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APPLICATION OF THE METHOD OF MATHEMATICAL EXPERIMENTAL PLANNING IN THE SELECTION OF A COMPLEX OF EXCIPIENTS FOR EFAVIRENZ CAPSULATED MASS

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Abstract: This article presents the results of studies on the selection of excipients for the production of efavirenz encapsulated mass using the 5x5 two-factor analysis of variance method with repeated observations (n=30). According to the results obtained for the encapsulated mass of efavirenz, the use of a mixture of microcrystalline cellulose and lactose as a filler, and croscarmellose sodium as a disintegrator, has been scientifically substantiated. The selection of the antifriction substance was carried out based on the results of studying such pharmacotechnological indicators as flowability and angle of repose. It has been ascertained that the use of magnesium stearate provides the mass with the necessary flowability index to obtain high-quality products. Based on the selected composition, a technology for producing capsules has been developed, which has been tested in industrial conditions.

Key words: efavirenz, capsules, excipients, method of mathematical experimental planning, filler, disintegrator, antifriction substance.

In the modern pharmaceutical industry, it is almost impossible to obtain a dosage form without the use of excipients. Excipients are a group of substances of organic and inorganic nature, of both ionic and non-ionic origin, also classified into natural and synthetic [1-5]. Substances of this group have a wide range of functionality. For example, they are used to give a medicinal substance a form convenient for use, to prolong the action, immediate release or improve the solubility of active substances, to correct organoleptic characteristics, create protective shells, for emulsification, system stabilization, etc. [6-16].

The results of numerous studies confirm the influence of excipients on the biopharmaceutical properties of dosage forms, such as dissolution, penetration, osmotic activity, etc. [17-20]. There is also information about the development of unwanted side effects caused by

this group of substances, in particular in pediatric practice [1,5,21]. The results obtained became the basis for tightening the requirements for the quality and safety of excipients and the further organization of the International Council of Manufacturers, Distributors and Consumers of Pharmaceutical Ingredients (International Pharmaceutical Excipients Council, IPEC). The main function of this organization is the development and harmonization of international requirements for excipients, their safety, as well as the introduction of new substances [3-4].

Thus, the choice of the type of excipients when developing a particular dosage form is a complex task, one of the ways to solve which is to study their effect on the biopharmaceutical parameters of the finished product.

In connection with the above, various variations of methods for mathematical experimental planning are increasingly being used to scientifically substantiate the choice of a particular excipient [22-27].

Purpose of the study. To select excipients to obtain an encapsulated mass of efavirenz using the method of mathematical experimental planning.

Experimental part.

Materials and methods: Efavirenz, which has antiretroviral activity, was chosen as the pharmaceutical active substance of the capsules. The dose of efavirenz was selected taking into account the existing and currently produced in-demand drugs based on it in the form of tablets.

Based on the data on the structural, mechanical and technological indicators of the efavirenz substance, we decided to select two types of excipients: a filler (factor A) and a disintegrator (factor B). They were the factors chosen when applying the method of two-factor analysis of variance with repeated observations [28]. As a response, we used the release rate of the pharmaceutical active substance in biopharmaceutical experiments *in vitro.*

When selecting an excipient, we were guided by literature data, as well as the demand for excipients at domestic pharmaceutical enterprises. The following were selected:

a_1 - lactose monohydrate (Ph. Eur.);

a_2 - maltodextrin (Ph. Eur.);

a_3 - microcrystalline cellulose (SP RUz I ed., Ph. Eur.);

a_4 – a mixture of microcrystalline cellulose (SP RUz I ed., Ph. Eur.) and lactose monohydrate (Ph. Eur.);

a_5 - a mixture of microcrystalline cellulose (SP RUz I ed., Ph. Eur.) and maltodextrin (Ph. Eur.).

The following was used as a disintegrator:

b_1 – absence of disintegrator;

b_2 - potato starch (SF RUz I ed., Ph. Eur.);

b_3 – croscarmellose sodium (Ph. Eur.);

b_4 – alginic acid (USP);

b_5 – crospovidone (USP).

In vitro experimental conditions: device – “Rotating basket”, duration – 45 min, temperature 37±1 °C, volume of dissolution medium – 1000 ml, dissolution medium – 2% sodium dodecyl sulfate solution, basket rotation speed – 100 rpm.

For encapsulation, hard gelatin capsules No. 0 were used.

Results and discussion: The 5x5 experimental design and the results of experiments on the release of efavirenz from model capsules in 45 minutes are presented in Table 1.

Table 1

Release of efavirenz from model capsules in a two-factor 5x5 design with three repeated experiments, %

Factor A	Factor B					Amounts by levels of factor A
	b_1	b_2	b_3	b_4	b_5	
a_1	65.40	68.03	74.66	65.27	77.13	1061.76
	68.16	69.54	78.38	65.39	72.08	
	68.34	71.39	75.98	69.43	72.58	
	201.90	**208.96**	**229.02**	**200.09**	**221.79**	
a_2	72.48	87.27	86.44	82.27	75.18	1206.01
	77.12	80.60	81.39	78.09	78.49	
	74.49	83.97	82.58	85.34	80.30	
	224.09	**251.84**	**250.41**	**245.70**	**233.97**	
a_3	70.31	69.69	90.67	70.11	78.59	1152.75
	75.06	75.13	84.83	73.39	75.72	
	71.08	76.62	87.91	74.49	79.15	
	216.45	**221.44**	**263.41**	**217.99**	**233.46**	
a_4	72.58	82.43	93.32	83.60	90.24	1291.91
	74.16	86.20	91.15	88.76	92.13	
	71.49	88.91	95.67	87.54	93.73	
	218.23	**257.54**	**280.14**	**259.90**	**276.10**	
a_5	76.37	81.11	89.15	72.53	79.16	1218.94
	80.06	86.17	88.44	75.19	84.63	
	74.78	82.24	90.31	73.04	85.76	
	231.21	**249.52**	**267.90**	**220.76**	**249.55**	
Amounts by levels of factor B	1091.88	1189.30	1290.88	1144.44	1214.87	5931.37

Calculations of the release of the pharmaceutical active substance indicate that for factor A three effects were positive (a_2 = 1.32, a_4 = 7.04 and a_5 = 2.18), the remaining two effects had a negative sign (a_1 = -8.30; a_3 =-2.23). For factor B, 3 effects also had a positive sign (b_2=0.20, b_3=6.97 and b_5=1.91), and two effects had a negative sign (b_1=-6.29; b_4=-2.79). According to the concept of biopharmacy, in order to increase the yield of efavirenz from capsules, it is desirable to use such fillers as maltodextrin (a_2), a mixture of microcrystalline cellulose and lactose monohydrate (a_4), a mixture of microcrystalline cellulose and maltodextrin (a_5). In the case of a disintegrator, it is preferable to use potato starch (b_2), croscarmellose sodium (b_3) and crospovidone (b_5).

Numerous studies confirm that when excipients are used together, the % release of pharmaceutical active substances may be different than when using a separate component. Thus, when considering the effects of interactions, positive results are given by a_1b_1 (2.81), a_1b_5 (1.24), a_2b_1 (0.59), a_2b_2 (3.34), a_2b_4 (4.29), a_3b_1 (1.59), a_3b_3 (3.98), a_4b_3 (0.28), a_4b_4 (3.29), a_4b_5 (4.00), a_5b_1 (2.1), a_5b_2 (1.71), a_5b_3 (1.06), a_5b_5 (0.01). The data presented confirm the complex mutual influence of the factors being studied.

Next, the homogeneity of variances was checked using the Cochran test. The tabulated value of the Cochran criterion for f_1=2 and f_2=25 at the significance level α=0.05 was 0.2354, which is significantly greater than the experimental value (y_{exp}=0.0829), i.e. the experiments are equally accurate.

Table 2 shows the results of variance analysis.

The data obtained, $F_{exp} > F_{tab}$ (75.95>2.56; 58.25>2.56; 6.43>1.85) indicate a direct influence of the type of filler and disintegrant on the % release of the pharmaceutical active substance.

Table 2

Analysis of variance of experimental data to determine the release of efavirenz from model capsules

Variation sources	Number of freedom degrees	Sum of squares	Average squares	F_{exp}	F_{tab}
Factor A	4	1949.54	487.39	75.95	2.56
Factor B	4	1495.31	373.83	58.25	2.56
AB interaction	16	660.56	41.28	6.43	1.85
Error inside cell	50	320.86	6.42		
Total amount	74	4426.26			

In order to ascertain the effect of the analyzed excipients on the release of efavirenz from their model capsules, we applied Duncan's multiple rank test [28]. The preferred series of fillers looked like this: $a_4 > a_3 = a_2 = a_5 > a_1$, i.e. the use of a mixture of microcrystalline cellulose and lactose gives the highest percentage of release of the pharmaceutical active substance. Next in line of preference are maltodextrin, microcrystalline cellulose and a mixture thereof.

For disintegrators, the preference line was built as follows: $a_4 > a_3 = a_2 = a_5 > a_1$. Thus, of the disintegrants used in model capsules, croscarmellose sodium is optimal in terms of efavirenz release.

Further research was aimed at considering the issue of using antifriction substances. As is known, this group of excipients improves the sliding of granules and increases the flowability index, which is important for obtaining high-quality products. For a scientifically based choice of an antifriction substance, a model encapsulated mass was prepared using the selected filler and disintegrator. Next, the mass was divided into three parts:

No. 1 – left without adding an antifriction substance;

No. 2 - magnesium stearate was added in an amount of 1% relative to the total mass;

No. 3 – talc was added in an amount of 2% relative to the total mass.

The results of studying the flowability and angle of repose of model mixtures are shown in Table 3.

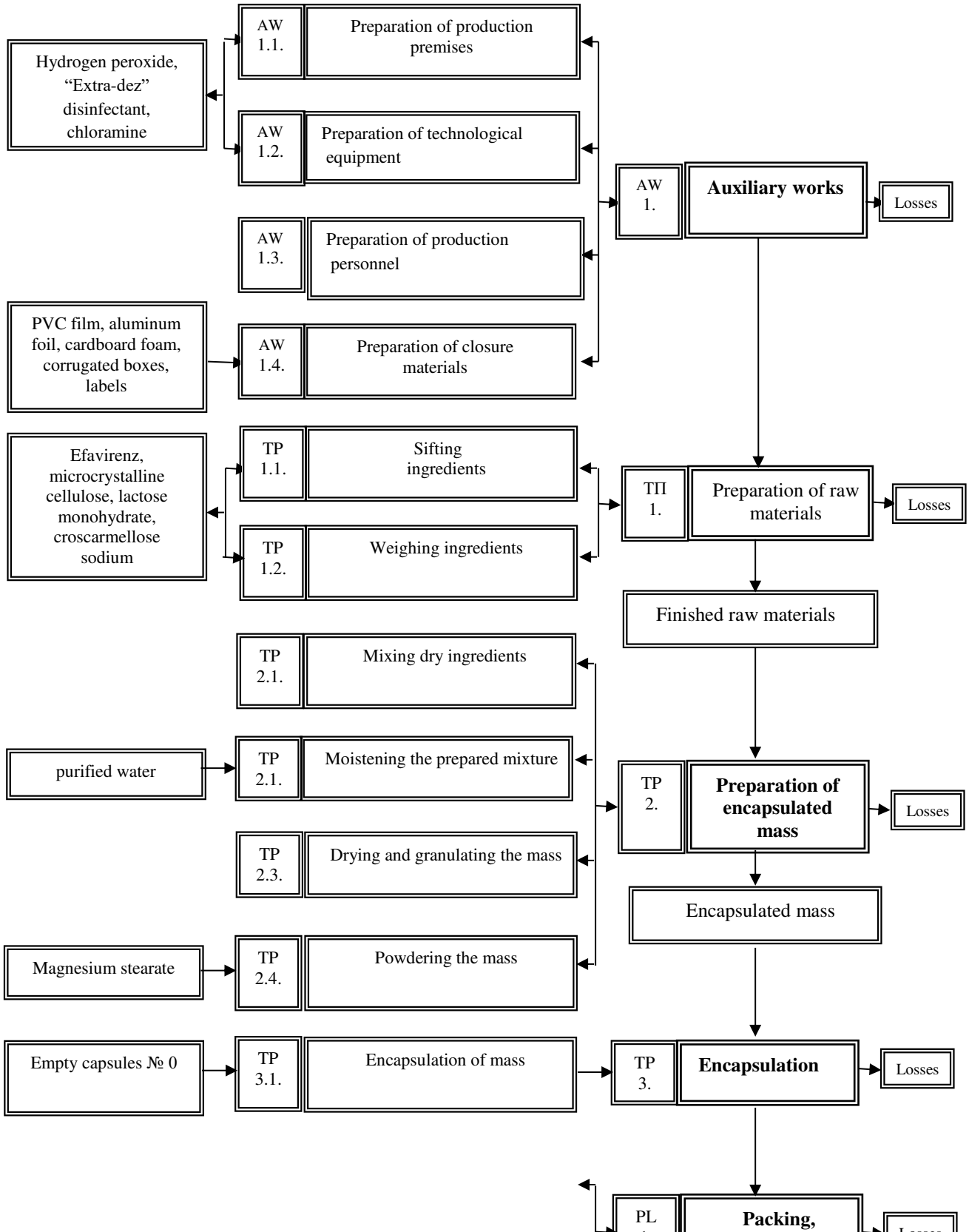
Table 3

Value of flowability and angle of repose of model mixtures of efavirenz

Indicator	Measurement unit	Model mixtures		
		№1	№2	№3
Flowability with vibration shaking	10^{-3} kg/s	4.06 ±0.53	6.74 ±0.82	5.70 ±0.46
Angle of repose	degree	48.0±3.0	37.0±2.0	43.0±2.0

The data in Table 3 indicate that the use of antifriction substances significantly improves the determined pharmacotechnological indicators. Thus, the use of magnesium stearate made it possible to increase the flowability index by 1.66 times, and the use of talc - by 1.40 times. Also, when determining the angle of repose, the best indicators were for the mixture with magnesium stearate: the determined indicator decreased by 1.30 times and amounted to 37.0 ± 2.0 degrees, and in the mixture powdered with talc, the value obtained was 1.12 times less (43.0±2.0) than in the mixture without antifriction substance. Thus, it was decided to use magnesium stearate as an antifriction substance in an amount of 1% relative to the total encapsulated mass.

producing capsules has been developed, which has been tested in industrial conditions.



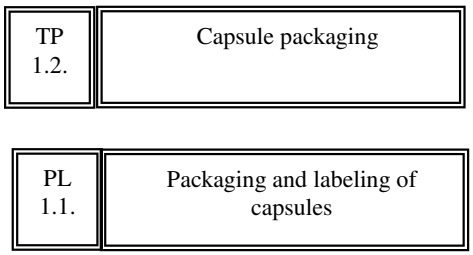


Fig. Scheme of the technological process for producing efavirenz capsules

Based on the results of the research, the following technology for producing efavirenz capsules has been developed: the pharmaceutical active substance, microcrystalline cellulose, lactose and croscarmellose sodium are pre-sifted and the required amount is weighed out. Next, all ingredients are mixed until a homogeneous mass is obtained and, with constant stirring, moistened with purified water. The resulting mass is laid out on pallets and dried in an oven at a temperature of 40-50 ^{0}C until the residual moisture content is 10-15%. This mass is granulated by rubbing through a sieve with a hole diameter of 1000 microns and continued drying in an oven at the above temperature until the optimum residual moisture content is reached (2-3%). The resulting mass is dusted with magnesium stearate, weighed and packaged in capsules of size 0 to 0.3 g.

The technological scheme for obtaining efavirenz capsules is shown in the figure.

The developed technology for producing efavirenz capsules was tested in industrial conditions on the basis of a domestic manufacturer.

Conclusion. The choice of excipients (filler and disintegrator) for efavirenz capsules was scientifically substantiated using a 5x5 two-factor analysis of variance with repeated observations (n=3). The selection of the antifriction substance was carried out based on the results of studying such pharmacotechnological indicators as flowability and angle of repose. Based on the selected composition, a technology for

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