

ТЕХНОЛОГІЯ ЛІКАРСЬКИХ ПРЕПАРАТІВ

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The choice of the quantitative composition of excipients when creating the natural zeolite paste

The properties of pastes depend on a number of factors, the most important of them are the concentration of the solid phase and the nature of the dispersion medium.

Aim. To study the effect of the amounts of active substances and excipients on the pharmacotechnological properties of a natural zeolite paste (clinoptilolite) and to optimize the composition of the finished dosage form.

Materials and methods. The objects of the study were model compositions of pastes containing the active substance – natural zeolite powder (clinoptilolite) in the concentrations of 20-30 %, a thickener – silicon dioxide in the concentrations of 6.0-8.0 %, and a plasticizer – glycerol in the concentrations of 6.0-8.0 %. Samples of pastes also contained flavoring agents – sorbitol and apple flavoring of 3 % each, and 0.02 % of a preservative – sorbic acid. To select the pharmaceutical factors significantly affecting the study object the fractional factorial experiment 2³ was used with equal duplication of experiments. Three quantitative factors were studied. The responses were consistency of the paste, effective viscosity at the shear rate $D_r = 5.0 \text{ s}^{-1}$, the thixotropic coefficient and the adsorption activity in relation to methylene blue. The relationship between factors and responses was expressed and interpreted using the regression equations.

Results and discussion. It has been determined that the samples studied belong to the thixotropically structured pseudoplastic systems with the structure of the coagulation type. It has been proven that natural zeolite (clinoptilolite) together with silicon dioxide has a structuring effect on the disperse system and the adsorption activity of the paste as a whole; the following composition is optimal (g): natural zeolite (clinoptilolite) 25.0; silicon dioxide 7.0; glycerol 5.0; sorbic acid 0.02; sorbitol 3.0; apple flavor 3.0; purified water 56.98.

Conclusions. The studies on the choice of the quantitative content of excipients for obtaining the natural zeolite paste have been conducted; the optimal composition of active substances and excipients has been proposed.

Key words: natural zeolite; clinoptilolite; silicon dioxide; glycerol; paste; excipients; quantitative factors

В. Д. Рибачук

Вибір кількісного складу допоміжних речовин при створенні пасти цеоліту природного

Властивості паст залежать від низки чинників, найважливішими з яких є концентрація твердої фази та природа дисперсійного середовища.

Мета роботи. Вивчити вплив кількостей діючих та допоміжних речовин на фармакотехнологічні властивості пасти цеоліту природного (кліноптилоліту) та оптимізувати склад готової лікарської форми.

Матеріали та методи. Об'єктами дослідження були модельні композиції паст, що містили діючу речовину – порошок цеоліту природного (кліноптилоліту) в концентраціях 20-30 %, загущувач – кремнію діоксид у концентраціях 6,0-8,0 % та пластифікатор – гліцерин у концентраціях 6,0-8,0 %. Зразки паст також містили коригенти смаку – сорбітол та ароматизатор яблуневий по 3 % кожний та консервант – кислоту сорбінову 0,02 %. Для вибору фармацевтичних факторів, які суттєво впливають на об'єкт дослідження, використовували дробний факторний експеримент 2³ з рівним дублюванням дослідів. Були вивчені 3 кількісні фактори. В якості відгуків слугували консистенція пасти, ефективна в'язкість при швидкості зсуву $D_r = 5,0 \text{ c}^{-1}$, коефіцієнт тиксотропності та адсорбційна активність по відношенню до метиленового синього. Взаємозв'язок між факторами та відгуками виражали та інтерпретували за допомогою рівнянь регресії.

Результати та їх обговорення. Визначено, що досліджені зразки відносяться до тиксотропно-структурованих псевдопластичних систем зі структурою коагуляційного типу. Доведено, що цеоліт природний (кліноптилоліт) разом з кремнію діоксидом чинять структуруючий вплив на дисперсну систему та адсорбційну активність пасти в цілому, а оптимальною є композиція складу, г: цеоліт природний (кліноптилоліт) – 25,0; кремнію діоксид – 7,0; гліцерин – 5,0; кислота сорбінова – 0,02; сорбітол – 3,0; ароматизатор яблуневий – 3,0; вода очищена – 56,98.

Висновки. Проведено дослідження з підбору кількісного вмісту допоміжних речовин для отримання пасти цеоліту природного та запропоновано оптимальний склад діючих та допоміжних речовин.

Ключові слова: цеоліт природний; кліноптилоліт; кремнію діоксид; гліцерин; паста; допоміжні речовини; кількісні фактори

В. Д. Рыбачук

Выбор количественного состава вспомогательных веществ при создании пасты цеолита природного

Свойства паст зависят от ряда факторов, важнейшими из которых являются концентрация твердой фазы и природа дисперсионной среды.

Цель работы. Изучить влияние количеств действующих и вспомогательных веществ на фармакотехнологические свойства пасты цеолита природного (клиноптилолита) и оптимизировать состав готовой лекарственной формы.

Материалы и методы. Объектами исследования служили модельные композиции паст, содержащих действующее вещество – порошок цеолита природного (клиноптилолит) в концентрациях 20-30 %, загуститель – кремния диоксид в концентрациях 6,0-8,0 % и пластификатор – глицерин в концентрациях 6,0-8,0 %. Образцы паст также содержали коррегенты вкуса – сорбитол и ароматизатор яблочный по 3 % каждый и консервант – кислоту сорбиновую 0,02 %. Для выбора фармацевтических факторов, которые существенно влияют на объект исследования, использовали дробный факторный эксперимент 23 с равным дублированием опытов. Было изучено 3 количественных фактора. Откликами служили: консистенция пасты, эффективная вязкость при скорости сдвига $D_r = 5,0 \text{ c}^{-1}$, коэффициент тиксотропности и адсорбционная активность по отношению к метиленовому синему. Взаимосвязь между факторами и откликами выражали и интерпретировали с помощью уравнений регрессии.

Результаты и их обсуждение. Определено, что исследуемые образцы относятся к тиксотропно-структурированным псевдопластическим системам со структурой коагуляционного типа. Доказано, что цеолит природный (клиноптилолит) вместе с кремния диоксидом оказывают структурирующее влияние на дисперсную систему и адсорбционную активность пасты в целом, а оптимальной является композиция состава, г: цеолит природный (клиноптилолит) – 25,0; кремния диоксид – 7,0; глицерин – 5,0; сорбиновая кислота – 0,02; сорбитол – 3,0; ароматизатор яблочный – 3,0; вода очищенная – 56,98.

Выводы. Проведены исследования по выбору количественного содержания вспомогательных веществ для получения пасты цеолита природного и предложен оптимальный состав действующих и вспомогательных веществ.

Ключевые слова: *цеолит природный; клиноптилолит; кремния диоксид; глицерин; паста; вспомогательные вещества; количественные факторы*

Efferent therapy as a method of eliminating toxic products from the body is gaining popularity in various fields of clinical medicine. Among all methods of efferent therapy enterosorption as a method of non-invasive detoxification attracts increasing attention; when adequately used, it allows achieving the local and systemic positive effect. Removal of compounds that adversely affect the body such as allergens, active peroxides, viruses, toxins, inflammatory mediators, as well as preventing their movement into the systemic circulation, stimulates the mechanisms of resistance of the body, prevents development of inflammatory reactions, improves metabolism [1, 2]. The quality and efficiency of enterosorption therapy is determined primarily by the type of the enterosorbent used. One of the promising sources of enterosorbents is natural minerals. A high and stable interest in this group of substances is due to the presence of a wide range of direct and indirect therapeutic and prophylactic effects that are achieved at the expense of their physicochemical properties, the ability to bind and remove toxic products from the body [3-6]. Natural zeolites are the promising mineral raw material for creating enterosorbents [7-8].

One of the optimal dosage forms for creating enterosorbent pharmaceuticals is pastes used successfully for many years in pharmaceutical practice. A characteristic feature of this group of dosage forms is the dispersed type of structures determining the rheological properties of the finished products. The properties of pastes depend on a number of factors, the most important of them are the concentration of the solid phase and the nature of the dispersion medium [9].

The aim of the work was to study the effect of the amounts of active substances and excipients on the pharmacotechnological properties of a natural zeolite paste (clinoptilolite) and to optimize the composition of the finished dosage form.

Materials and methods

The objects of the study were model compositions of pastes containing the active substance – natural zeolite powder (clinoptilolite) in the concentrations of 20-30 %, a thickener – silicon dioxide in the concentrations of 6.0-8.0 %, and a plasticizer – glycerol in the concentrations of 6.0-8.0 %. Samples of pastes also contained flavoring agents – sorbitol and apple flavoring of 3 % each, and 0.02 % of a preservative – sorbic acid. The range of the concentrations of active substances and excipients was chosen based on our previous studies [10].

Consistency of pastes was assessed visually using the five-point scale: 5 – the mass is homogeneous, uniformly colored, there is no stratification and formation of agglomerates of particles; 4 – the mass is homogeneous, uniformly colored, there is no stratification, but there are isolated clots of material in the diameter up to 2 mm; 3 – the mass is unevenly colored, a thin layer of liquid is observed on the surface, there is a partial stratification and formation of particle agglomerates. Determination of rheological parameters was performed on a MYR VR3000 (Spain) viscometer. Its work is based on the Brookfield method and allows to determine the structural and mechanical properties in the range of shear rates from 1 s^{-1} to 200 s^{-1} using coaxial cylinders. The values of dynamic viscosity were fixed at the shear rate $D_r = 5.0 \text{ s}^{-1}$. The coefficient of thixotropy was calculated

Table 1

The quantitative factors and their levels studied when optimizing the composition of the natural zeolite (clinoptilolite) paste

Factor	Variable interval	Levels of factors		
		Lower «-»	Basic «0»	Upper «+»
x_1 – the amount of the natural zeolite (clinoptilolite), %	5	20	25	30
x_2 – the amount of silicon dioxide, %	1	6	7	8
x_3 – the amount of glycerin, %	1	3	5	7

as a result of the division of the paste viscosity at the shear rate of 10.0 rpm/sec on the viscosity value of the paste at the shear rate 100.0 rpm/sec.

Determination of the sorption activity of pastes was studied in relation to the solution of methylene blue (MB) and expressed as the maximum amount of the marker (mg) absorbed by 1 g of the sorbent. For this purpose, the accurate weight of the sorbent weighing 0.15 g was placed in a test tube, 10 ml of the methylene blue solution with the concentration of 0.15 mg/ml was added and shaken on the apparatus for shaking for 30 min. After reaching the sorption equilibrium the solution was separated by centrifugation (3000 rpm), the optical density of the solution was measured using a KFK-2 photocolormeter at the wavelength of 490 nm in a 1 mm cuvette. The equilibrium concentration of MB was calculated using the calibration graph of the dependence of the optical density of the MB solution on its concentration.

To select the pharmaceutical factors significantly affecting the study object the random balance method was used. The planning of the experiment was carried out according to the algorithm described in the monograph “Mathematical planning of the experiment in carrying out scientific research in pharmacy” [11]. The plan of the experiment is given in Tab. 1. The relationship between the quantitative factors studied and the pharmaceutical parameters of the paste was expressed and interpreted using regression equations. The adequacy of the models and the statistical significance of the coefficients were verified using the F-criterion. The equations constructed were considered to be adequate when $F_{\text{exp}} < F_{\text{tabl}}$.

Results and discussion

The extended matrix of plan 2^3 and the results of the studies are given in Tab. 2. All dispersions obtained were checked by the Cochran criterion and were homogeneous.

When assessing the homogeneity of the natural zeolite paste all series of experiments were evaluated perfectly. Therefore, this report (y_1) does not show the regression equation.

The effect of the factors studied on the effective viscosity of the paste at the shear rate $D_r = 5.0 \text{ s}^{-1}$ is described by the following regression equation (1):

$$y_2 = 20.5708 + 17.4958x_1 + 3.3958x_2 - 1.3375x_3 + 2.0375x_1x_2 - 1.1792x_1x_3. \quad (1)$$

In this and the following regression equations, only statistically significant coefficients are indicated. According to the above equation the value of the variables studied is affected by all the experimental factors, and six coefficients are significant. By the value of the impact on this indicator, the factors studied can be arranged in the following sequence: $x_1 > x_2 > x_3$. To a greater degree, the homogeneity depends on the concentration of natural zeolite (factor x_1), which increase leads to a significant increase in viscosity. The content of silicon dioxide and the interaction of factors x_1 and x_2 also affect the change in viscosity in the direction of its growth. The increase in the amount of glycerin in the composition and the interaction of factors x_1 and x_3 , on the contrary, leads to a decrease in viscosity of the systems.

Table 2

The experiment planning matrix and research results

Series, No.	x_1	x_2	x_3	x_1x_2	x_1x_3	x_2x_3	$x_1x_2x_3$	y_1	y_2	y_3	y_4
1	+	+	+	+	+	+	+	5	41	15	61.43
2	-	+	+	-	-	+	-	5	4.2	11	45.67
3	+	-	+	-	+	-	-	5	30.1	5.2	57.37
4	-	-	+	+	-	-	+	5	1.6	3	43.47
5	+	+	-	+	-	-	-	5	46	12	54.13
6	-	+	-	-	+	-	+	5	4.7	10	41.17
7	+	-	-	-	-	+	+	5	35.1	3.7	50.9
8	-	-	-	+	+	+	-	5	1.8	4	40

Notes: y_1 – consistency, points; y_2 – effective viscosity at the shear rate $D_r = 5.0 \text{ s}^{-1}$, $\text{Pa} \cdot \text{s}$; y_3 – the coefficient of thixotropy, units; y_4 – the adsorption activity in relation to methylene blue, mg/g.

The relationship between the factors studied and values of thixotropy is described by the regression equation (2):

$$y_3 = 8.0333 + 1.0667x_1 + 4.0333x_2 + 0.675x_3 + 0.6x_1x_2 + 0.4775x_1x_3 + 0.425x_2x_3. \quad (2)$$

The analysis of regression equations shows that for this indicator seven coefficients are significant. By the value of the impact on thixotropy the factors studied can be arranged in the following sequence: $x_2 > x_1 > x_3$. According to the regression equation the greatest effect on thixotropy of pastes has the amount of a thickener in their composition. When increasing the concentration of silicon dioxide the value of this parameter increases. The increase in thixotropy is also observed with an increase in the concentration of zeolite and glycerin, but the force of influence of these substances is less. It should also be noted that the duplex interaction of factors positively affects thixotropy.

The relationship between the factors studied and the adsorption activity of the paste is described by the regression equation (3):

$$y_4 = 49.2675 + 6.69x_1 + 1.3325x_2 + 2.7175x_3 + 0.49x_1x_2 + 0.725x_1x_3 + 0.2325x_2x_3. \quad (3)$$

Analysis of the regression equations shows that for this indicator six coefficients are significant. By the value of the impact on the adsorption activity the factors studied can be arranged in the following sequence: $x_1 > x_3 > x_2$. This indicator increases to the greatest extent when increasing the content of natural zeolite. The adsorption activity also increases with the increase in the concentration of silicon dioxide and glycerin, but their effect is 3-4 times less compared to factor x_1 . It should also be noted that the effect of the interaction between factors x_1 , x_2 and x_3 also manifests itself in increasing the values of the parameter studied.

The studies conducted have shown (Tab. 2) that for any ratio between the substances used the series of the paste samples studied have excellent homogeneity indices, pastes belong to the thixotropically structured systems. However, parameters of viscosity and thixot-

ropy of pastes depend on the solid phase content and increase within the range of 1.6-46 Pa·s and 3-15 units, respectively, with an increase in the content of the solid phase in the paste. The adsorption activity also increases when increasing the content of natural zeolite and silicon dioxide. For more precise determination of concentrations of the substances the additional studies were conducted by the "steep climb" scheme to the optimum. Since the paste developed is for oral use, it was decided to choose the viscosity of food products, namely mayonnaise and condensed milk, as a reference for its viscosity and program this indicator within the range of 5-15 Pa·s. Taking into account the results of the previous studies of the rheological properties of pastes [10] and the fact that viscosity of pastes with the maximum and minimum content of substances was outside of the period chosen it was decided to fix factor x_2 at the basic level. Since the adsorption capacity of pastes depended to a greater extent on the content of natural zeolite, and viscosity decreased with increasing the concentration of glycerin as a starting point, the upper level was chosen for factor x_1 , and the lower level for factor x_3 . The variable interval for the factors was 0.5, factor x_1 was changed in the direction of decrease, while factor x_3 was increased. The model series of pastes were studied with similar responses. As a result of our research, the optimal composition of the paste has been determined (g), it is natural zeolite (clinoptilolite) – 25.0; silicon dioxide – 7.0; glycerine – 5.0; sorbic acid – 0.02; sorbitol – 3.0; apple flavor – 3.0; water purified – 56.98. The resulting composition had an excellent homogeneity, its viscosity was 14.5 Pa·s, thixotropy was 8.0 units, the adsorption activity in relation to methylene blue was 52.5 mg/g.

CONCLUSIONS

1. The study on the choice of the quantitative content of excipients for obtaining the natural zeolite paste has been conducted.

2. Using the regression analysis the optimal composition of the natural zeolite paste (clinoptilolite) has been determined (g), it is natural zeolite (clinoptilolite) – 25.0; silicon dioxide – 7.0; glycerine – 5.0; sorbic acid – 0.02; sorbitol – 3.0; apple flavor – 3.0; purified water – 56.98.

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