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OPTIMIZATION OF THE TECHNOLOGY AND COMPOSITIONOF “SKUTEX”TABLETS

Using the symmetric composite uniform-plan of 2nd order the theoretically-grounded composition of tablets based on dry extract of Scutellaria baicalensis has been received.

Keywords: tablets, Scutellaria baicalensis, the optimal composition.

С помощью использования симметричного композиционного униформ-плана 2-го порядка получили теоретически обоснованный состав таблеток на основе сухого экстракта шлемника байкальского.

The pilot experiment study of the impact of quantitative factors on some indicators showed that their increase did not improve all pharmaco-technological properties for tableting powdery mass and the quality of tablets based on the extract of Scutellaria baicalensis code-named “Skutex”. In order to find the optimal composition of the studied tablets it was necessary to determine the optimal ratio of the excipients in the tablet DF in narrower ranges (Table 1). For this purpose the symmetric rotatable composite uniform-plan of 2nd order was used (Table 2).

During the process of making “Skutex” tablets formulation according to the plan of the experiment in the cases when factors were studied at lower levels or lower “star” points, the average tablet mass was increased with the addition of dried starch in the required quantities.

The obtained results were subjected to statistical analysis, which allowed to detect not only significant factors but also to establish the presence (or absence) of interaction among the factors studied. As the result, equations for each parameter were obtained and then used as the base for single-factor figures building.

The relationship between the studied factors and tableting masses flowability is described by the following regression equation:

$$y_1 = 4{,}001 - 0{,}096x_1 + 2{,}249x_2 + 0{,}063x_3 + 0{,}036x_1x_2 + 0{,}026x_1x_3 - 0{,}039x_2x_3 + 0{,}021x_1^2 - 0{,}048\,x_2^2 + 0{,}016x_3^2.$$

In regression equation only coefficients $b_0 > 0{,}155$ and $b_2 > 2{,}249$ were statistically significant. Therefore, the regression equation for tableting mass flowability is as follows:

$$y_1 = 4{,}001 + 2{,}249x_2$$

Table 1

Quantitative pharmaceutical factors studied during the “Skutex” tablets optimization

Factor	Level of factor				
	Lower«star» point «-α»	Lower level «–»	Main level «0»	Upper level «+»	Upper «star» point «+α»
x_1 – microcrystalline cellulose weight per tablet, g	0,0026	0,003	0,005	0,007	0,0074
x_2 – GranuLac 200 mass per tablet, g	0,099	0,100	0,150	0,200	0,210
x_3 – croscarmellose sodium mass per tablet, g	0,010	0,012	0,022	0,032	0,034

Table 2

Experiment planning matrix and research results for tableting powdery mass and “Skutex” tablets

Series №	x_1	x_2	x_3	y_1	y_2	y_3	y_4
1	+1	+1	+1	4,13	74,2	0,43	16,3
2	-1	+1	+1	4,29	73,8	0,46	15,2
3	+1	-1	+1	3,96	69,1	0,62	13,6
4	-1	-1	+1	4,03	67,2	0,68	9,1
5	+1	+1	-1	4,07	74,5	0,41	18,7
6	-1	+1	-1	4,10	73,5	0,40	16,9
7	+1	-1	-1	3,51	69,7	0,61	15,4
8	-1	-1	-1	3,92	65,8	0,64	11,6
9	+a	0	0	3,86	75,4	0,42	17,3
10	–a	0	0	4,24	72,3	0,44	14,1
11	0	+a	0	4,52	75,2	0,38	18,2
12	0	–a	0	3,19	66,0	0,70	12,9
13	0	0	+a	4,05	73,7	0,45	8,7
14	0	0	–a	4,02	74,7	0,40	19,4
15	0	0	0	4,06	71,8	0,45	15,8
16	0	0	0	4,11	73,2	0,40	12,6
17	0	0	0	3,98	70,5	0,43	16,2
18	0	0	0	3,72	73,3	0,41	15,0
19	0	0	0	4,05	71,0	0,47	14,9
20	0	0	0	4,11	69,6	0,50	13,1

Notes: y_1 - flowability of tableting mass, g/s; y_2 - resistance to crushing, N; y_3 - tablet abrasion, %; y_4 - disintegration, min.

The granulated tableting mass flowability, according to the equation, depends only on the content of lactose monohydrate of GranuLac 200 brand in its composition. The studies showed that, regardless of the studied levels of factors x_1 i x_2, the flowability most noticeably improves with the increased GranuLac content within the tableting mass from 0.1 to 0.2 g per tablet.

The regression equation, which reflects the dependence of the stability of tablets based on Scutellaria baicalensis extract to crashing on the content of excipients, is as follows:

$$y_2 = 71{,}604 + 0{,}909x_1 + 2{,}905x_2 - 0{,}065x_3 - 0{,}55x_1x_2 - 0{,}325x_1x_3 - 0{,}1x_2x_3 + 0{,}385x_1^2 - 0{,}765\,x_2^2 + 0{,}509x_3^2.$$

In this regression equation, similar to the previous one, only the coefficients $b_0 > 0{,}155$ and $b_2 > 2{,}249$ were statistically significant. Therefore, the regression equation for the tablet resistance to crushing is as follows:

$$y_2 = 71{,}604 + 2{,}905x_2.$$

The strength of the studied tablets is only affected by the content of GranuLac 200 in their composition.

The research showed that the increasing content of GranuLac 200 in the composition of "Skutex" tablets positively affects the stability of tablets to crushing, and this effect almost does not depend on the studied level of factors x_1 and x_3.

After the statistical analysis of the results of tablets abrasion based on Scutellaria baicalensis extract the following equation was obtained:

$$y_3 = 0{,}441 - 0{,}011x_1 - 0{,}102x_2 + 0{,}016x_3 + 0{,}009x_1x_2 + 0{,}009x_1x_3 - 0{,}04x_2x_3 + 0{,}009x_1^2 + 0{,}048\,x_2^2 + 0{,}007x_3^2.$$

In this regression equation coefficients b_0, b_2, b_{23} and b_{22} are statistically significant, therefore the equation is as follows:

$$y_3 = 0{,}441 - 0{,}102x_2 - 0{,}04x_2x_3 + 0{,}048\,x_2^2.$$

So, the abrasion of Scutellaria extract tablets depends on the content of GranuLac 200, as well as on the ratio of this excipient with sodium croscarmellose.

Effect of the content of lactose monohydrate of GranuLac 200 brand on the abrasion of the studied tablets is shown by means of lines in Figure 1.

As seen from the figure, the increase of GranuLac 200 content in tablets based on Scutellaria baicalensis extract impairs their abrasion. This is especially observed within the range of 0.1 to 0.2 g of GranuLac 200 per tablet in any of its combination with sodium croscarmellose.

Based on the research results of Scutellaria baicalensis extract tablets disintegration the regression based on the research results of Scutellaria baicalensis extract tablets disintegration the equation for this indicator was made.

$$y_4 = 14{,}612 + 1{,}214x_1 + 1{,}927x_2 - 1{,}933x_3 - 0{,}675x_1x_2 + 0{,}025x_1x_3 + 0{,}276x_1^2 + 0{,}223\,x_2^2 - 0{,}307x_3^2.$$

The coefficients b_0, b_1, b_2 and b_3 in this regression equation are statistically significant; considering this we have:

$$y_4 = 14{,}612 + 1{,}214x_1 + 1{,}927x_2 - 1{,}933x_3.$$

Based on the regression equation we can conclude about the dependence of the disintegration process of the studied tablets on all the three factors.

The effect of MCC content on tablet disintegration time is shown in Figure 2.

Disintegration time of the studied tablets slightly increases with the increasing content of MCC in their composition, but does not exceed 15 minutes. The fastest tablet disintegration was observed when all other factors were studied at the bottom "star" point-line 5.

Using lines figure 3 reflects the influence of lactose monohydrate of GranuLac200 brand on disintegration time of tablets based on Scutellaria baicalensis extract.

As seen from this figure, disintegration time of the studied tablets noticeably increases together with the icrease of GranuLac content from 0.1 to 0.21 g.

Effect of sodium croscarmellose on the disintegration time of tablets based on Scutellaria baicalensis is shown in figure 4.

Since sodium croscarmellose is a leavening agent, it is obvious that the increase of its content improves the process of the studied tablets disintegration. This dependence is most expressed within the range of 0.12-0.032 g croscarmellose sodium per tablet.

(Line 1 – factors x_1 i x_2, forinstance, aresubstituted into the equation at the main level;

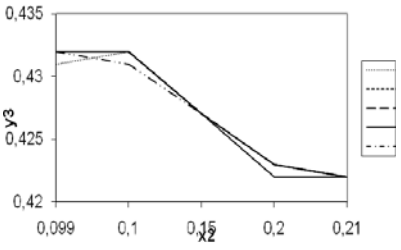

Fig. 1. Dependence of the abrasion of Scutellaria baicalensis extract tablets on the content of GranuLac 200 in their composition

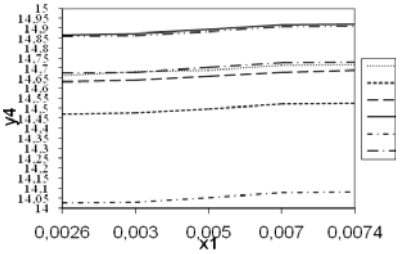

Fig. 2. Dependence of disintegration time of Scutellaria baicalensis extract tablets on the content of MCC in their composition

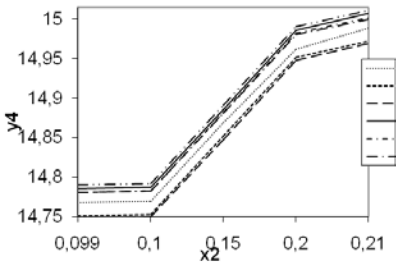

Fig. 3. Dependence of disintegration time of Scutellaria baicalensis extract tablets on the content of GranuLac 200 in their composition

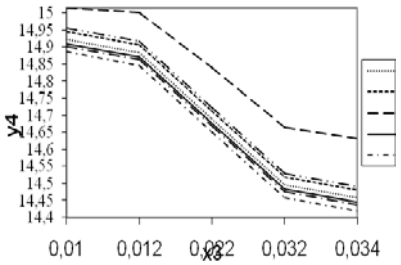

Fig. 4. Dependence of the disintegration time of Scutellaria baicalensis tablets on the content of sodium croscarmellose in their composition

line 2 – at the upper;

line 3 – at the upper"star" point;

line 4 – at the lower level;

line 5 – at the lower"star" point

line 6 – x_1 factorat the upper, x_2 at the lower level;

line 7 – x_1 factorat the lower, x_2 at the upper level.

As long as based on the analysis of regression equations and single-factor figures no interaction between the factors studied was found, to determine the optimal composition of tablets based on Scutellaria baicalensis extract there is no need in finding extremum through the model of 2nd order by bringing it to a canonical form. When choosing optimal quantities of excipients only the boundary optimum should be considered.

The analysis showed that the top level of lactose monohydrate of GranuLac 200 brand provides the satisfactory value of flowability, abrasion and resistance to crushing. The further increase of the content of the excipient from 0.2 to 0.21 g per tablet is not reasonable as it practically does not improve the above-mentioned statements but negatively affects the disintegration of tablets. Therefore it was decided to stabilize factor $x_2$on the upper level.

Since the MCC and sodium croscarmellose only affect disintegration of tablets based on Scutellaria baicalensis extract, while determining their optimal quantities the results of the previous experiment were also taken into account. Accordingly, it was decided to stabilize factors x_1 i x_5 at a lower level.

Conclusions. So, based on symmetric composite rotatable design of 2nd order the theoretically-grounded composition of tablets code-named "Skutex" was obtained which was also proved experimentally.

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