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Optimization of the composition and development of technology of the ointment base Enziphobe

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ABSTRACT:.By the method of mathematical planning of the experiment, the basis for the ointment (transesterification) was obtained, which allows to reduce the consumption of raw materials and save time. In this case, the melting (liquefaction) point, viscosity, acid value (number) and iodine value (number) were studied as optimization criteria, the content (amount) of the enzyme, the ratio of fat to oil, temperature regime (mode), transesterification time were studied as factors influencing these criteria. The physical and chemical properties of the resulting hydrophobic ointment base meet the requirements of regulatory and technical documentation.

KEYWORDS:mathematical planning of the experiment, optimization criteria, factors, hydrophobic base, transesterification.

1. INTRODUCTION

The physicochemical properties of fatty acids depend on their structure. For example, the melting point of fatty acids increases with chain length, and the density and amount of neutralizations decrease. If the number of carbon atoms in the chain is the same, the melting point of saturated fatty acids will be higher than the melting point of unsaturated fatty acids[1].

The goal of our work is to develop a technology base for soft dosage forms. For this, it is proposed to use vegetable and animal oils and fats. One of the main characteristics of a base is its melting point. The melting point of a mixture of fats and oils is usually corrected by rearrangement and redistribution of fatty acids, which can be accomplished by both chemical and enzymatic methods (transesterification). For enzymatic transesterification, lipase can be used. By selecting the nature and concentration of the enzyme, the technological parameters of the transesterification, as well as the ratio of solid fats and vegetable oils, it is possible to obtain a transesterificate that meets all the requirements of the bases for soft dosage forms[2].

In many European countries, transesterification rather than hydrogenation is preferred to obtain hardened fats. Fat and oil products are produced using fatty bases obtained from transesterified mixtures of saturated fats and soft oils or natural fats with a high content of saturated acids. By blending these bases with soft oils, fat systems are obtained for a wide range of products. The ability to change the melting characteristics and functional properties associated with crystallization without changing the fatty acid composition gives the transesterification process a number of unique possibilities. Enzymatic transesterification (as opposed to chemical transesterification) is carried out at a low temperature, while there is no formation of by-products. The reaction is relatively slow and can be stopped at any time to obtain the desired degree of transesterification[3].

II. METHODS

In order to choose the scientifically grounded composition and technology of a hydrophobic ointment base, we took advantage of a mathematical method of experimental design, the method of the 4×4 Latin square, and performed variance analysis. The use of this method makes it possible to significantly reduce the experimental error and to

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Vol. 8, Issue 8 , August 2021

quantify the effect of various factors on the optimization criteria[4, 5, 6]. In this case, the melting (liquefaction) point, viscosity, acid value (number) and iodine value (number) were selected as the optimization criteria (see table 1); while the content (amount) of the enzyme, the ratio of fat to oil, temperature regime (mode), transesterification time were selected as factors affecting optimization criteria (see table 2). Optimization criteria were studied using conventional methods.

Table 1. Optimization criteria for an experiment

Optimization criteria (Y)			
Y1	Y2	Y3	Y4
Melting point,°C	Viscosity, Pa*s	Acid value, mg KOH/g oil	Iodine value, g J/100 g

Table2. Factors affecting optimization criteria for theointment base Enziphobe

Factors	Level of factors
A – amount of enzyme	a_1- 3% a_2- 2% a_3- 1% a_4- 0.5%
B – the ratio of beef fat and sunflower oil	b_1- 40:60 b_2- 48:52 b_3- 55:45 b_4- 60:40
C–temperature mode	c_1- 25°C c_2- 30°C c_3- 35°C c_4- 45°C
D – transesterification time	d_1- 20 d_2- 40 d_3- 60 d_4- 80

In order to study the influence of different factors on optimization criteria of the ointment base Enziphobe the various combinations of factors were designed according to the matrix for planning the experiment. The matrix for planning the experiment and research results on the effect of the different factors on the optimization criteria for the hydrophobic ointment base Enziphobeare presented in Table 3.

Table3.Matrix for planning the experiment and research results on the effect of the different factors on the optimization criteria for the hydrophobic ointment base Enziphobe

Experiment number	Factors				Optimization criteria				D
	A	B	C	D	(Y_1), ^{0}degree	(Y_2), Pa*s	(Y_3), mg KOH/g oil	(Y_4),g J/100 g	
1	a_1	b_1	c_1	d_1	32	7.0	1.4	43	0.2265
2	$\mathbf{a_2}$	$\mathbf{b_2}$	$\mathbf{c_2}$	$\mathbf{d_2}$	**36**	**8.45**	**0.7**	**51**	**0.8681**

ISSN: 2350-0328
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Vol. 8, Issue 8 , August 2021

3	a_1	b_3	c_3	d_3	34	7.5	0.48	40	0.4572
4	a_1	b_4	c_4	d_4	36	7.8	1.6	41	0.3970
5	a_2	b_1	c_1	d_2	38	7.92	0.68	52	0.6419
6	a_2	b_2	c_2	d_1	32	8.0	0.72	35	0.8012
7	a_2	b_3	c_3	d_3	34	8.3	0.86	33	0.4970
8	a_2	b_4	c_4	d_4	33	8.7	1.5	34	0.4088
9	a_3	b_1	c_4	d_3	32	8.6	1.75	30	0.3070
10	a_3	b_2	c_1	d_2	36	8.74	0.72	50	0.5620
11	a_3	b_3	c_3	d_1	32	9.0	2.3	37	0.4680
12	a_3	b_4	c_2	d_4	34	9.5	2.47	41	0.2196
13	a_4	b_1	c_1	d_4	33	6.1	2.4	44	0.2255
14	a_4	b_2	c_2	d_3	32	5.5	2.3	34	0.2630
15	a_4	b_3	c_4	d_2	36	7.98	0.71	56	0.5282
16	a_4	b_4	c_3	d_1	34	5.8	2.2	30	0.2573

The effect evaluation for each factor was performed by variance analysis (table 4) [6], which upon studying the effect of excipients on the optimization criteria showed that:

- the level of factor A (amount of enzyme) has a significant effect on theviscosity of ointment base Enziphobe and does not have a significant effect on its melting point,acid value and iodine value;
- the level of factor B (the ratio of beef fat and sunflower oil) and C (temperature mode) do not have a significant effect on melting point, viscosity,acid value and iodine value of ointment base Enziphobe;
- the level of factor D (transesterification time) has a significant effect on themelting point and iodine value of ointment base Enziphobe and does not have a significant effect on its viscosityandacid value/

Table4. Variance analysis of the experimental data from the study of optimization criteria for the hydrophobic ointment base Enziphobe*

Optimization criteria	Source of variation	Degrees of freedom (f)	Sum of the squares (SS)	Mean square (MS)	F_{exp}	$F_{0.05\ table}$
Melting point, °C	Factor A	3	2.50	0.83	0.19	3.49
	Factor B	3	0.50	0.17	0.04	3.49
	Factor C	3	4.50	1.50	0.36	3.49
	Factor D	3	38.00	12.67	9.5	3.49
	Residual	3				
	Total sum	15				
Viscosity, Pa*s	Factor A	3	14.64	4.88	10.29	3.49
	Factor B	3	1.40	0.47	0.30	3.49

ISSN: 2350-0328
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Vol. 8, Issue 8 , August 2021

	Factor C	3	1.51	0.50	0.32	3.49
	Factor D	3	2.01	0.67	0.44	3.49
	Residual	3	-	-	-	-
	Totalsum	15	-	-	-	-
Acid value, mg KOH/g oil	Factor A	3	3.023	1.008	2.38	3.49
	Factor B	3	1.994	0.665	1.30	3.49
	Factor C	3	0.132	0.044	0.07	3.49
	Factor D	3	3.612	1.204	3.21	3.49
	Residual	3	-	-	-	-
	Total sum	15	-	-	-	-
Iodine value, g J/100 g	Factor A	3	62.7	20.9	0.27	3.49
	Factor B	3	95.7	31.9	0.43	3.49
	Factor C	3	303.2	101.1	1.75	3.49
	Factor D	3	781.2	260.4	14.58	3.49
	Residual	3	-	-	-	-
	Total sum	15	-	-	-	-

*Variance analysis was conducted on the experimental data from table 3, and the statistical indicators in table 4 were calculated, using ANOVA module of the statistics software MiniTab.

The overall (generalized) evaluation of the optimization criteria was carried out using a desirability function [6, 7].For instance, in order to generalize the values of the optimization criteria that have different units of measurement, we used the well-known and widely accepted Harrington's desirability function, first introduced by him in solving quality control problems of mass production. The Harrington's scale establishes a correspondence between linguistic evaluations of desirability of the values of the optimization criteria *x* and the numerical intervals *d(x)* (table 5) [6, 8].

Table5. Numerical intervals of the Harrington's scale

Linguistic evaluation	**Intervals of desirability function values *d* (*x*)**
Very good	1.00-0.80
Good	0.80-0.63
Satisfactory	0.63-0.37
Bad	0.37-0.20
Very bad	0.20-0.00

ISSN: 2350-0328
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Vol. 8, Issue 8 , August 2021

In order to construct the desirability function scale of the optimization criteria for the hydrophobic ointment base Enziphobe, the method of quantitative analysis was used with the range of desirability values between 0 and 1 (Fig. 1). The value d = 1 corresponds to the best value of the indicators (properties), while d = 0 - to their worst value of ones. The intermediate values of the desirability function reflect specific levels of the product quality: very bad (0.00 - 0.20), bad (0.20 - 0.37), satisfactory (0.37 - 0.63), good (0.63 - 0.80) and very good (0.80 - 1.00). Conversion of the natural values (Y) into individual desirability values (d) with a one-sided limit $Y \leq Y_{max}$ or $Y \geq Y_{min}$ was performed using the following equation:

$$d = exp[-exp\ (Y')] \qquad (1)$$

where $Y' = b_0 + b_1$. The coefficients b_0 and b_1 were calculated by assigning the corresponding desirability values d for two of the property values, preferably selected within the range $0.2 < d < 0.8$. The desirability curve (Fig. 1) were plotted in the (Y', d) coordinates based on the equation of the desirability function. At the same time, Y_{max} or Y_{min} on the dimensional scales corresponded to 0 (zero) on the dimensionless scale Y'. The desirability scale (Fig. 1)was used to convert the response values (Y_1, Y_2, Y_3, Y_4) into the dimensionless desirability function (d_1, d_2, d_3, d_4) i.e. to find individual desirability values for the measured values of the optimization parameters Y_i.

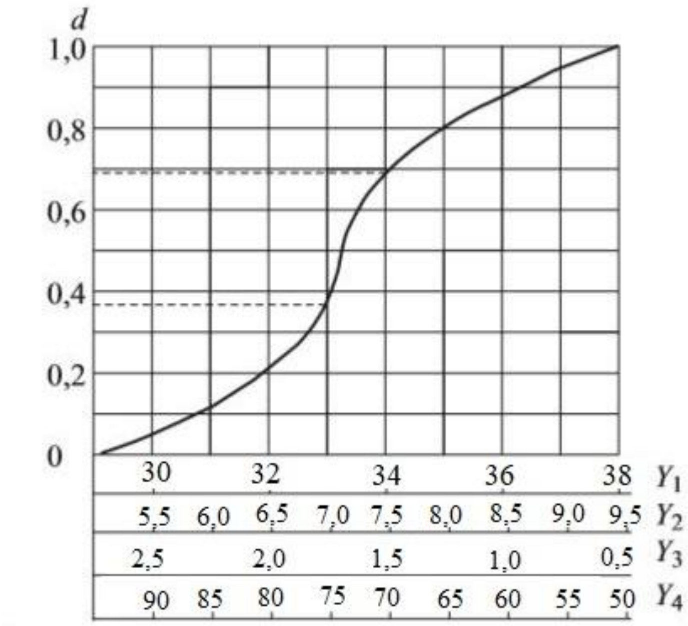

Figure 1. The desirability function scale of the optimization criteria for the hydrophobic ointment base enziphobe

Based on the generalized evaluation of the optimization criteria for the hydrophobic ointment base Enziphobe, carried out using a desirability function, the levels of factors can be arranged in the order of preference as follows:

- Factor A - Amount of enzyme: $a_2 > a_1 > a_3 > a_4$;
- Factor B - The ratio of beef fat and sunflower oil: $b_2 > b_3 > b_1 > b_4$;
- Factor C - Temperature mode: $c_2 > c_3 > c_1 > c_4$;
- Factor D - Transesterification time: $d_2 > d_1 > d_3 > d_4$.

Based on the results of the mathematical method of experimental design and using a desirability function an optimal composition and technology of the ointment base enziphobe were developed as well. The overall (generalized) desirability function, which is calculated using the formula (2)as the geometric mean of individual properties, represents a more successful approach towards optimization of the parameters for the hydrophobic ointment base Enziphobe:

$$D = \sqrt[4]{d_1 d_2 d_3 d_4} \qquad (2)$$

ISSN: 2350-0328
International Journal of Advanced Research in Science, Engineering and Technology
Vol. 8, Issue 8 , August 2021

The values of the overall (generalized) desirability function for the hydrophobic ointment base Enziphobe are presented in table 3 (values of *D*).

The most optimal combination of factors' levels that ensure the required parameters for the hydrophobic ointment base Enziphobe (table 3, combination No. 2) was selected based on the values of the overall (generalized) desirability function (*D*) of the optimization criteria. The levels of factors in the combination No. 2 are listed in table 6.

Table 6. The most optimal combination of factors' levels that ensure the required parameters for the hydrophobic ointment base enziphobe

Name of the ointment base	No. of the optimal combination	The levels of factors in the optimal combination
Enziphobe	Combination No. 2 In table 3	a_1- amount of enzyme– 3% b_2 – the ratio of beef fat and sunflower oil – 48:52 c_2– temperature mode– 30°C d_2– transesterification time – 40 min

III. RESULTS

According to the results of the mathematical method of planning the experiment, we recommended the following composition and technology:

Composition:

1. Beef fat – 48 g
2. Sunflower oil - 52 g
3. 17% lipase solution - 3 ml
4. Phosphate buffer - 10 ml.

Technological process.A mixture of sunflower oil and internal beef fat is brought to a homogeneous consistency within 10 minutes by stirring at 40^0C in a water bath. Next, 3 ml of a 17% solution of lipase of animal origin are added to the homogeneous mass, 10 ml of phosphate buffer successively to pH 7 are added and the reaction mass is constantly stirred for 1 hour at 40^0C. In this case, the target product is obtained in the form of a dense buttery mass with a yield of 98.8% relative to the mass fraction of the ingredients taken.Then a physical and chemical analysis of the ointment base enziphobewas conducted the results of which are presented in Table 7.

Table 7. Results of physical and chemical analysis of the ointment base Enziphobe

№	The studied indicators	Unit of measurement	Results
1	Sustainability		**Does not delaminate**
2	Hardness		**Does not soften**
3	Colour		Pale yellow to yellow
4	Smell and taste		Odorless, taste of impersonal oil
5	Consistency at 15-20°C		Dense and hard, oily
6	Transparency		Transparent
7	Acid value	mg KOH/g oil	0.68-0.73

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International Journal of Advanced Research in Science, Engineering and Technology
Vol. 8, Issue 8 , August 2021

8	Iodine value	g J / 100 g	50.1-52.3
9	pH		7
10	Peroxide number	½ O mmol / kg	0.33
11	Melting point	°C	34-38
12	Viscosity	Pa*s	8.45

The results obtained meet the requirements of the normative document.

IV. CONCLUSION

Thus, using the mathematical method of the experimental design, the 4 × 4 Latin square, the composition and technology of the hydrophobic ointment base were developed using the method of mathematical experimental design. In this case, the content of the enzyme, the ratio of fat to oil, temperature, transesterification time were studied as optimization criteria, melting point, viscosity, acid value and iodine value were studied as factors influencing these criteria. According to the results of the experiment, factors' combination number 2 turned out to be the most optimal among the studied combinations. The physical and chemical properties of the resulting hydrophobic ointment base meet the requirements of regulatory and technical documentation[9,10].

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