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DEVELOPMENT AND OPTIMIZATION OF QUANTITATIVE COMPOSITION OF RECTAL SUPPOSITORIES WITH DIOSMIN AND HESPERIDIN BY THE METHOD OF MATHEMATICAL PLANNING OF THE EXPERIMENT

Key words: diosmin, hesperidin, suppositories, mathematical planning of the experiment, excipients

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РОЗРОБЛЕННЯ ТА ОПТИМІЗАЦІЯ КІЛЬКІСНОГО СКЛАДУ СУПОЗИТОРІЇВ РЕКТАЛЬНИХ ІЗ ДІОСМІНОМ ТА ГЕСПЕРИДИНОМ МЕТОДОМ МАТЕМАТИЧНОГО ПЛАНУВАННЯ ЕКСПЕРИМЕНТУ

Ключові слова: діосмін, гесперидин, супозиторії, математичне планування експерименту, допоміжні речовини

The development of a rectal drug with a dispersed medium of the biphasic type involves a large number of experimental studies at all stages of pharmaceutical development. This aspect, combined with the consumption of expensive reagents and active pharmaceutical ingredients (APIs), can become a significant problem in today's pharmaceutical developments. Therefore, the methods of mathematical planning of the experiment are used extensively to optimize the biopharmaceutical and technological study of rectal drug [1].

These methods allow conducting research through the construction of a model that will reproduce the critical qualitative and quantitative characteristics of the system with given conditions at a certain stage of development. The method of mathematical planning of the experiment feature is the diversity of approaches to model construction. This means that these methods are theoretically predict the results of a future experiment and to analyze the data obtained, to prevent the repetition of experiments [2].

The value of this type of research increases in the study of quantitative characteristics of rectal medicine, because in the technology of their creation the ratio of basic factors and random variables can affect the obtaining of unsatisfactory final results of the experiment. In conducting experimental studies of these dosage forms, biopharmaceutical and mucoadhesion parameters have an important role in ensuring maximum absorption with the mucous membrane of the anorectal area. Therefore, it is important not only to conduct physical and chemical studies of APIs, but also the rational selection of excipients of the suppository base [3]. If the excipients forms are multicomponent system of dispersed medium of suppositories, the method of mathematical planning of the experiment is rational for optimizing the quality parameters provided by the regulatory documentation.

The aim of the present research was to develop and optimize of quantitative composition of rectal suppositories with diosmin and hesperidin by the method of mathematical planning of the experiment.

Materials and methods

The following substances were chosen as APIs of suppositories: diosmin and hesperidin (Tayga (Shanghai) Co., Ltd., China). According to the preliminary results of literary studies, we have chosen the ratio of diosmin and hesperidin 9:1 in a dose of 300 mg per 1 suppository [4, 5, 6].

The hydrophilic part of the dispersed system of suppositories is represented by sodium alginate gel with the addition of Ca^{2+} as a complexing cation. Sodium alginate (Naturalissimo Ltd., China) with the predominance of copolymer blocks M over G was chosen as the viscosity regulator of the system [7]. The cationic part of calcium stearate (TD Himfarminvest, Ukraine) was used as a metal-forming matrix structure of suppositories. A mixture of Witepsol W_{32} (IOI OleoGmbH, Germany) and emulsifiers was used as the hydrophobic phase. Due to the optimal physicochemical parameters of Witepsol W_{32} (t_m = 35.5 ºC, hydroxyl number – 25–35 KOH/g, viscosity – 59–65 mPa • s), this type of hydrophobic base will provide the necessary structural and mechanical properties for suppositories [8]. The mixture of emulsifiers was selected based on preliminary results of the study of literature sources, taking into account the indicators of hydrophilic-lipophilic balance. Two types of emulsifiers were used: oil-in-water emulsifier Montanov L (Seppic, France; INCI name: C_{14-22}Alcohol&C_{12-22}Alkylglucoside) and water-in-oil emulsifier sorbitan oleate (Aroma-zone, France) in a ratio of 5:1. This ratio of emulsifiers was chosen to prevent possible irreversible inversion of the phases of the biphasic system [9].

For research samples of suppositories were made as follows. Sodium alginate (constant value – 1.5% of the total mass of the sample – 0.06 g) was added to the purified water (changing value – amount of hydrophilic phase) with constant stirring. The resulting gel was left for a certain period of time to form a homogeneous system (hydrophilic medium), followed by the addition of diosmin and hesperidin (constant value 0.3 g in the ratio of 9:1). Then, Witepsol W-35 (changing value) and emulsifiers (montanov L and sorbitan oleate in a ratio of 5:1, changing value) were melted in a laboratory reactor made of stainless steel, with constant stirring (200 turnover/minute) at a temperature of 60–70 ºC (hydrophobic medium); after that, it was cooled to 40 ºC and calcium stearate (constant value – 0.5% of the total mass of the sample – 0.02 g) was added. Both parts of the base were combined with constant stirring. The total weight of the one suppositories is 4.0 g.

The release of active substances (diosmin and hesperidin) from suppositories was carried out by the method of dialysis through a semipermeable membrane, followed by spectrophotometric study of their quantitative content in the dialysate. As a membrane material was used inert porous material Cuprophan (type 150 pm, thickness of the swollen material 11.0 ± 0.5 μm, area 2 000 mm^2). The study of optical density was performed on a Specord 200 Plus (Analytik Jena, Germany) at a wavelength of 360 nm. A standard comparison solution was prepared according to the following method: 20 mg of bioflavonoid fraction was dissolved in 10 ml of 0.5 M NaOH; the resulting solution was transferred to a volumetric flask and diluted with purified water to 100 ml.

The study of the distribution of the particles of the dispersed phase in the dispersed medium was performed by laser diffraction using an analyzer Mastersizer 3000 (Malvern Instruments Ltd, Worcestershire, UK). Purified water was used as a research medium. 1 ml of a sample of suppositories was added to the test medium (performed pre-melting of the sample and added as an emulsion). The study time of each sample was determined automatically by the device.

Mathematical processing of the results of the experimental study was performed using the program MathCad-2016 and Excel software. The study was conducted by constructing a model with the method of least squares and obtaining regression equations of the 2nd order. For the study, we selected the following responses that characterize the sample

for the different structural and mechanical properties, namely: disintegration time (y1), hardness (y2), adhesion (y3).

The tester Erweka ST 32 (ERWEKA GmbH, Germany) was used as a device for disintegration time determination. Purified water was used as a disintegration medium. The research temperature was 37 °C. Sample of rectal suppositories was placed between the perforated discs (distance between discs of 30 mm) and fixed on the test station [10]. The time of disintegration was determined by the visual method (disintegration indicators: complete dissolution of suppositories; division of the biphasic medium into hydrophobic and hydrophilic parts is observed; significant change in the shape of the test sample). The test results were corresponding to the quality indicators if the disintegration time didn't exceed 60 minutes.

The tester TA.XTExpressC (Stable Micro Systems Ltd, Godalming, Surrey, UK) was used as a device for determination of the hardness and mucoadhesion.

Studies of the mucoadhesion were carried out according to the system «back extrusion». A metal flat disc with diameter of 50 mm was used as a working platform for research of adhesion. The samples of suppositories were melted at 37 °C (volume of tested samples – 50 ± 2 ml) and placed in a container (capacity of 100 ml), which was located under the disc. The parameters of the study, including speed rate (2 mm/s) and distance (depth of insertion – 10 mm), were chosen. Three replicate analyses were performed for each sample at ambient temperature, providing the same conditions for each measurement.

The parameter of mucoadhesion was determined from the force–time graph (Fig. 1). When the disk moved down, the positive part of the back extrusion graph was created, showing the maximum compressing force required for the sample deformation i.e firmness of suppositories (molten state). The area of the graph above zero demonstrated cohesiveness of the sample. The higher the value, the denser was consistency of the sample. Once the disk was returned to its starting position, its upward movement created a negative part of the graph: area below zero showed mucoadhesive and sample resistance during separation from the disk (minimum retracting force of sample). The higher the value, the more energy was required to break the contact of the sample with the disk surface, and, accordingly, the better was the adhesion of the sample [11].

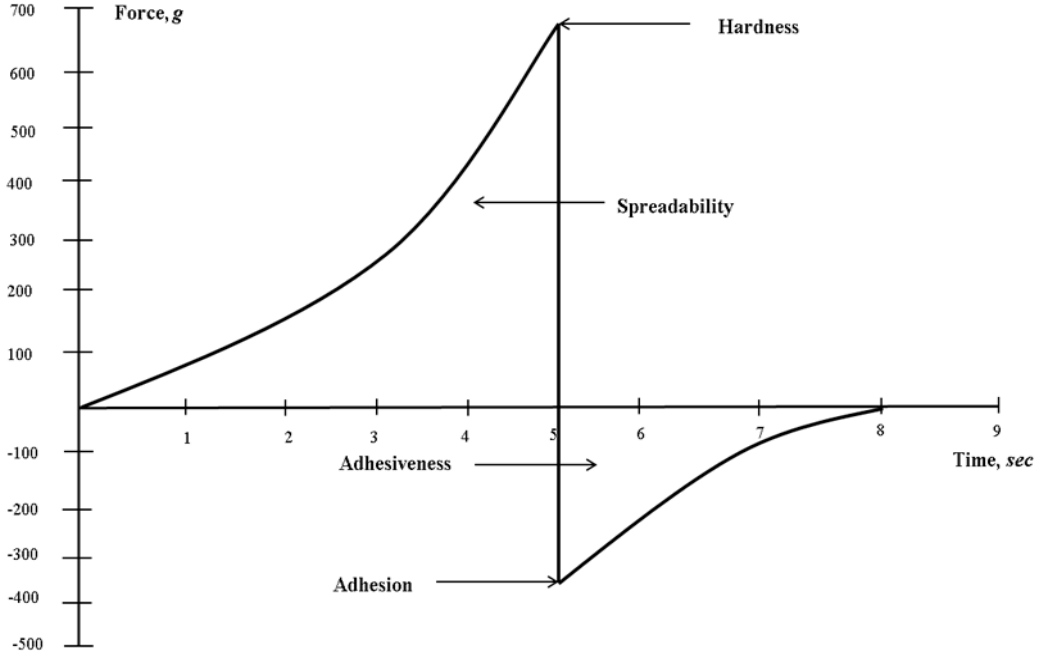


Fig. 1. **Mucoadhesion graph during the analysis**

A study of the hardness index was carried out according to the system «needle probe». The penetration depth of a standard 5-mm needle (P/5N) at a constant 5 kg-load force was measured to represent the hardness of the sample (for solid suppository). The sample was placed centrally under the needle probe, which penetrate the sample in 3 mm distance. Three replicate analyses were performed for each sample at ambient temperature, providing the same conditions for each measurement. The parameter of hardness was determined from the force–time graph (Fig. 2).

The results of hardness and mucoadhesion tests were processed using «Exponent Connect» software.

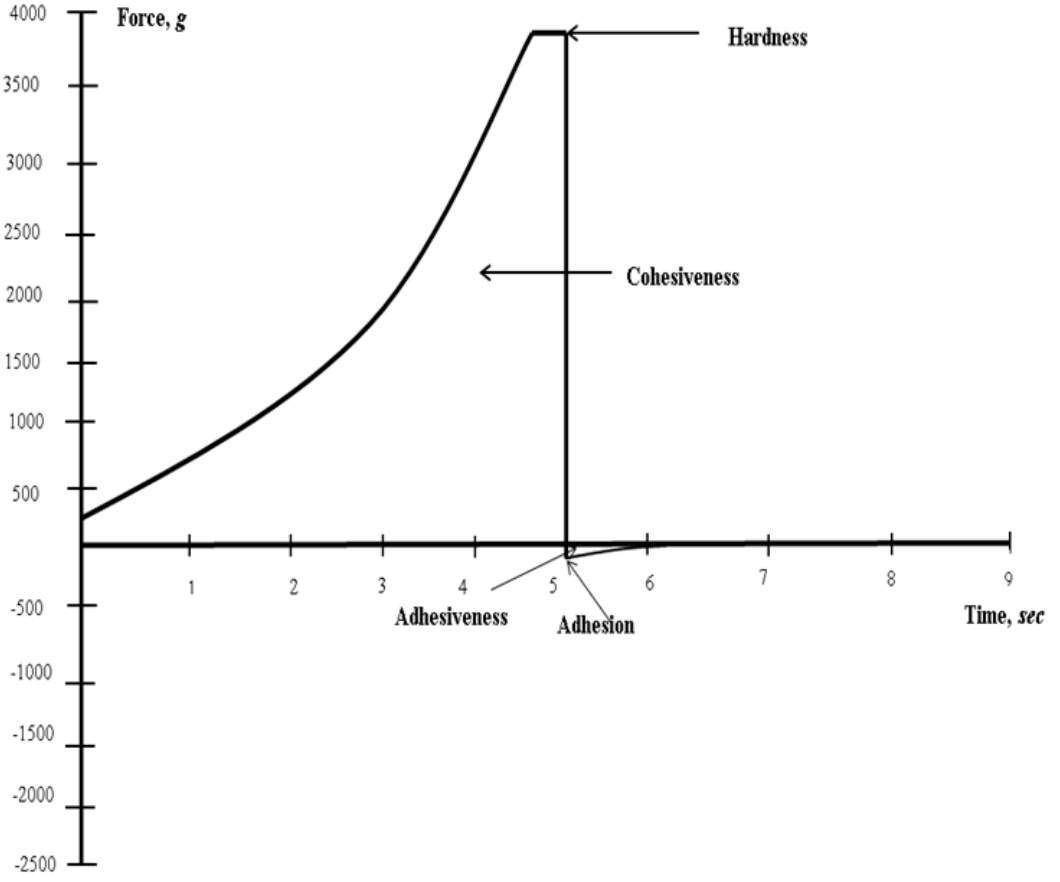


Fig. 2. **Hardness graph during the analysis**

Results and discussion

The first stage of our work was to determine the percentage range of the hydrophobic and hydrophilic part of the dispersed medium for the subsequent experiment by the method of mathematical planning. The research was carried out in the following areas: the release of active substances from the medicine and the study of the distribution of the APIs by laser diffraction.

According to preliminary results of the literature research, it was found that to create the necessary structural and mechanical properties of the biphasic system of suppositories, the hydrophobic part of the biphasic medium should be from 30 to 80% [12]. Therefore, in the study of the release and distribution of the APIs were prepared 11 samples of suppositories (content of the hydrophobic part of the biphasic medium with a difference of 5%). The content of the hydrophilic phase was decreasing in proportion to the increase in the percentage of the hydrophobic phase (Table 1).

Table 1

Percentage composition of suppositories to study the release and distribution of the APIs

Hydrophobic phase (Witepsol W_{32}), %	Hydrophilic phase (purified water +1.5% of sodium alginate), %	APIs (diosmin and hesperidin), %	Emulsifier (montanov L and sorbitan oleate 5:1), %	Calcium stearate, %
80	4	7.5	8	0.5
75	9			
70	14			
65	19			
60	24			
55	29			
50	34			
45	39			
40	44			
35	49			
30	54			

Note: $n = 3$; $p < 0.05$.

As a comparison samples in the study of release of APIs were used media with a monocomponent composition of Witepsol W_{32} (hydrophobic base) and a polymer gel of sodium alginate (hydrophilic base). The results of the release study are shown in Fig. 3 and Fig. 4.

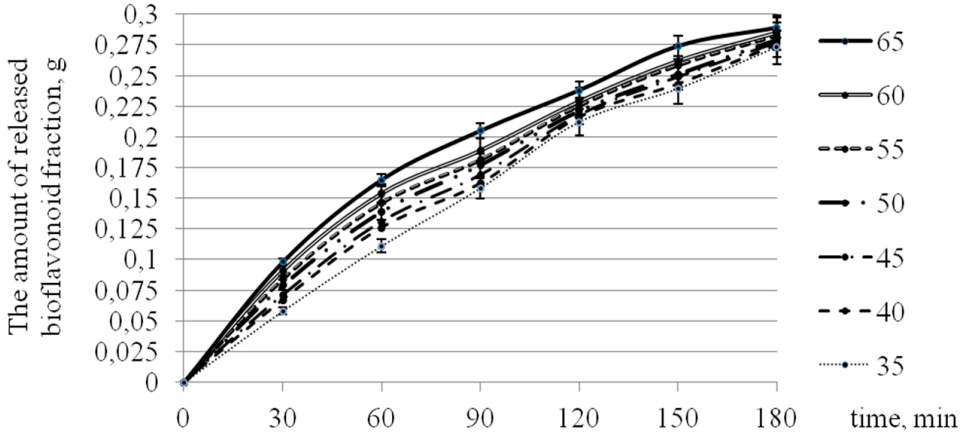


Fig. 3. **The results of the study of the release of diosmin and hesperidin depending on the time of the experiment and the content of the hydrophobic phase (from 35 to 65%)**

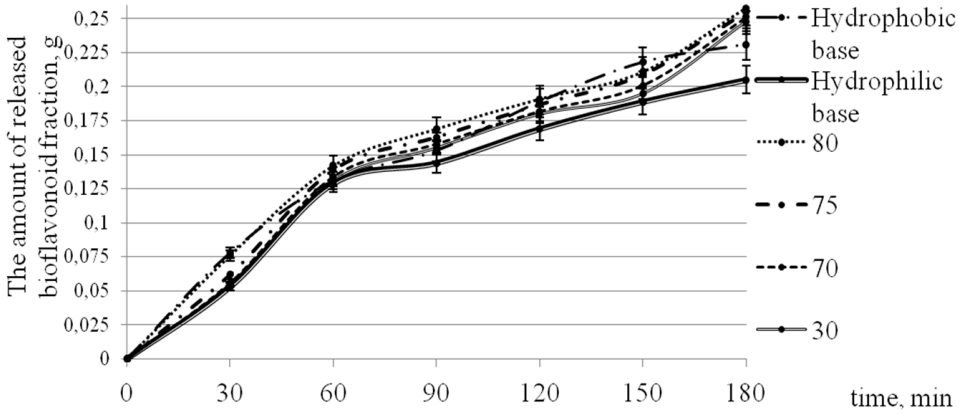


Fig. 4. **The results of the study of the release of diosmin and hesperidin depending on the time of the experiment and the content of the hydrophobic phase (30%; 70 to 80%; hydrophobic and hydrophilic base)**

The results of the research (Fig. 3 and Fig. 4) allow us to predict the dependence of the amount of released dispersed phase on the percentage of hydrophobic medium. The obtained data show that in samples with hydrophobic part content between 35 and 65% are a uniform increase in the release of diosmin and hesperidin over time, which allow predicting the formation of a stable system of suppositories.

The next step was to conduct a study to establish the distribution of API in the biphasic bases by laser diffraction (Fig. 5, 6, 7), which allows to analyze the absence of coagulation and the processes of inclusion of Ca^{2+} in the formed dispersed medium.

In the Fig. 5, 6, 7 show the average results of the distribution of the dispersed phase in the samples that study, because the difference in their indicators didn`t have significance.

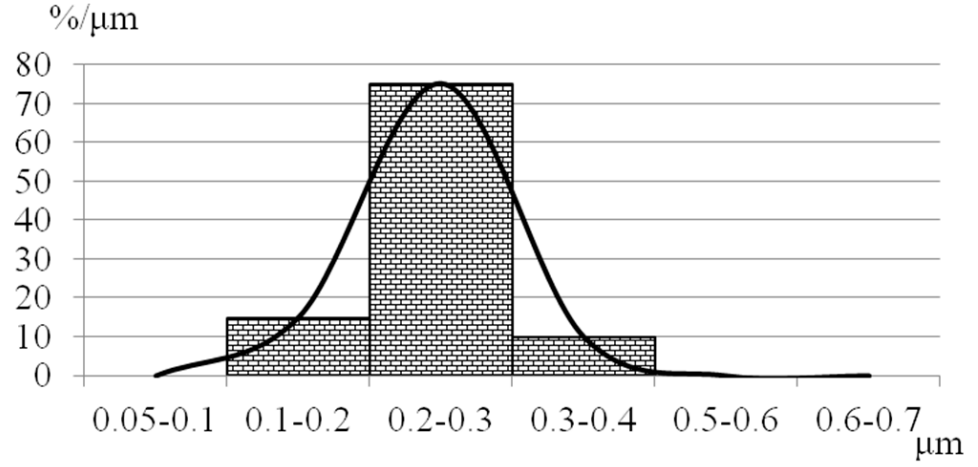


Fig. 5. **Diagram of the distribution of the components hydrophilic phase (diosmin and hesperidin) in samples with a percentage of hydrophobic phase of 35 to 65%**

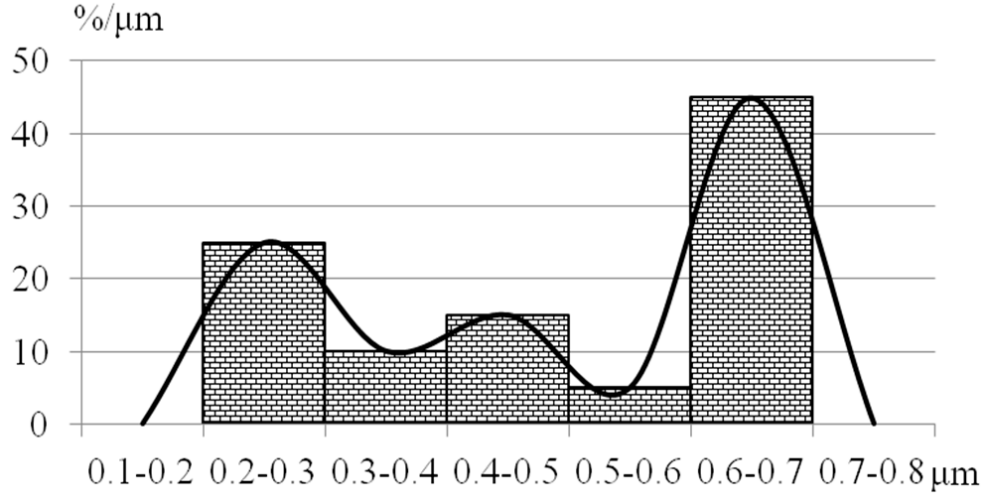


Fig. 6. **Diagram of the distribution of the components hydrophilic phase (diosmin and hesperidin) in sample with a percentage of hydrophobic phase of 30%**

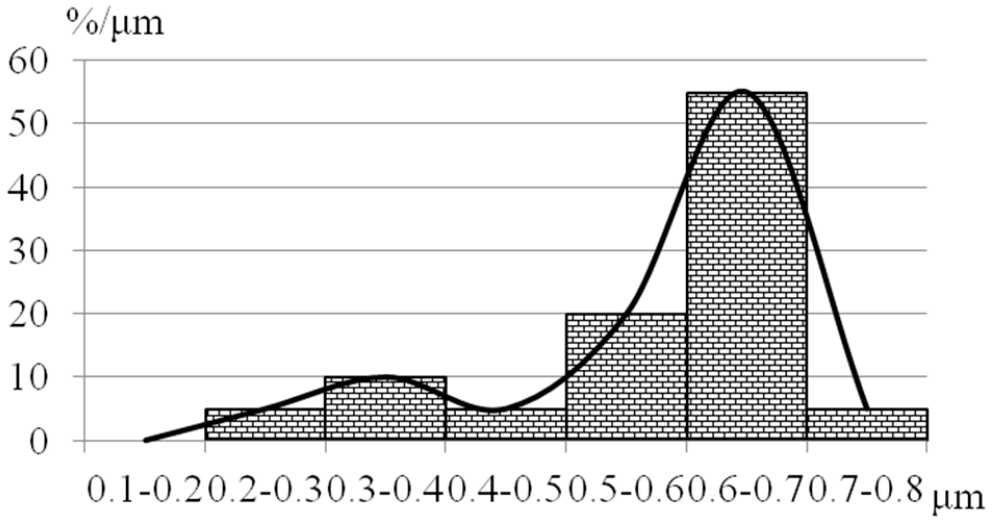


Fig. 7. **Diagram of the distribution of the components hydrophilic phase (diosmin and hesperidin) in sample with a percentage of hydrophobic phase of 70 to 80%**

As can be seen from Fig. 5, the monodisperse of the components of the hydrophilic part (diosmin and hesperidin) is inherent in samples with a percentage of hydrophobic part of the dispersed medium from 35 to 65%. The differential distribution curve in these samples has one distinct peak, indicating a predominance of 0.2–0.3 particles. The obtained results may indicate that the APIs are subject to the law of normal particle size distribution, they didn`t have coagulation phenomena between them. These data are confirmed by the results of our previous studies of the particle-size distribution (sieve analysis) of APIs and microscopy of finished samples of suppositories.

As can be seen from Fig. 6 and Fig. 7 the change in the percentage content of biphasic medium leads to the appearance of particles of different sizes, as evidenced by the presence of several peaks. The results of the study may indicate the production of an unstable system due to the presence of partial coagulation.

Thus, the studies suggest the absence of coagulation processes only in samples with a hydrophobic phase content of 35 to 65. Smaller particle size of APIs would provide a larger active surface area (while APIs absorption in rectum), which generally would lead to increase of bioavailability [13, 14]. The formation of the reticulate structure of the alginate complex with calcium stearate would provide improving the distribution of APIs in the dosage form, which would prevent sedimentation and coagulation. [15].

The next stage of the work was a study to optimize the quantitative composition of rectal suppositories by the method of mathematical planning of the experiment. Variations in the limits of excipients used in the technology of drug development are given in Table 2.

Table 2

Excipients studied in optimizing the composition of biphasic rectal suppositories with diosmin and hesperidin

Factors	Y = f(d)	
	min	max
x_1 – Witepsol W_{32}	38.0	63
x_2 – hydrophilic part	20	40
x_3 – emulsifier	5	10

Note: x_1 – hydrophobic part of suppositories (Witepsol W_{32}); x_2 – hydrophilic part of suppositories (purified water with the addition of sodium alginate); x_3 – emulsifiers (Montanov L and sorbitan oleate in a ratio of 5:1).

Acceptable values of basic level responses must satisfy the following conditions: hardness and mucoadhesion should be close to the maximum, and the disintegration time - to the minimum.

The experiment planning matrix and the values of responses based on the results of studies of suppository samples are given in Table 3. The content of active pharmaceutical ingredients and complexing agent (calcium stearate) was unchanged during the experiment (table 1).

Table 3

Matrix of the experiment to study the effect of excipients on the properties of rectal suppositories

№	x_1, (%)	x_2, (%)	x_3, (%)	y_1, (kg*sec)	y_2, (min)	y_3, (g*sec)
1	58.0	20.0	10.0	3.5	47.0	375.0
2	43.0	40.0	5.0	2.6	22.0	450.0
3	38.0	40.0	10.0	2.6	27.0	410.0
4	63.0	20.0	5.0	3.4	41.0	381.0
5	53.0	30.0	5.0	3.3	36.0	392.0
6	48.0	30.0	10.0	3.4	38.0	388.0
7	60.5	20.0	7.5	3.4	42.0	380.0
8	40.5	40.0	7.5	2.6	23.0	435.0
9	50.5	30.0	7.5	3.3	33.0	398.0

Note: x_1 – Witepsol W_{32}; x_2 – hydrophilic part; x_3 – emulsifier; y_1– hardness, kg; y_2 – disintegration time, min; y_3 – mucoadhesion g*sec.

Taking into account the dependence of the indicators of suppository samples on the amount of excipients, we found the empirical functional dependences $y_i = f(d)$, which are given in Table 4.

Table 4

Regression equation

Y	Y = f(d)
y_1	$y_1(x_1, x_2, x_3) := 1{,}784 + -0{,}125 \cdot x_1 + 0{,}214 \cdot x_2 + -2{,}627 \times 10^{-3} \cdot x_2 \cdot x_3 + 3{,}118 \times 10^{-3} \cdot x_1 \cdot x_3$
y_2	$y_2(x_1, x_2) := 64{,}275 + -5{,}133 \cdot x_2 + -0{,}016 \cdot x_1^2 + 0{,}4 \cdot x_2^2$
y_3	$y_3(x_1, x_2, x_3) := 348{,}134 + 8{,}811 \cdot x_1 + = 27{,}605 \cdot x_2 + 0{,}476 \cdot x_2 \cdot x_3 + -0{,}126 \cdot x_1 \cdot x_3$

Note: depending on y_2 by the effect of x_3 has not been established.

In addition, a statistical check of the regression equations was performed on the adequacy of the model and the significance of the coefficient of determination R^2, the significance of the Fisher criterion and the *p*-value of the coefficients. The obtained data are given in Table. 5

According to the results from the present study, it can be concluded that the factors of the quantity of the hydrophilic part and emulsifier have an important effect on the technological properties of the samples. Correct application of these factors to hydrophobic phase would prevent the aggregative instability of the biphasic suppositories (occurrence of flocculation and phase separation).

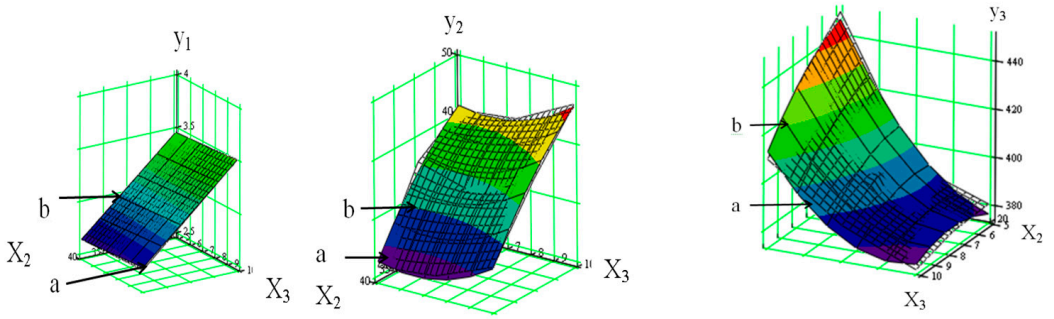
The base for suppositories should conform to all quality indicators at once. The behavior of the studied system of equations in terms of multicriteria optimization can be characterized by a two-dimensional vector X = {a, b}. The system can also be evaluated by a vector-function, the components of which are given by the existing functions of the variable X.

Table 5

Statistical verification of the adequacy of the model and the significance of the coefficients

	Value	Obtained resuls			
Regression statistics	Plural R	0.98691072			
	Square R	0.97399277			
	Normalized R-square	0.947985539			
	Standard error	5.933025043			
	Observation	9			
Analysis of variance	Significance of Fisher's criterion	0.001993947			
	Significance criteria	**Coefficient of determination**	***p*-value**	**Lower 95%**	**Upper 95%**
	Y – crossing	348.1333333	0.001836556	216.4030739	479.8635928
	x_1	8.811245283	0.003957096	4.712697413	12.90979331
	x_2	-27.6054843	0.009639337	-44.07744009	-11.1335284
	$x_1 x_3$	-0.12626415	0.039342126	-0.242523879	-0.01000442
	$x_2 x_3$	0.476377358	0.018287254	0.132923361	0.819831356

Mathematical processing of the results is revealed the interaction of the following factors (shown in Fig. 8, Note: a) experimental data; b) theoretical calculations.)



A *B* *C*

Fig. 8. **Dependence of the influence of excipients on indicators: *A* – hardness, *B* – disintegration time; *C* – mucoadhesion**

Thus, based on the studies, the optimal content of the mixture of emulsifiers was calculated – 6.29%, solid fat – 39.51%, the hydrophilic part of the biphasic medium – 29.58%. This amount of excipients provides the necessary properties of suppositories.

Conclusion

1. The quantitative composition of rectal suppositories was optimized by mathematical planning and the results of experimental studies were processed.

2. In the course of calculations, empirical functional dependencies were found – it is multiple regression equations of type 2.

3. To determine the quantitative composition of excipients, restrictions were set on the content of the hydrophobic part of the biphasic medium.

4. According to the results of the study it was found that the optimal content of the mixture of emulsifiers – 6.29%, solid fat – 39.51%, the hydrophilic part of the biphasic medium – 29.58%.

5. Responses that will provide the system with the necessary structural-mechanical and pharmaco-technological properties are within: y_1 (2.713); y_2 (22.639); y_3 (439.283).

6. The obtained data will be used in further studies to optimize the composition and technology of rectal suppositories with diosmin and hesperidin.

Conflict of interests. There are no conflicts of interest regarding this study.

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DEVELOPMENT AND OPTIMIZATION OF QUANTITATIVE COMPOSITION OF RECTAL SUPPOSITORIES WITH DIOSMIN AND HESPERIDIN BY THE METHOD OF MATHEMATICAL PLANNING OF THE EXPERIMENT

Key words: diosmin, hesperidin, suppositories, mathematical planning of the experiment, excipients

A B S T R A C T

In the development of suppositories biphasic media are rarely used. It is due to the occurrence of possible instabilities within the system «dispersed phase and a dispersing medium». To solve such problems, it is rational to use the methods of mathematical planning of the experiment. The method of mathematical planning of the experiment feature is the diversity of approaches to model construction. This means that these methods are theoretically predict the results of a future experiment, analyze the data obtained, prevent the repetition of experiments and optimize the technology of medicine.

The aim of the present research was to develop and optimize of quantitative composition of rectal suppositories with diosmin and hesperidin by the method of mathematical planning of experiment.

Objects of the study were samples of suppositories of the biphasic type with diosmin and hesperidin. The dispersing medium of these samples consisted of hydrophobic (Witepsol W_{35} and emulsifiers) and hydrophilic parts (sodium alginate gel with the addition of Ca^{2+} as a complexing cation). Preliminary results of determining the percentage limits of the hydrophobic part of the dispersed medium were carried out by studying the indicators of the release of active substances from the dosage form and the laser diffraction method. As responses of experiments was used such indicator as: disintegration time, hardness and mucoadhesion.

As a result of the studies, the functional dependence of the indicators on the amount of components of the suppository dispersed medium was established. It was found that acceptable values of the responses should conform to the following conditions: hardness and mucoadhesion should be close to the maximum, and the disintegration time – to the minimum.

According to the results of the study it was found that the optimal content of the mixture of emulsifiers – 6.29%, solid fat – 39.51%, the hydrophilic part of the biphasic medium – 29.58%. Responses that will provide the system with the necessary structural-mechanical and pharmaco-technological properties are within: y_1 (2.713); y_2 (22.639); y_3 (439.283). The obtained data will be used in further studies to optimize the composition and technology of rectal suppositories with diosmin and hesperidin.

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РОЗРОБЛЕННЯ ТА ОПТИМІЗАЦІЯ КІЛЬКІСНОГО СКЛАДУ СУПОЗИТОРІЇВ РЕКТАЛЬНИХ ІЗ ДІОСМІНОМ ТА ГЕСПЕРИДИНОМ МЕТОДОМ МАТЕМАТИЧНОГО ПЛАНУВАННЯ ЕКСПЕРИМЕНТУ

Ключові слова: діосмін, гесперидин, супозиторії, математичне планування експерименту, допоміжні речовини

А Н О Т А Ц І Я

Під час розроблення ректальних супозиторіїв дифільні основи використовують досить рідко. Це пов'язано з виникненням можливих нестабільностей усередині системи «дисперсна фаза та дисперсне середовище». Для розв'язання подібних технологічних задач раціонально використовувати методи математичного планування експерименту. Їх головною особливістю є різноманітність підходів до побудови математичної моделі. Це означає, що у розробника існує можливість теоретично прогнозувати результати майбутнього експерименту, аналізувати отримані дані, запобігати повторенню експериментів і оптимізувати технологію лікарських засобів.

Метою цього дослідження було розроблення та оптимізація кількісного складу ректальних супозиторіїв із діосміном та гесперидином методом математичного планування експерименту.

Об'єктами дослідження були зразки супозиторіїв дифільного типу із діосміном та гесперидином. Дисперсне середовище цих зразків складалося із гідрофобної (Witepsol W_{35} та емульгатори) та гідрофільної (гель альгінатного натрію із додаванням Ca^{2+} як комплексоутворюючого катіона) частин. Попередні результати визначення процентних меж гідрофобної частини дисперсного середовища отримували шляхом дослідження показників вивільнення діючих речовин із лікарської форми та методом лазерної дифракції. Як відповіді для експерименту використовували такі показники, як час розпадання, твердість та мукоадгезія.

У результаті проведених досліджень встановлено функціональну залежність показників від кількості компонентів дисперсного середовища супозиторіїв. Встановлено, що допустимі значення відгуків

мають відповідати таким умовам: твердість і мукоадгезія мають наближатися до максимуму, а час розпаду – до мінімуму.

За результатами дослідження встановлено, що оптимальний вміст суміші емульгаторів – 6,29%, твердий жир – 39,51%, гідрофільної частини дифільного середовища – 29,58%. Відгуки, що забезпечать системі необхідні структурно-механічні та фармакотехнологічні властивості, варіюються в межах: y_1(2,713); y_2 (22,639); y_3(439,283). Одержані дані буде використано в подальших дослідженнях по оптимізації складу та технології ректальних супозиторіїв із діосміном та гесперидином.

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РАЗРАБОТКА И ОПТИМИЗАЦИЯ КОЛИЧЕСТВЕННОГО СОСТАВА СУППОЗИТОРИЕВ РЕКТАЛЬНЫХ С ДИОСМИНОМ И ГЕСПЕРИДИНОМ МЕТОДОМ МАТЕМАТИЧЕСКОГО ПЛАНИРОВАНИЯ ЭКСПЕРИМЕНТА

Ключевые слова: диосмин, гесперидин, суппозитории, математическое планирование эксперимента, вспомогательные вещества

А Н Н О Т А Ц И Я

При разработке ректальных суппозиториев дифильные основы используют крайне редко. Это связано с образованием возможных нестабильностей внутри системы «дисперсная фаза–дисперсная среда». Для решения подобных технологических задач рационально использовать методы математического планирования эксперимента. Их главной особенностью является разноплановость подходов к построению математической модели. Это означает, что у разработчика существует возможность теоретически прогнозировать результаты будущего эксперимента, анализировать полученные данные, исключать повторение экспериментов и оптимизировать технологию лекарственных средств.

Целью этого исследования была разработка и оптимизация количественного состава ректальных суппозиториев с диосмином и гесперидином методом математического планирования эксперимента.

Объектами исследования были образцы суппозиториев дифильного типа с диосмином и гесперидином. Дисперсная среда этих образцов состояла из гидрофобной (Witepsol W_{35} и эмульгаторы) и гидрофильной (гель альгинатного натрия с добавлением Ca^{2+} в качестве комплексообразующего катиона) части. Предварительные результаты определения процентных границ гидрофобной части дисперсной среды получали путем исследования показателей высвобождения действующих веществ из лекарственной формы и с помощью метода лазерной дифракции. В качестве откликов для эксперимента использовали такие показатели, как время распадания, твердость и мукоадгезия.

В результате проведенных исследований установлена функциональная зависимость показателей от количества компонентов дисперсной среды суппозиториев. Установлено, что допустимые значения откликов должны соответствовать таким условиям: твёрдость и мукоадгезия должны приближаться к максимуму, а время распада – к минимуму.

По результатам исследования установлено, что оптимальное содержание смеси эмульгаторов – 6,29%, твердого жира – 39,51%, гидрофильной части дифильной среды – 29,58%. Отклики, которые обеспечат системе необходимые структурно-механические и фармако-технологические свойства, варьируют в пределах: y_1(2,713); y_2 (22,639); y_3(439,283). Полученные данные будут использованы в дальнейших исследованиях оптимизации состава и технологии ректальных суппозиториев с диосмином и гесперидином.

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