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Use of mathematical planning methods for optimization of antibovasin unguent composition

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Abstract

This article presents the results of experimental studies to determine the composition of the ointment "Antibovasin" with a wound healing and anti-inflammatory effect. 16 series of studies of ointment compositions were performed using the method of planning the experiment, a 4x4 Latin square. The optimal composition of the ointment was calculated by the function of desirability, which corresponded to the specified values of the quality indicators.

Keywords: ointment composition, mathematical design of the experiment, factors, desirability function, antibovasin, mumiyo, propolis.

INTRODUCTION

A distinctive feature of the modern stage of the development of natural science is mathematization, and the use of statistical methods to test the hypotheses advanced, the reasonable formation of samples, and the construction of mathematical models of various phenomena and processes is an integral part of it. There is practically no such method of statistical analysis that would not find application in science and business.

In the process of using these methods, difficulties arise,due to objective reasons:

- strong variability of the studied characteristics due to the influence of a very large number of uncontrolled and uncontrolled factors;
- problems in the formation of samples (experimental designs) of the required volume and structure;
- the impact of psychological attitudes on test results;
- measurement of many important indicators using non-quantitative scales (usually classification and order);
- difficulties in mastering the methods of statistical analysis by workers who do not have a special mathematical education.

However, statistical methods occupy a strong position in the arsenal of modern science. The application of statistical methods in medicine and pharmacy has become so widespread that it has been singled out in a special scientific discipline called biometrics, and econometrics in economics [1].

It is impossible to imagine a full-fledged marketing research without using statistical methods to process its results.

Recently, special attention has been paid to the development of evidence-based medicine and pharmacy issues based on the use of modern information technologies.

Statistical analysis methods are also used in the production process of various products (including drugs), which allows us to design the creation of optimal technological processes for a number of criteria (technological, economic, environmental, pharmacological), and to control the quality of the obtained raw materials, manufactured products [2].

The creation of dosage forms with high pharmacotherapeutic efficacy is associated with the study of the interaction of the whole complex of variable factors, a wide factor in biopharmaceutical research. The search for the scientifically substantiated composition of the Antibovasin ointment, the development and optimization of the technological process was carried out using methods of mathematical modeling of the experiment, one of which is Latin plans [3]. The use of such plans makes it possible to reduce the number of experimental studies, the expenditure of valuable materials, and the large expenditures of time. At the same time, the use of Latin plans makes it possible to significantly reduce the

experimental error and quantify the influence of the studied factors [4].

The main objective of the research is to choose the right ointment base with surfactants that ensure maximum release of the substance from the dosage form. Let us consider in detail the totality of pharmacokinetic factors affecting the bioavailability of active medicinal substances to optimize the composition and technology of Antibovasin ointment.

MATERIALS AND METHODS

The selection of the basis for the multicomponent ointment "Antibovasin" is a complex process and requires taking into account a number of variable factors that ensure the bioavailability of active medicinal substances, in particular, the type of base (factor A), emulsifier (factor B) and the method of introducing medicinal substances (drugs) into the base.

The optimization criteria were the intensity of the release of drugs, in particular mumiyo, propolis and anesthesin from the dosage form, as well as the study of the rheological parameters of ointments (shear stress limit and effective viscosity of preparations) prepared on various bases. The intensity of the release of mumiyo and propolis from the ointment was determined by the in vitro method: direct diffusion in 2% agar-agar gel, while at the contact points of mumiyo and propolis, a 0.5% solution of FeCl3 was used as color-forming reagents (black is formed -green staining) or a solution of lead acetate of the main (a yellow precipitate forms).

The method of determination. An agar gel is prepared at a 2% concentration in a pre-calibrated glass beaker that is tightly closed with a lid. Chopped food agar (GOST 16280-2002) was poured with purified water and allowed to swell for 30 minutes. Swollen agar is heated to a boil, brought to the required mass, and an indicator of 0.5% FeCl3 solution is added to the warm gel, mixed and poured into Petri dishes (diameter 98-100 mm, height 20 mm) 10 ml each and left to solidify. After the first portion of agar has hardened, three glass cylinders (outer diameter 8 mm, height up to 10 mm) are placed on its surface in each cup and a second layer of agar is poured. After agar solidification, the cylinders are carefully removed. Then, 2.0 g of Antibovasin ointment prepared in various bases using cleaved emulsifiers are placed in the resulting wells.

Table 1: Factors and their levels studied in the development of ointment technology

Type of basis (A-factors)	Type of emulsifier (B-factors)	The method of introduction of drugs into the base (C-factors)
A1-hydrophobic (petrolatum)	B1- Stearox-6	C1 - pre-dissolving the drug in the part of the molten base
A2-emulsion (petroleum jelly + emulsifier + water)	B2-Emulsifier T2	C2 - pre-dissolving the drug in the minimum amount of purified water
A3 adsorption (petrolatum + emulsifier)	B3- Lanolin	C3 - pre-dissolving the drug in a minimum amount of glycerol
A4 hydrophilic (Na-CMC)	B4- Twin-80	C4- in the form of a suspension, previously grinded

The rate of release of anestezin from Antibovasin ointment was also determined in vitro. To identify the anesthesin released and diffusing from the ointments, a diazotization reaction was carried out where β-naphthol was used as an indicator (azo dye of red color was formed).

The prepared ointments are added to the wells of the agar plates with a glass rod and lightly compacted so that the ointment is in good contact with the agar. Petri dishes are numbered and placed in a thermostat at a temperature of 37 ± 1 0C.

Medicinal substances - mummy, propolis and anestezin, released from the ointment, diffuse into the agar gel, interacting with the indicator, form a colored zone. After 0.5, 1 and 2 hours, the diameter of the stained area is measured with a ruler. In the case of the formation of an ellipse, measure the larger and smaller diameters and determine the average value of the colored zone [5]. The research results are shown in table 2 (the value of indicators U1 and U2).

It is well known that ointment bases and ointments proper are structural dispersed systems that do not obey Newton's second law, otherwise they can also be called non-Newtonian bodies. Nevertheless, the structural and mechanical properties (effective viscosity, shear stress limit and plastic viscosity of the preparation) of ointments directly affect their stability and therapeutic effectiveness. Therefore, as the optimization parameters, we studied the rheological parameters of ointments prepared on various bases and in various ways of introducing medici-

nal substances into the base, in particular, when determining the rheological parameters of Antibovasin ointments, we studied such parameters as: shear stress limit and effective viscosity of drugs, which was performed on a Reotest-2 device using a cell consisting of a cylinder system S / S1 with a constant Z = 5.8. The effective viscosity (ηeff) was determined at a different velocity gradient (γ) for the preparation in a shear flow at 250 ° C. The instrument □ was recorded in mode II at a different value.

RESULTS AND DISCUSSION

According to the scientific work of A.A. Arkusha, I.M. Pertsev, V.G. Gunko, by definition of the rheological optimum for ointments, the optimum of hydrophilic ointments (at 20° C) is characterized by a shear stress limit of 45–160 Pa and an effective viscosity of 0.34–108 Pa · s, and for lipophilic ointments, the rheological optimum of consistency (at 20 ° C) is determined by the shear stress limit of 35–140 Pa and the effective viscosity of 0.32–93.3 Pa · s [6].

The results of studying the limit of shear stress (U3), and effective viscosity (U4) are presented in Table 2.

To optimize the composition and technology of the Antibovasin ointment, we used the method of mathematical planning of the experiment - a Latin 4x4 square, where each factor studied was studied at 4 levels of change. To test the significance of these factors according to the design of the experiment, 16 experiments were conducted under the conditions provided by the planning matrix. The planning matrix and the results of studies to optimize the composition and technology of the Antibovasin ointment are shown in Table 2.

Table 2: Experiment planning matrix and research results on optimizing the composition and technology of the Antibovasin ointment

Test №	Factors			U1, mm	U2 mm	U3, Pa	U4, Pa · s	D
	A	B	C					
1	a_1	B_1	c_1	1,8	0,4	32	16,9	0,62
2	a_1	B_2	c_2	1,7	0,3	31	14,5	0,60
3	a_1	B_3	c_3	1,5	0,2	32	13,5	0,58
4	a_1	B_4	c_4	1,4	0,1	30	12,7	0,57
5	**a_2**	**B_1**	**c_3**	**4,0**	**1,6**	**46**	**18,2**	**0,97**
6	a_2	B_2	c_1	3,7	1,4	42	18,0	0,92
7	a_2	B_3	c_4	3,5	1,2	38	18,2	0,93
8	a_2	B_4	c_2	3,2	1,2	37	18,0	0,87
9	a_3	B_1	c_3	2,2	0,7	36	15,9	0,70
10	a_3	B_2	c_4	1,9	0,5	34	14,8	0,72
11	a_3	B_3	c_1	1,8	0,3	32	14,5	0,70
12	a_3	B_4	c_2	1,8	0,3	30	14,1	0,68
13	a_4	B_1	c_4	2,7	1,3	39	17,6	0,82
14	a_4	B_2	c_3	2,6	1,2	36	17,4	0,77
15	a_4	B_3	c_2	2,5	1,1	34	17.2	0,76
16	a_4	B_4	c_1	2,2	1,0	32	16,8	0,75

Table 3: The results of the analysis of variance of studies to optimize the composition and technology of Antibovasin ointment

The studied indicators	Variance source	Degrees of freedom	Sum of squares	Middle square	F_{test}	F_{table}
Kinetics of the release of mumiyo and propolis from ointment (after 2 hours)	A Factor	3	25,47	23,06	11,14	3,3
	B Factor	3	23,31	10,45	5,05	3,3
	C Factor	3	23,20	6,99	3,35	3,3
	Remnant	-	49,675	-	-	-
	Total amount	15	99,35	-	-	-

Table 3 cont'd

Kinetics of anestezin release from ointment (after 2 hours)	A Factor	3	0,8	0,1	0,034	3,3
	B Factor	3	0,86	0,03	0,10	3,3
	C Factor	3	0,81	0,003	0,01	3,3
	Remnant	-	6,98	-	-	-
	Total amount	15	13,96	-	-	-
Shear stress limit	A Factor	3	4968,18	4933,62	11,13	3,3
	B Factor	3	4937,18	2451,06	5,53	3,3
	C Factor	3	4928,06	1631	3,69	3,3
	Remnant	-	10635,56	-	-	-
	Total amount	15	4216,95	-	-	-
Effective Viscosity	A Factor	3	1056,06	1039,92	11,82	3,3
	B Factor	3	1044,13	513,99	5,85	3,3
	C Factor	3	1041,60	341,82	3,89	3,3
	Remnant	-	2108,48	-	-	-
	Total amount	15	21271	-	-	-

Note: the table shows the average values of the studied factors from two parallel definitions.

The experimental data was subjected to analysis of variance, the results of which are shown in Table 3.

When comparing the obtained dispersion relations with the tabular values of the Fisher criterion, it was found that the intensity of the release of active substances from the Antibovasin ointment was significantly affected by all studied factors A, B and C, in particular, the release of mumiyo and propolis factors A, B and C, on the release of anestezin, there is no significant effect of factors, since Experiment <Ftab

The obtained F - Fisher value for the studied factors of the 3rd interaction is larger than the tabulated one, therefore it can be concluded that the kinetics of the release of mumiyo and propolis from the ointment, the shear stress limit and effective viscosity factors significantly affect the qualitative parameters of the Antibovasin ointment, and, therefore, their bioavailability.

To optimize the process of obtaining multicomponent ointment "Antibovasin" three criteria (response) were studied, it became necessary to combine them into one common indicator, so that its value determines the whole technological process as a whole. Therefore, to optimize processes with a large number of criteria, a generalized desirability function was used [5], which is defined as the geometric mean of desirability of individual properties:

$D=\sqrt{d_1 d_2 d_3 \ldots d_n}$,

where n is the number of used indicators of the comparison parameters for this system. Moreover, the number of these indicators may be different for different systems. This allows you to compare generalized coefficients even when some of the comparison parameters for various systems or data on them is missing. The root of the nth degree "smooths out" the deviations that arise, and the result allows us to evaluate the system (with a certain degree of accuracy), so to speak, "mathematically".

The generalized desirability function satisfies all the necessary requirements for optimization parameters. Harrington's desirability scale is a quantitative, unambiguous, single, universal indicator of the quality of an object as an optimization parameter. The function has the properties of effective and static sensitivity, although it is not without its individual disadvantages. So, all parameters are accepted equally "valuable", although this is not always true [6].

Table 4: Desirability Standard Marks

Desired grade	Desirability Scores
Very good	1,00-0,80
Good	0,80-0,63
Satisfactorily	0,63-0,37
Bad	0,37-0,20
Very bad	0,20-0,00

The translation of natural quantities into particular functions of desirability is carried out using the scale of desirability. To construct the scale of desirability, the method of quantitative estimates is used with an interval of desirability values from zero to one, intermediate values

of desirability correspond to points 0.2, 0.37, 0.63, 0.8, which reflect the levels of product quality very poorly, poorly, satisfactorily, good (table 4).

A graphic image of the desirability scale is shown in Figure 1. Using this scale, the values of y1 y2 and y3 y4 were translated into particular desirability criteria d1, d2, d3, d4 and a generalized desirability function was found (table 2, D). From table 2 it can be seen that the optimal conditions for the technology of Antibovasin ointment are No. 5, where the interaction of factors at these levels, the value of the generalized desirability function is more than 0.69, which corresponds to good quality (Figure 1).

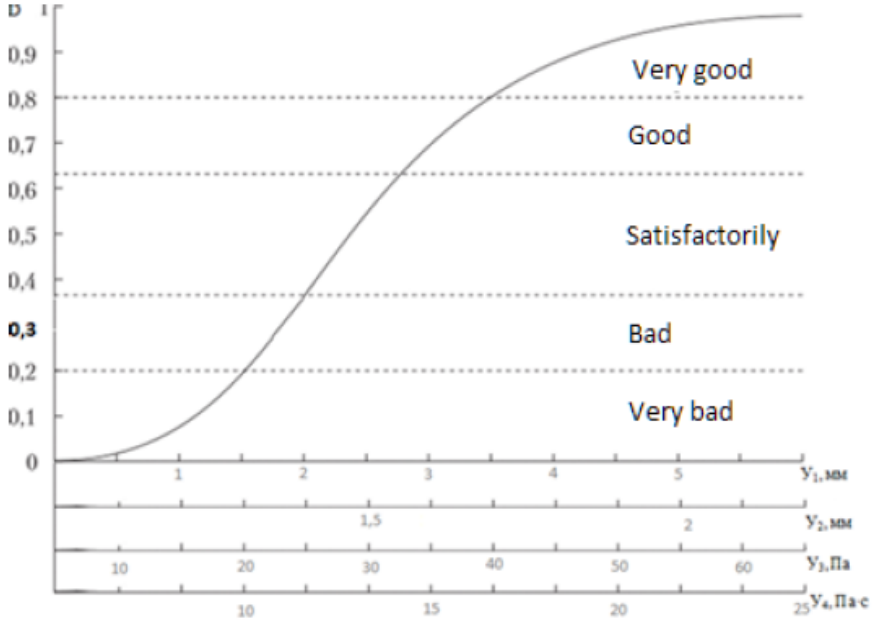

Figure 1: Generalized desirability function

It has been revealed that the bases and emulsifiers used for Antibovasin ointments by their ability to provide the most intensive release of drugs can be arranged in the following series: a2> a4> a3> a1, i.e. emulsion (petrolatum + emulsifier + water)> hydrophilic (Na-CMC)> adsorption (petrolatum + emulsifier)> hydrophobic (petroleum jelly); emulsifiers - b1> b2> b3> b4, i.e. Stearox-6> emulsifier T2> lanolin> tween-80, and the method of introducing drugs into the base is c3> c2> c1> c4, where the most acceptable route of administration is to pre-dissolve the drug in a minimum amount of glycerol.

The effective viscosity of the preparation meets the requirements, however, the shear stress limit values are slightly lower than those described in the literature, despite the fact that we conducted the experiment at 25 ° C. However, the higher the value, the more difficult the preparation is smeared, in general, the preparation It has an optimal consistency from a consumer point of view.

In the quantitative assessment of the influence of the studied factors on the release of the optimization criteria, it is obvious that the effect of the interaction of factors A and C remains significant, under this condition, factor B can be neglected.

As a result, the optimization of the composition and technology of the Antibovasin ointment was recommended as follows, the most acceptable composition containing purified mummy - 4.0; propolis tincture - 3.0; anestezin - 1.5; iron ammonium alum - 1.0; petroleum jelly - 79.5; stearox-6 - 5.0; glycerol - 1.0 and purified water - 5.0.

CONCLUSION

Thus, to determine the optimal composition of Antibovasin ointment for external use, we used an experiment of mathematical planning of the experiment - a Latin 4x4 square, where each studied factor was studied at 4 levels of change. According to the results of the experiment, the composition was selected: purified mummy - 4.0; propolis tincture - 3.0; anestezin - 1.5; iron ammonium alum - 1.0; petroleum jelly - 79.5; stearox-6 - 5.0; glycerol - 1.0 and purified water - 5.0. The ointment prepared above the composition is a dark brown, homogeneous, soft mass with a good smeared consistency.

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