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UDC 615.453.3

DOI: 10.15587/2519-4852.2018.122007

STUDY OF EXCIPIENTS QUANTITIES INFLUENCE IN THE COMPOSITION OF THE POWDER IN SACHET PACKAGES

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При розробці порошку в пакетах саше з протизапальною дією особливим завданням є встановлення оптимального якісного та кількісного складу допоміжних речовин. Метою дослідження було вивчити вплив кількостей допоміжних речовин на фармако-технологічні показники порошку.

***Методи.** З активних компонентів і допоміжних речовин були складені різні композиції з використанням методу математичного планування експерименту. Методом випадкового балансу вивчено їх вплив на фізико-хімічні, технологічні та органолептичні властивості порошку.*

***Результати дослідження.** Аналіз діаграм розсіювання результатів дослідження впливу кількісних факторів на зовнішній вигляд маси показав, що найсуттєвіше на цей показник впливають вміст кальцію фосфату, натрію цитрату, куркуміну й ароматизатора лимон-лайм. Значущими факторами для насипної густини і густини після усадки є кількості кальцію фосфату, натрію цитрату, ароматизатора лимон-лайм і титану діоксиду. На результати дослідження індексу Карра найбільше впливають кількості кислоти лимонної безводної, титану діоксиду та куркуміну. Експериментальні значення текучості найсуттєвіше залежать від вмісту кальцію фосфату. Кількості кальцію фосфату, натрію цитрату і титану діоксиду є найбільш значущими для кута відкосу. Найбільший вплив на показники втрати в масі при висушуванні проявляють кількості куркуміну та кислоти яблучної. На основі діаграм розсіювання зовнішнього вигляду розчину встановлено визначальний вплив кількості кальцію фосфату, натрію цитрату, ароматизатора лимон-лайм і титану діоксиду. Цілком очевидним є значущість кількості ароматизатора лимон-лайм на запах розчину. Аналіз діаграми розсіювання смаку розчину показав, що найбільш значущими є вміст кальцію фосфату і кислоти лимонної безводної. Найбільш значущими факторами для рН розчину є кількості кальцію фосфату та ароматизатора лимон-лайм.*

***Висновки.** Досліджено вплив кількостей допоміжних речовин на фармако-технологічні та органолептичні властивості порошку в пакетах саше склад саше*

***Ключові слова:** порошок, саше, кількість допоміжних речовин, фармако-технологічні показники, випадковий баланс*

1. Introduction

Powders in packs are well appreciated by patients, because they have the combined benefits of tablets (precise dosage) and the possibility of easier ingestion (do not need to swallow the tablets) [1].

2. Statement of the problem

During developing a drug, you must take into account a number of key moments. After all, the purpose of pharmaceutical development is not only the creation of an effective and safe drug, but also the organization of appropriate conditions of the production process, which

would ensure its reproducibility. The choice of the optimal composition of the drug and the development of technology makes it possible to establish a range of permissible values of the parameters of the process and components of the recipe, the observance of which guarantees the conformity of the final product to the requirements of the specification [2].

In order to develop a drug with anti-inflammatory properties, active pharmaceutical ingredients were selected, depending on the mechanisms of action. When creating powder in sachets with 0.325 g of paracetamol, 0.05 g ascorbic acid, 0.01 g of phenylep-

hrine hydrochloride and 0.02 g of pheniramine maleate, first of all, the ratio of active pharmaceutical ingredients and their physico-chemical properties were taken into account. When developing the powder, a special task is to establish an optimal qualitative and quantitative composition of excipients [3]. Based on the study of technological characteristics of powders were identified excipients.

3. Analysis of recent research and publications

In work [4, 5], using the plans of mathematical planning of the experiment, the influence of quantitative factors on the basic pharmaco-technological parameters of the tablets was investigated, which allowed to reveal and substantiate the correlation of excipients for the development of the optimal composition of solid dosage forms. On an example of optimizing the composition of rapidly soluble tablets of clonazepam, a mathematical model was proposed to be tested by controlling the pharmaco-technological parameters [6].

Research, using mathematical methods of planning (random balance method, factor experiment, the Boxes-Wilson method), are successfully used to optimize various technological processes. The main advantage of the methods of mathematical planning in comparison with the classical methods of research is the possibility of simultaneous study of a large number of factors operating in the system [7].

Using the scientific approaches of mathematical planning of the experiment, namely, the method of random balance, authors [8–10] studied the influence of quantitative factors on the main indicators of the quality of drugs. The most significant factors influencing the formulation and the main indicators of quality of developed preparations in the form of suspensions [8, 9] and tablets [10] were determined.

4. Identification of aspects of the problem unsolved previously

In previous studies, the effect of nature of 27 excipients on the pharmaco-technological properties of the powder in sachet packs was studied. According to the obtained results, the excipients that have the most significant influence on the pharmaco-technological parameters of the medicinal form were selected. Then it is necessary to study the quantitative characteristics of the excipients, since when they change in composition will change the pharmacological and technological properties of the powder. Study of pharmaco-technological parameters of the dosage form will allow to optimize the excipients quantity in the composition and to manage the quality of the drug.

5. Objective statement of the article

The aim of the work was to study the effect of excipients quantity on the pharmaco-technological parameters of the powder in sachet packs.

6. Presentation of the main material of the research

From the active components and excipients, different compositions were compiled using the method of mathematical planning of the experiment. By accidental balance method, their influence on physico-chemical, technological properties of powders and quality indicators of a solution were studied.

Based on the results of the previous experiment on the influence of qualitative factors, it was gotten excipients quantity for use during making research and shown in Table 1.

Using the random balance method [7], a research plan was drawn up (Table 2). The average weight of 22.13 g was regulated by the quantity of powdered sugar.

Table 1
Factors and their levels in the study of quantitative characteristics of excipients in powder in sachet packs

Designation of the factor	Factor	Level of the factor		
		Lower «-»	Basic «0»	Upper «+»
x ₁	Quantity of calcium phosphate, g	0.0820	0.7000	1.3180
x ₂	Quantity of acid citric anhydrous, g	0.6500	0.9360	1.2220
x ₃	Quantity of malic acid, g	0.0500	0.0900	0.1300
x ₄	Quantity of sodium citrate, g	0	0.0605	0.1210
x ₅	Quantity of curcumin, g	0.0213	0.0383	0.0400
x ₆	Quantity of lemon-lime flavor, g	0.1915	0.2000	0.2085
x ₇	Quantity of titanium dioxide, g	0.0014	0.0032	0.0050

Table 2

The experiment planning matrix, the results of the research of powder in sachets

batch	x ₁	x ₂	x ₃	x ₄	x ₅	x ₆	x ₇	y ₁	y ₂	y ₃	y ₄	y ₅	y ₆	y ₇	y ₈	y ₉	y ₁₀	y ₁₁
1	-	-	-	+	+	+	-	5	0.6086	0.8844	31.18	56.8	48.3	0.30	5	5	4	3.05
2	-	+	-	+	-	+	-	4	0.6403	0.8658	26.05	44.9	47.5	0.31	5	4	5	2.78
3	+	-	-	-	-	-	+	5	0.7403	1.0193	27.37	52.7	41.0	0.32	4	4	3	4.01
4	+	+	-	-	+	-	+	5	0.7393	1.0071	26.59	50.1	40.5	0.46	4	4	5	3.74
5	-	-	+	+	-	-	+	4	0.6502	0.8824	26.31	17.5	46.9	0.37	5	4	4	3.10
6	-	+	+	-	+	+	-	5	0.6187	0.8517	27.36	18.4	46.6	0.46	5	5	5	2.58
7	+	-	+	+	+	-	-	5	0.7246	1.0016	27.66	69.1	41.7	0.46	4	4	3	3.98
8	+	+	+	-	-	+	+	4	0.7444	1.0066	26.05	66.6	41.4	0.39	4	5	3	3.70
9	0	0	0	0	0	0	0	5	0.6944	0.9742	28.72	62.6	43.6	0.50	4	4	5	3.60
10	0	0	0	0	0	0	0	5	0.7075	0.9988	29.16	57.6	45.2	0.42	4	4	4	3.60

Notes: y₁ – appearance of the mass, points; y₂ – bulk density, g/ml; y₃ – density after shrinkage, g/ml; y₄ – Carr's index, %; y₅ – flow rate, s/100 g; y₆ – slope angle; y₇ – mass loss during drying, %; y₈ – appearance of the solution, points; y₉ – the smell of the solution, points; y₁₀ – taste of the solution, points; y₁₁ – pH of the solution

Experimental studies of pharmaco-technological quality indices were carried out in accordance with pharmacopoeial methods, in particular: mass loss during drying, bulk density, density after shrinkage, flow, slope angle and pH of a solution [11, 12]. The technological properties of the powder masses and the physical characteristics of the solution from the contents of the sachet package in 200 ml of purified water were studied.

Determination of significant factors was carried out using scattering diagrams. The median value indicated the significance of the factor. The significance of the selected effects was verified using Student's criterion.

Test results are presented in Table 2.

The analysis of the scattering diagram of the results of the study of the influence of quantitative factors on the appearance of the mass (y_1) showed that the most significant of this indicator is infused with calcium phosphate, sodium citrate, curcumin and lemon-lime flavor. With an increase in the quantity of calcium phosphate, curcumin and the study of the lower levels of factors x_4 , x_6 , the intensity of colour and appearance of the powder is significantly increased. The analysis of the influence of other factors showed their insignificant effect on this indicator.

The influence of quantitative factors on the bulk density (y_2) and the density after shrinkage (y_3) is given in Fig. 1.

From the diagrams it is seen that the significant factors are x_1 , x_4 , x_6 , x_7 . Increasing the quantities of calcium phosphate and titanium dioxide, as well as reducing the content of sodium citrate and flavor of lemon-lime is accompanied by an improvement in the studied parameters.

Analysis of the scattering diagram of the Carr's index (y_4) showed that the results of the study are most influenced by the factors x_2 , x_7 and x_5 . With an increase in the content of lemon acid anhydrous and titanium dioxide, the bulk density of the powder mass improves from 27.5 % to 26.3 %. The introduction of a greater quantity of the curcumin is accompanied by an increase in the Carr's index from 26 % to 27 %, which indicates deterioration of mass flowability and may be the cause of deterioration of filling in the packaging stage.

The analysis of the scattering diagram of the results of the study of the effect of quantitative factors on the flow (y_5) showed that the experimental values most significantly depend on the quantity of calcium phosphate. The increase in the factor x_1 is accompanied by a deterioration of the powder flowability from 32.0 s/100 g to 59.0 s/100 g. This indicator is somewhat improved (varies in the range from 51.0 s/100 g to 42.0 s/100 g) with administration of a greater amount of malic acid due to the crystalline structure of its particles.

In assessing the influence of quantitative factors on the slope angle (y_6), using the scatter diagram, it was noted that the factors x_1 , x_4 , x_7 are the most significant. At the same time, when the content of calcium phosphate and titanium dioxide decreases, the difference in the average from 47° to 41°. However, the introduction of more sodium citrate is accompanied by opposite changes. It should be noted that the increase in the quantity of lemon-lime flavor improves the slope of the range from 44° to 47°.

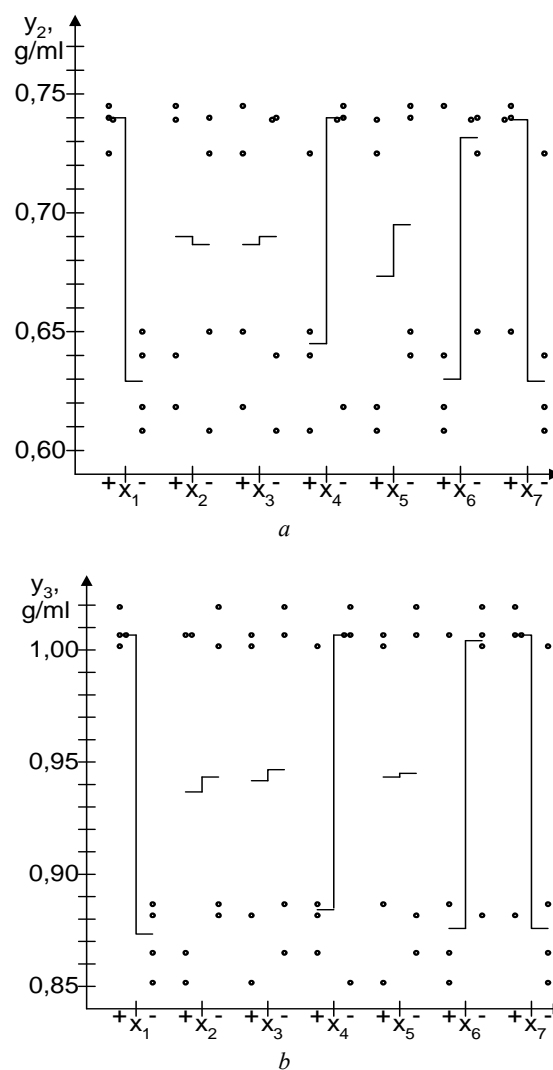


Fig. 1. Diagram of dispersion of the influence of quantitative factors on the density of the powder: a – on the bulk density; b – on the density after shrinkage

Loss in mass during drying is an important indicator of quality, especially in the process of storing powder in sachet packs. High moisture content can cause the powders to soften and impair their characteristics. The influence of quantitative factors on mass loss during drying (y_7) is shown in Fig. 2.

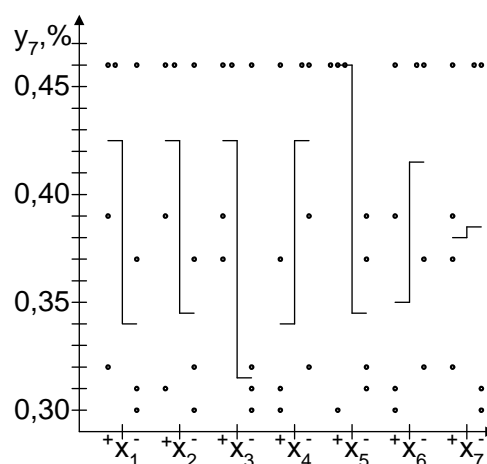


Fig. 2. Diagram of scattering of the influence of quantitative factors on mass loss during drying

It can be seen from the diagram that the factors x_5 and x_3 show the greatest influence on the mass loss index during drying. The lowest values of this index were observed with the addition of 0.0213 g of curcumin. The introduction of malic acid at the lower investigated level also significantly reduces the moisture content of the powder. Reducing the quantities of calcium phosphate and citric anhydrous acid leads to an improvement in the investigated index. However, an increase in sodium citrate content and a lemon-lime flavour can reduce the loss of mass in the mass during drying.

For the powder for oral solution important parameters are also organoleptic characteristics of the solution from the content of the sachet pack. In order to quantify their contents, one packet of powder was dissolved in 200 ml of purified water and the solution was analysed in appearance, smell, taste and pH. The first three indicators were evaluated on a 5-point scale. The analysis of the results was carried out using scattering diagrams.

On the basis of the scattering diagram of the appearance of the solution (y_8), the determining influence of the factors x_1, x_4, x_6, x_7 is established. With increasing quantities of sodium citrate and lemon-lime flavor transparent solution with intense coloration was obtained. Administration of higher contents of calcium phosphate and titanium dioxide causes turbidity of the solution.

Obviously, the significance of the quantity of lemon-lime flavor on the smell of the solution (y_9), and with the increase in its content, the results improve. There is also an insignificant influence of other factors on the smell of the solution.

Analysis of the scattering diagram of the taste of the solution (y_{10}) showed that the most significant are the factors x_1 and x_2 . With an increase of the quantity of acid citric anhydrous, there is a sour taste pleasant, and an increase in calcium phosphate content contrary effects on the taste of the solution. Adding more malic acid also causes unpleasant

taste sensations. An increase in the quantities of curcumin and lemon-lime flavor add sour taste, and this allows some improvement in the investigated parameter.

One of the most important characteristics was the pH of the solution (y_{11}). It depended on the solubility of the content of the sachet package. At low values, the pH of the powder was completely dissolved and left no residue. The influence of quantitative factors on the pH of the solution is shown in Fig. 3.

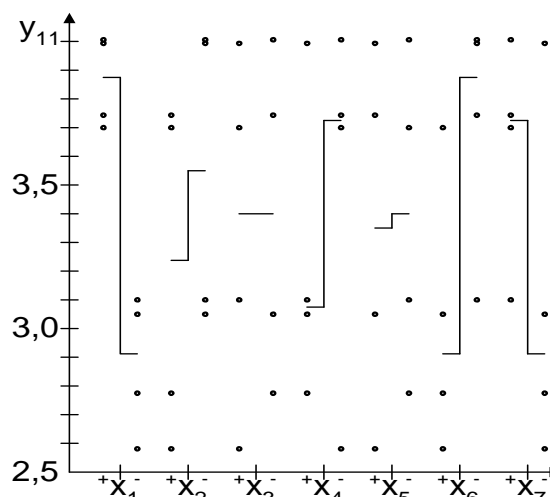


Fig. 3. Diagram of scattering of the influence of quantitative factors on the pH of the solution

The diagram shows that the most significant factors are x_1 and x_6 . Significant influence is shown by the factors x_7 and x_4 . The lowest pH values were observed with the addition of 0.0820 g of calcium phosphate, 0.1210 g of sodium citrate, 0.2085 g of lemon-lime flavor and 0.0014 g of titanium dioxide.

To summarize the experimental data obtained, it was constructed a Table 3.

Table 3

The results of the experiment are summarized in the development of the composition of the powder in sachets packages

Factor/indicator	x_1	x_2	x_3	x_4	x_5	x_6	x_7
y_1	+*	0	0	-*	+*	-*	0
y_2	+*	+	-	-*	-	-*	+*
y_3	+*	-	-	-*	-	-*	+*
y_4	-	+*	+	-	-*	+	+*
y_5	-*	+	+*	+	-	+	-
y_6	-*	-	0	+*	+	+*	-*
y_7	-*	-*	-*	+*	-*	+*	+
y_8	-*	0	0	+*	0	+*	-*
y_9	-	+	+	-	+	+*	-
y_{10}	-*	+*	-*	+	+*	+*	+
y_{11}	-*	+	0	+*	+	+*	-*

Note: * – significant factor

7. Conclusions and prospects for further research

1. Quantitative factors of excipients were studied when creating a powder in sachets packages.

2. It was studied the influence of the quantities of excipients on the pharmaco-technological and or-

ganoleptic properties of the medicinal product: the appearance of the mass, the bulk density, the density after shrinkage, the Carr's index, the flowability, the slope, the mass loss in drying, the appearance of the solution, the smell of the solution, the taste solution, pH of the solution.

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Дата надходження рукопису 31.10.2017

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