ТЕХНОЛОГІЯ ЛІКАРСЬКИХ ПРЕПАРАТІВ

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Development of the laboratory technology of the combined pessaries with acyclovir and essential oils

The range of pessaries at the Ukrainian pharmaceutical market is represented by medicines containing substances of the synthetic origin for the treatment of genital herpes (GH). However, combined drugs with a wide range of pharmacological action and minimal side effects for treating GH are practically absent, except for rectal suppositories "Panavir" containing the purified extract from *Solanum tuberosum* stem. For this reason the question of expansion of the range of pessaries based on substances of the plant or synthetic origin is topical and important.

Aim. To develop the laboratory technology of the combined pessaries with acyclovir and essential oils of tea tree and thyme.

Materials and methods. The technological process for preparing pessaries was carried out in accordance to the generally accepted rules for preparing suppositories taking into account the nature and physicochemical properties of active pharmaceutical ingredients (API) and excipients. According to the methods of the State Pharmacopoeia of Ukraine (SPhU) the following parameters were determined on the samples of pessaries: description, uniformity, pH, melting point, time of complete deformation, disintegration time, and resistance. Quantitative determination of acyclovir was conducted by the method of absorption spectrophotometry in the UV spectrum at a wavelength of (265 ± 2) nm. The thermogravimetric studies were performed on a Q-1000 derivatograph of F. Paulik, I. Paulik, L. Efdei system.

Results and discussion. Based on the biopharmaceutical and pharmacotechnological studies conducted the laboratory technology of the combined pessaries with acyclovir and essential oils of tea tree and thyme has been developed. The complex of experimental studies on selection of the amount of an emulsifier, fineness and the the choice of solvent for acyclovir, the choice of the rational technology for pessaries has been conducted. The technology proposed allows obtaining pessaries in accordance with the requirements of the SPhU.

Conclusions. For the first time the laboratory technology of pessaries with acyclovir and essential oils of tea tree and thyme has been developed. The results obtained have shown the prospects for further study of the combined pessaries with acyclovir and essential oils of tea tree and thyme in order to introduce this dosage form into production.

***Key words**: genital herpes; pessaries; development; technology; acyclovir; essential oils*

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Розробка лабораторної технології комбінованих песаріїв з ацикловіром та ефірними оліями

Наявний асортимент песаріїв на фармацевтичному ринку України представлений лікарськими засобами для лікування генітального герпесу (ГГ), до складу яких входять речовини синтетичного походження. При цьому комбінованих препаратів для лікування ГГ з широким спектром фармакологічної дії та мінімальними побічними ефектами вкрай мало, за винятком ректальних супозиторіїв «Панавір», що містять очищений екстракт із пагонів рослини *Solanum tuberosum*. Саме тому питання розширення асортименту песаріїв рослинного походження або комбінованого складу із синтетичними речовинами є важливим і актуальним.

Мета роботи – розробка лабораторної технології комбінованих песаріїв із ацикловіром та ефірними оліями чайного дерева і чабрецю.

Матеріали та методи. Технологічний процес приготування песаріїв здійснювали відповідно до загальноприйнятих правил приготування супозиторіїв із урахуванням природи і фізико-хімічних властивостей активних фармацевтичних інгредієнтів (АФІ) та допоміжних речовин. На зразках песаріїв за методиками ДФУ проведено визначення показників: опис, однорідність маси, pH, температури плавлення, час повної деформації, час розпадання, стійкість. Кількісне визначення ацикловіру проводили методом абсорбційної спектрофотометрії в УФ-області спектру за довжини хвилі (265 ± 2) нм. Термогравіметричні дослідження проводили на дериватографі Q-1000 системи Ф. Паулік, І. Паулік, Л. Ефдей.

Результати та їх обговорення. На підставі проведених біофармацевтичних і фармако-технологічних досліджень розроблено лабораторну технологію комбінованих песаріїв із ацикловіром та ефірними оліями чайного дерева і чабрецю. Проведено комплекс експериментальних досліджень з підбору кількості емульгатора, здрібненості та вибору розчинника для ацикловіру, вибору раціональної технології песаріїв. Запропонована технологія дозволяє отримати песарії у відповідності з вимогами ДФУ.

Висновки. Вперше розроблено лабораторну технологію песаріїв із ацикловіром та ефірними оліями чайного дерева і чабрецю. Результати проведеного дослідження показали перспективність подальшого вивчення комбінованих песаріїв із ацикловіром та ефірними оліями чайного дерева і чабрецю з метою впровадження даної лікарської форми у промислове виробництво.

Ключові слова: *генітальний герпес; песарії; розробка; технологія; ацикловір; ефірні олії*

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Разработка лабораторной технологии комбинированных пессариев с ацикловиром и эфирными маслами

Ассортимент пессариев на фармацевтическом рынке Украины представлен лекарственными средствами для лечения генитального герпеса (ГГ), в состав которых входят вещества синтетического происхождения. При этом комбинированных препаратов для лечения ГГ с широким спектром фармакологического действия и минимальными побочными эффектами очень мало, за исключением ректальных суппозиториев «Панавир», в состав которых входит очищеный экстракт из стеблей растения *Solanum tuberosum*. Поэтому вопрос о расширении ассортимента пессариев на основе веществ растительного происхождения или комбинированного состава с веществами на основе растительного и синтетического происхождения очень важен и актуален.

Цель работы – разработка лабораторной технологии комбинированных пессариев с ацикловиром и эфирными маслами чайного дерева и чабреца.

Материалы и методы. Технологический процесс приготовления пессариев проводили в соответствии с общепринятыми правилами приготовления суппозиториев с учетом природы и физико-химических свойств активных фармацевтических ингредиентов (АФИ) и вспомогательных веществ. На образцах пессариев по методикам ГФУ проведено определение показателей: описание, однородность массы, pH, температура плавления, время полной деформации, время распадаемости, стойкость. Количественное определение ацикловира проводили методом абсорбционной спектрофотометрии в УФ-области спектра при длине волны (265 ± 2) нм. Термогравиметрические исследования проводили на дериватографе Q-1000 системы Ф. Паулик, И. Паулик, Л. Эфдей.

Результаты и их обсуждение. На основе проведенных биофармацевтических и фармако-технологических исследований разработана лабораторная технология комбинированных пессариев с ацикловиром и эфирными маслами чайного дерева и чабреца. Проведен комплекс экспериментальных исследований по подбору количества эмульгатора, измельченности и выбору растворителя для ацикловира, выбору рациональной технологии пессариев. Предложенная технология позволяет получить пессарии в соответствии с требованиями ГФУ.

Выводы. Впервые разработана лабораторная технология пессариев с ацикловиром и эфирными маслами чайного дерева и чабреца. Результаты проведенного исследования показали перспективность дальнейшего изучения комбинированных пессариев с ацикловиром и эфирными маслами чайного дерева и чабреца с целью внедрения данной лекарственной формы в промышленное производство.

Ключевые слова: *генитальный герпес; пессарии; разработка; технология; ацикловир; эфирные масла*

Among sexually transmitted diseases genital herpes (GH) takes the second place by prevalence after trichomoniasis. According to the statistic data only in the USA every 4-6 inhabitants of the country are carriers of the virus [1]. In this connection there is the active worldwide search of antiherpes drugs, it has led to creation of a group of anomalous nucleosides – acyclovir and its derivatives [2, 3]. Acyclovir is one of most often prescribed antiviral drugs, the "gold" standard of the treatment of GH. Among the existent antiviral drugs of the synthetic origin it is the safest, however, with rather low bioavailability (about 20 %) [4]. It is known that one of ways of increasing bioavailability and efficiency of acyclovir is its use in the combination with other drugs. The best results are observed while using drugs with different mechanisms of action. The studies on the antiherpes activity of substances of acyclovir, essential oil of tea tree, essential oil of thyme and pessaries with acyclovir have demonstated that they effectively suppressed reproduction of herpes virus type 2. It has been shown on the experimental model of herpes infections in guinea pigs that pessaries with the original composition cotaining acyclovir and essential oils are an effective prophylactic and therapeutic drug [5].

It is known that when developing the technology of vaginal dosage forms the type and amount of excipients are important since completeness and speed of release of medicinal substances from pessaries depend exactly on them.

Materials and methods

The technological process for preparing pessaries was carried out in accordance to the generally accepted rules for preparing suppositories described in the State Pharmacopoeia of Ukraine (SPhU) [6]. The following parameters were determined on the samples of pessaries: description, homogenity, pH, melting point, the time of complete deformation, disintegration time, and resistance [7]. Quantitative determination of acyclovir was conducted by the method of absorption spectrophotometry in the UV-spectrum at a wavelength of (265 ± 2) nm using the method developed by authors [8]. The thermogravimetric studies were performed on a Q-1000 derivatograph of F. Paulik, I. Paulik, L. Efdei system (with platinum-rhodium thermocouple when heating the samples in platinum crucibles from 18 ºC to 250 ºC in the air).

It is known that when developing pessaries for the treatment of GH, in accordance to medical and biological requirements, it is better to use fatty suppositorial

bases, such as witepsol, hard fat, etc. The use of the well-known hydrophilic bases, namely macrogols possessing the osmotic activity in this disease is unacceptable.

As experimental studies preliminary conducted shows, it is better to use witepsol as a base in pessaries with acyclovir and essential oils for the treatment of GH.

The rational dose of the active substance – acyclovir was determined according to the literature data and confirmed by the biological studies conducted [9]. Essential oils of tea tree and thyme were preliminary dissolved in a hydrophobic base.

Pessaries with the weight of 4.0 g were prepared in the laboratory conditions by the pouring method using the following technology: acyclovir was weighed in a mortar and stirred for 5 min. In an intermediate container lecithin was weighed, it was previously wet in water with pH 3.5-4.5 at the temperature of 38 ºC and put in a mortar carefully triturating with acyclovir.

The base was weighed in a porcelain cup, melt on a water bath, cooled, and essential oils were introduced while stirring. To the mixture in the mortar the base with oils was transferred from a porcelain cup and accurately mixed. The resulting suppository mass was placed in a porcelain cup, melt and poured out in the suppositories forms preliminary prepared.

The organoleptic and physicochemical properties were studied on the samples of pessaries obtained.

It is known that one of the quality indexes of pessaries containing API that are insoluble neither in water nor in the base is degree of their dispersion. It affects the uniform distribution of API in the suppository mass, dosing accuracy, as well as the release process and the therapeutic action manifestation. These parameters can be affected due to API disintegration and introduction of surfactants. The following parameters as description, mass uniformity, average weight, melting point, time of complete deformation, disintegration time, pH of water solutions were determined according to the SPhU.

Results and discussion

The estimation criterion for the composition of samples of pessaries studied were organoleptic and physicochemical parameters (uniformity, melting point, disintegration time, time of complete deformation).

The results of microscopic analysis have shown that acyclovir powder has a polydisperse composition, according to the requirements of the SPhU it allows to refer it to fine powders. In addition, the powder is capable of agglomeration under the action of electrostatic forces, and this can have negative consequences when pouring the suppository mass from the reactor (nonuniformity of dosing and appearance of sedimentation).

The analysis of the acyclovir powder image in 100 times magnification has shown that particles, mainly, belong to the following fractions: up to 63 μm and 180-250 μm. To obtain the homogeneous powder the additional stage of disintegration was conducted for 3, 5, 7 min. The studies showed that after disintegration of acyclovir powder for 5 min the basic fraction of the powder was in the range up to 63 μm, it was about 93 %; this size of particles should provide uniformity of the suppository mass.

When developing the technological process the method of acyclovir introduction to the composition of pessaries was studied. The content of acyclovir in pessaries was 5 %, and it should be introduced into a medicinal form as a suspension (Fig. 1).

According to the literature data acyclovir is poorly soluble in water. To improve dispersologic indicators of acyclovir surfactants, namely lecithin and Tween-80, were chosen. Preliminary, lecithin was wet in water with pH 3.5-4.5 at 38 ºC, and then triturated with acyclovir.

The samples of pessaries on witepsol with the surfactants selected (lecithin and Tween-80) were prepared for our studies. The organoleptic and physicochemical properties were studied in these samples.

When choosing surfactants only those permitted to the use in pharmacy practice were used. The amount of the emulsifier selected must provide the complete and prolonged release of acyclovir; it will allow maintaining its effective concentration in the vagina for a long time.

For optimization of the composition lecithin and Tween-80 were added in the concentrations of 1, 3, 5, 7 %. When introducing these surfactants in the suppository bases in the amounts of 1 and 3 % the uniformity of substances in all samples was not reached. When introducing Tween-80 in the concentration of 5 % the suppository mass became soft, and had low values of damage tolerance. When using lecithin in the concentration of 5 and 7 % the uniformity and damage tolerance were observed in the suppository mass according to the requirements of the SPhU. Therefore, it was sufficient to

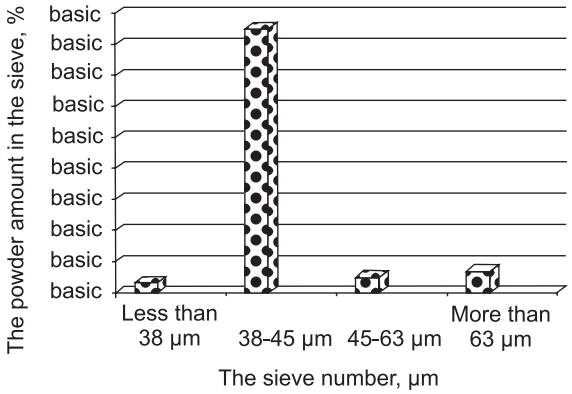


Fig. 1. The nominal particle size (the sieve number) after disintegration of acyclovir for 5 min

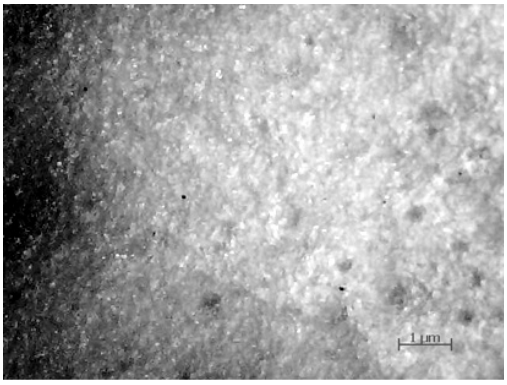


Fig. 2. The degree of dispersion of the suppository mass of pessaries with acyclovir and essential oils, magnification × 100

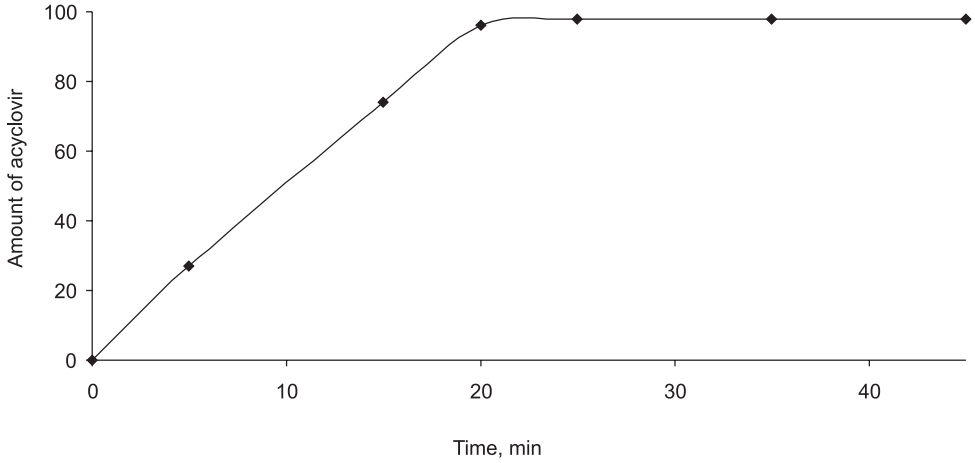


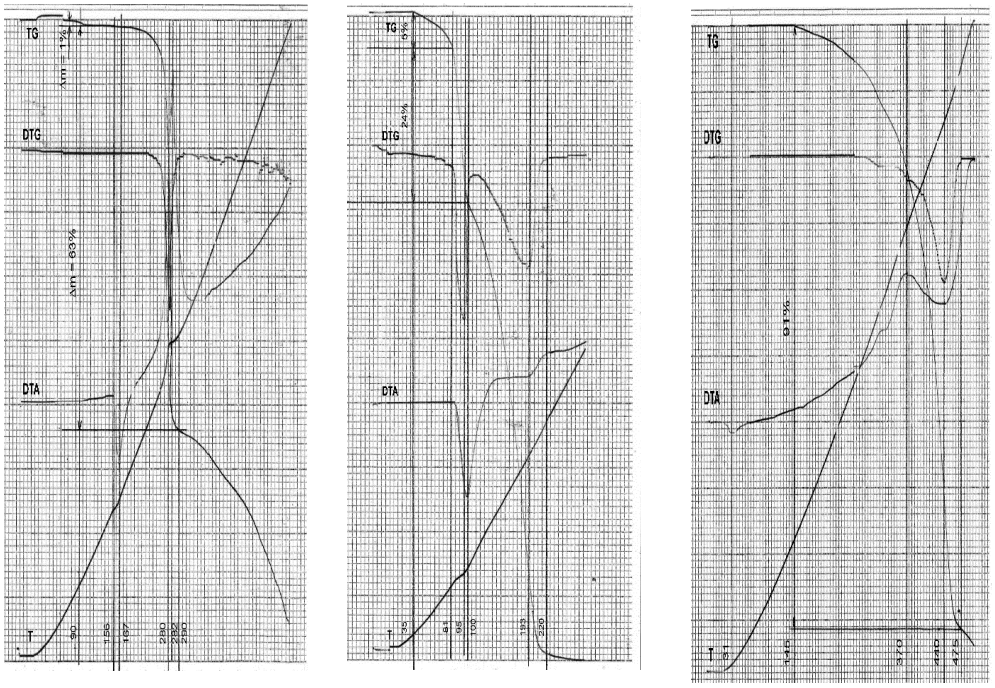
Fig. 3. Kinetics of acyclovir release (G %) in the samples of pessaries with lecithin

introduce lecithin in the concentration of 5 %. It was also found that disintegration of acyclovir with lecithin allowed decreasing its degree of dispersion to 5-10 μm (Fig. 2).

In order to study the effect of surfactants on acyclovir release the biopharmaceutical studies were conducted on the samples of pessaries with the content of lecithin of 5 %. To assess availability of the medicinal form the test "Dissolution" for solid dosage forms was used. As a medium 0.1 M solution of hydrochloric acid was used at 37 ºC. The samples of the dialysate were taken in 5, 15, 25, 35 and 45 min. The amounts taken were filled with new portions of the dialysis medium. Quantitative determination of acyclovir in the dialysate was conducted by the method of absorption spectrophotometry.

During the whole experiment there was a gradual increase of the acyclovir concentration in the acceptor medium, and in 20 min approximately 98 % was found. The process of acyclovir release from pessaries prepared on the witepsol base, but without lecithin, was considerably slower and did not reach the required completeness. The results of the experiment indicate that the amount of surfactants selected in the samples of pessaries provides the complete and prolonged acyclovir release, and it allows maintaining its effective concentration in the vagina for a long time. The research results on acyclovir release are presented in Fig. 3.

The thermogravimetric studies allowed to detemine the effect of the temperature modes of API on the technological process of the suppository mass production, as well as the compatibility of active substances and excipients in the composition of pessaries. This method allows to find the thermal effects of decomposition of medicinal substances and excipients in the multicomponent suppository mass [10]. Thermograms of the samples of the substances studied are given in Fig. 4.



a) acyclovir b) tea tree oil c) pessaries

Fig. 4. Thermograms of the AFI and pessaries studied

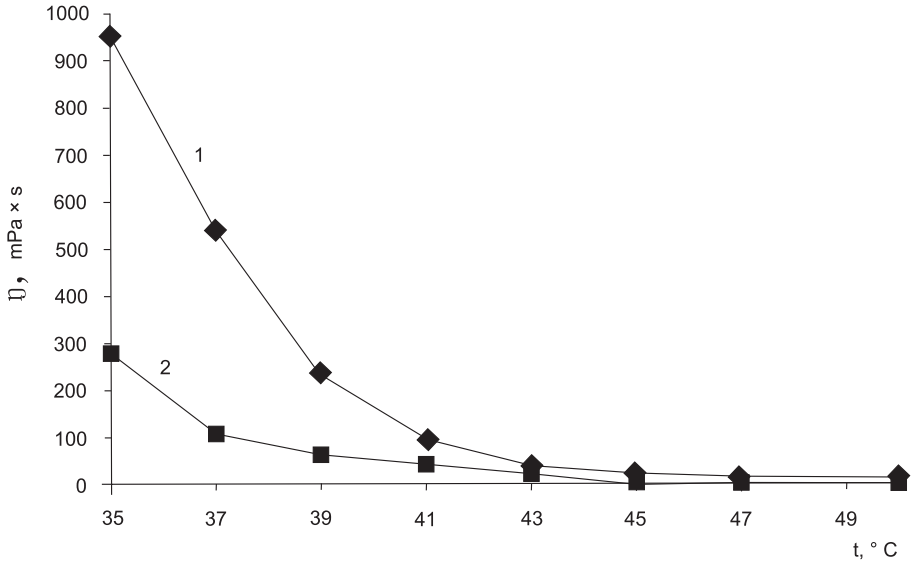


Fig. 5. The dependence of structural viscosity of the suppository mass (1) and the base (2) on temperature

Table

The pharmacotechnological indexes of pessaries with acyclovir and essential oils of tea tree and thyme

Description of the sample of pessaries	Melting point, ºC	Uniformity	Total deformarion time, min	Disintegration time, min	pH
Pessaries are light yellow on witepsol	Not more than 37	There should be no speckles on the cut. There can be the presence of air	Not more than 15	Not more than 30	4.50-5.50
Conformed with norms	36.7	Conformed with norms	12.8	23	4.95

According to the data of the thermogravimetric analysis conducted it has been found that acyclovir in the temperature range of 45-90 °C is characterized with the gradual processes of moisture evaporation. The loss in the maximum at 280 °C is 63 %, i.e. the substance of acyclovir is relatively thermostable and does not change the chemical structure to 160 °C.

Essential oils of tea tree and thyme begin to decompose at a temperature of 80-81 °C and are characterized with one considerable exothermal effect with the maximum at the temperature of about 100 °C. The process of the sample destruction ends at the temperature of 220 °C [11, 12].

The process of decomposition for pessaries occurs in three stages. The first stage (30-40) ºC is characterized with the insignificant loss of the mass and is accompanied with the endo-effect, i.e. a gradual loss in mass. The second (130-160) °C and the third (330-400) °C stages are characterized with the rapid ongoing process of destruction and accompanied with considerable exothermal effects. Losses on these stages are 91 %.

Based on the studies conducted it has been found that active substances and excipients are relatively heat-resistant. According to the results presented in Fig. 4a, 4b, 4c it is seen that in the temperature range studied there is no decomposition of medicinal substances and the chemical interaction between the components of the suppository mass.

To determine the optimal temperature of the manufacturing process and the suppository mass dosing, the rate and time of mixing the rheoparameters of pessaries were studied within the range of 35-50 ºC [13].

At a temperature above 45 ºC the suppository mass (witepsol base) has very low rheoparameters, therefore, sedimentation of acyclovir is possible when preparing and dosing the drug, and it can result in stratification of pessaries. When decreasing the temperature to 35 ºC the structural and mechanical properties of the suppository mass increase, the fluidity slows down, and this results in difficulty of the dosing process. Hence, the optimal temperature for preparing and dosing the suppository mass is 40-45 ºC (Fig. 5).

Thus, the studies conducted allowed to develop the technology of pessaries with acyclovir and essential oils, as well as to determine the pharmacotechnological indexes of pessaries met the requirements of the SPhU (Table).

CONCLUSIONS

1. Based on the biopharmaceutical and pharmacotechnological studies conducted the laboratory technology of the combined pessaries with acyclovir and essential oils of tea tree and thyme has been developed.

2. The technological process of pessaries with acyclovir and and essential oils in the pharmacy conditions has been described in the standard operating procedure.

Conflict of Interests: authors have no conflict of interests to declare.

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