dark place at a temperature of + 8-16 ° C) and the shelf life (2 years) of the obtained suppository products. The average mass and deviations from the average mass of vaginal suppositories were determined by successively weighing 20 suppositories together, calculating the average mass (M), then weighing each suppository separately, comparing their mass with the average mass, and determining the deviation from the average mass in %. The uniformity of dosing was determined by the spectrophotometry method, calculating the quantitative content of glycyrrhizic acid in each individual (n = 6) experimental suppository for analysis. The average melting point of the experimental suppositories was 35,63±0,4^{0}C. Positive deviations from the average temperature were mainly observed. The values of acid, iodine and peroxide numbers were estimated in 3 batches of suppositories, on average, the acid number was - 1.05, iodine number - 0.48, peroxide number - 0.61, which did not exceed the norm. A mandatory indicator of the stability of the vaginal gel composition is the pH of the aqueous extract. The quality of the intimate gel was assessed potentiometrically, mainly the deviations of the hydrogen index from the average had a negative value, in recalculation to % it was 0,10±0,08, which characterized the neutrality of the environment and, accordingly, the absence of undesirable impurities in the experimental intimate gel. The quality of the gel can also be controlled by the following parameters: description, identification, average mass and mass homogeneity, disintegration, content homogeneity, melting point or time of complete deformation,

solubility, microbiological purity, quantitative content of medicinal substances, however, the requirements set out in the article "Ointments" are not included in the mandatory pharmacopeial requirements.

Three samples of vaginal suppositories stored at different temperatures (t 8,0 – 15,0^{0}C, and t 16,0 – 22,0^{0}C) were analyzed for microbiological purity. The following microbiological purity of the samples was established: - the total number of aerobic bacteria was 120 CFU per unit of the drug (g); - the total number of yeast and mold fungi was 30 CFU per unit of the drug (g); - Gram-negative bacteria resistant to the action of bile, Staphylococcus aureus, Escherichia coli and Salmonella spp. were not detected in the samples under study. Consequently, the developed suppositories were not contaminated with unacceptable microorganisms during storage, while the presence of acceptable ones was within the normal range. Additionally, the rheological characteristics (shear stress and dynamic viscosity) of the experimental vaginal suppositories were checked at 30^{o}C, 35^{o}C, and 45^{o}C.

Under the analyzed temperature conditions, the structure of the suppositories was not subject to significant destruction.

The shear stress indicator increases with increasing rotation speed, the dynamic viscosity indicator decreases, which proves that the product submitted for analysis manifested itself as a structured system with thixotropic properties. Preservation of thixotropy under various temperature conditions characterizes the analyzed suppositories as a non-Newtonian system. The dominance of thixotropic properties was confirmed by calculation mechanical stability (MS≈1.53) of the composition. The MS value indicates high sedimentation stability, ensuring uniform distribution of active and auxiliary ingredients in the suppository base.

When studying the antimicrobial and antifungal effects, it was found that the suppositories do not exhibit direct antimicrobial and antifungal properties. The observed production of lactobacilli growth proved that the analyzed object does not violate the biocenosis of the genitals.

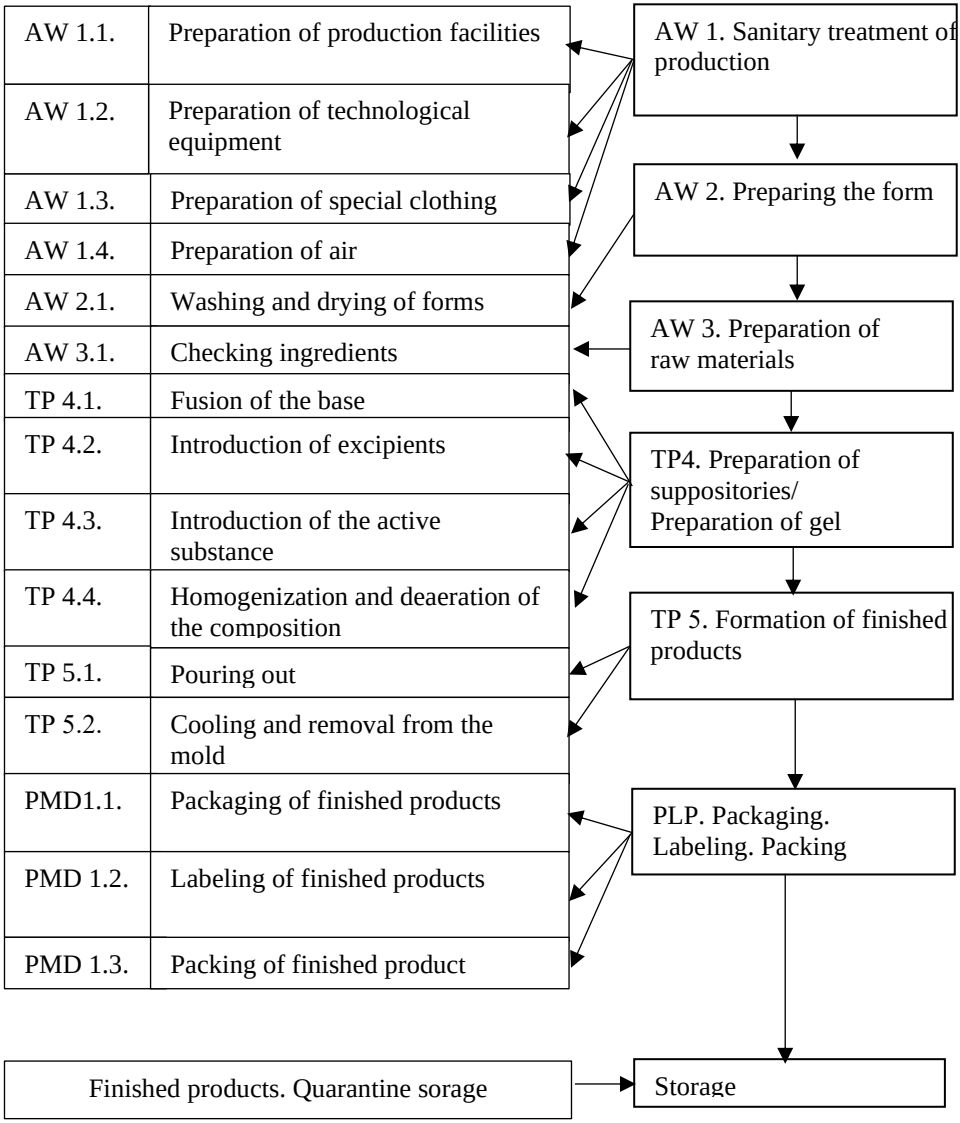

Figure 1. Flow diagram for the production of vaginal suppositories and intimate gel in pilot industrial conditions.

Evaluation of the antioxidant activity of various concentrations of thick licorice extract (the average value of the TAC was 7.52±0.53 mmol / l, the TOS 21.88±2.10 μmol / l and the OSI 0.29±0.007) showed that the most significant antioxidant effect of licorice extract is at a concentration of 5 g., this is the dose we recommended in the composition of the intimate gel.

CONCLUSIONS

1. Based on a comparative analysis of the structural and mechanical characteristics of the suppository bases and the availability of glycyrrhizic acid from the experimental vaginal suppositories, we identified the priority suppository base, excipient, and its concentration. We developed a composition of vaginal suppositories, including: a suppository base of a mixture of cocoa butter, sea buckthorn, and milk thistle (6:3:1) - 4.0 g, thick extract of licorice - 0.2 g and polysorbate 80 - 0.1 g. We calculated the replacement coefficient of the base with excipients when obtaining suppositories by the pouring method.
2. By calculating the kinetic stability coefficient, we established the priority gelling agent and the optimal concentration of the emulsifier for intimate gel with a thick extract of licorice. The priority of the selected gelling agent was confirmed by comparing osmotic activity of MC with other cellulose derivatives (OAMS up to 254%). The composition of the prophylactic intimate gel was developed, including: thick extract of licorice 5.0 g; gelling agent methylcellulose - 6.0 g; Lanette®SX - 2.0 g; nipagin / nipazole (1: 3) 0.15-0.23 g; glycerin - 20.0 g; purified water to 100.0.
3. Models of the technological scheme for the production of vaginal suppositories and prophylactic vaginal intimate gel with a thick extract of licorice root were proposed.
4. Determination of quality standards for vaginal suppositories showed compliance with the appearance (torpedo-shaped, smooth, brown with a specific odour), authenticity, and absence of unwanted impurities. Determination of stability during storage allowed to establish optimal storage conditions in a dark place at a temperature of +8-16 and the shelf life of vaginal suppositories with a thick extract of licorice (2 years). The quality of the finished product was also checked by the average weight and deviation from it (4.089 ± 0.06% gr.), dosing uniformity, melting point (t 35^0C), pH (6.3 ± 0.04), acid

(1.05), iodine (3.48) and peroxide (0.61) numbers, and microbiological purity. The deviation of the hydrogen index of the intimate gel from the average had a negative value (0.10 ± 0.08), which characterized the neutrality of the environment and the absence of undesirable impurities.

5. The study of the rheological properties of the suppositories characterized the product as a structured system with thixotropic properties. The calculated mechanical stability (MS≈1.53) indicated high sedimentation stability of the system. It was revealed that the suppositories do not exhibit direct antimicrobial and antifungal effects.

PRACTICAL RECOMMENDATIONS

1. The program of dispensary observation of women of different ages should include monitoring of diseases of the FGT, among which special attention should be paid to inflammatory diseases and viral infections: herpes simplex, papillomavirus and cytomegalovirus.
2. In order to prevent and treat diseases of the gallbladder, it is recommended to use immunotropic, anti-inflammatory and antiviral herbal remedies of licorice.
3. The high anti-inflammatory and antioxidant activity of the developed vaginal suppositories and intimate gel based on a thick extract of licorice makes it possible to recommend them for PID.
4. Considering the effectiveness, safety, harmlessness and lack of side effects of the dosage forms we have developed, it is recommended to use them in gynecology.

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LIST OF ABBREVIATIONS

AW – Auxiliary works
DF – Dosage replacement factor
FGT – Female genital tract
M – Average mass
MC – Methylcellulose
MS – Mechanical stability
OA – Osmotic activity
OSI – Oxidative stress index
PEO – Polyethylene oxide
PID – Pelvic inflammatory diseases
PMD – Packaging and labeling operation
TAC – Total antioxidant capacity
TOS – Total oxidant status
TP – Technological preparation

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