THE OPTIMIZATION OF TECHNOLOGY OF "DIABDERM" CREAM

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Abstract: Based on the liquid extract "Diabderm", the composition of the technology of the therapeutic and prophylactic cream "Diabderm" was developed, intended for the prevention and treatment of diabetic dermatopathies. In order to optimize the composition and technology of the "Diabderm" cream, the method of mathematical planning of the experiment was used - three-factor fractional plans of Latin squares 4x4, which allow statistical methods to select the most appropriate composition and technology, and also reduce the number of experiments.

Key words: diabetes mellitus, diabetological dermopathies, plant raw materials, biologically active substance (BAS), alcohol-water extract, liquid extract, parapharmaceutical drug, agents for external use, ointment, "Diabderm" cream, boric acid, base for ointment, mathematical planning of the experiment method, optimization of the composition and technology, quality indicators, bioavailability.

Introduction: According to statistics from the International Diabetes Federation (IDF), at the beginning of 2022, more than 537 million people worldwide, aged from 20 to 79 years have diabetes. As to forecasts, this number will increase to 643 million by 2030, and to 783 million by 2045.

The damage of diabetes mellitus leads to the development of neuropathy, nephropathy and retinopathy. Diabetic dermopathy is a kind of skin marker of diabetes mellitus and occurs in more than 40% of patients. Among the complications of diabetes mellitus, the most alarming is the syndrome of diabetic foot, a feature of this complication is the damage of the lower extremities, in particular, nerves and blood vessels of the legs. This complication develops mainly in diabetic patients from the onset of the disease and by 7-10 years from the onset of the disease, and in 85% of cases it is represented with foot ulcers of varying severity. For example, due to the development of a fungal infection on the nails, long-healing trophic ulcers form on the legs. Neglecting such changes or improper self-treatment often ends with gangrene and

amputation. Of the total number of amputations of the lower extremities, approximately 50-75% are patients with diabetes mellitus, and approximately 40-50% of patients are at risk.

To date, the Republic of Uzbekistan also has certain problems associated with the damages of diabetes mellitus (more than 245 thousand patients are registered in the dispensary). Against the background of diabetes mellitus, complex physicochemical processes occur in the tissues of the skin, resulting the formation and accumulation of organic and inorganic acids and pathogenic microflora (S. aureus, E. faecalis, P. aeruginosa, P. Mirabilis, according to V.V. Privolov et al., 2008), leading to the development of necrotic processes.

For the prevention and treatment of skin complications of diabetes mellitus, angioprotectors (parmidine, etamsylate, calcium dobesilate, tribenoside, etc.) are successfully used today, as well as herbal remedies that have healing properties when used externally - for washing wounds and baths. (V.F. Korsun, E. V. Korsun, 2013). However, to date, among these funds there is no drug that has a complex therapeutic and prophylactic effect.

Therefore, the development of the composition and technology of a therapeutic and prophylactic drug that has a complex local effect in skin damages of diabetes mellitus is an urgent task of pharmaceutical technology.

In order to prevent and treat this disease, a new collection and liquid extract "Diabderm" was developed on the basis of local plant raw materials. Based on the above, the purpose of this research was the development and optimization of the composition and technology of the anti-inflammatory ointment (cream) of the complex composition "Diabderm".

Material and Methods: The composition of the multicomponent cream is filled with a liquid extract obtained on the basis of the collection "Diabderm" (containing flowers of calendula officinalis, leaves of dioica nettle, white mulberry, common yarrow herb and common chicory roots), which has anti-inflammatory and regenerative properties, (5%), also boric acid (3%), menthol (0.5%) and carbamide (10%), hydrophobic, hydrophilic and emulsion bases were used as a base.

Table 1.
Model compositions of the cream "Diabderm", prepared on various bases

Name of ingredients	Quantity of ingredients			
	1	2	3	4
"Diabderm" liquid extract	5,0	5,0	5,0	5,0
Boric acid	1,0	1,0	1,0	1,0
Menthol	0,1	0,1	0,1	0,1
Carbamide	10,0	10,0	10,0	10,0
Vaseline	83,9	56,2	50,0	-

Lanolin anhydrous	-	27,7	-	-
Bentonite	-	-	-	25,0
Glycerin	-	-	-	18,9
Emulsifier T-2	-	-	8,4	-
Purified water	-	-	25,5	40,0
Total weight	100,0	100,0	100,0	100,0

From the medicinal substances listed in Table 1, creams were prepared according to 4 compositions under standard conditions, taking into account the physicochemical characteristics of the ingredients:

Method I (Vaseline base). Vaseline (melting point 37-50°C) is melted in an evaporating porcelain cup in a water bath. Menthol is dissolved in a warm alloy (at a temperature of 40-45 ° C) and mixed well. Next, half the amount of the molten base is added to the mixture of carbamide and boric acid (according to the rule of Prof. B.V. Deryagin) and thoroughly mixed and the remaining amount of the base that has not cooled down yet is gradually added. Cream is stirred until cools to the room temperature point. At the end, the liquid extract "Diabderm" is introduced and mixed until a homogeneous mass is obtained. The cream is homogenized for 2-3 hours in the MI-2 mixer. This forms a cream of yellowish soft consistency. After assessing the quality, the cream was packaged in tubes and jars.

Method II (base vaseline/anhydrous lanolin, ratio 6:3). To prepare the cream "Diabderm" on a vaseline-lanolin base, vaseline (melting point 37-50°C) and anhydrous lanolin (melting point 36-42°C) are melted in an evaporating cup in a water bath. Menthol is dissolved in a warm mixture (temperature 45-50°C) and mixed well. Next, half the amount of the molten base is added to the mixture of carbamide and boric acid (according to the rule of Prof. B.V. Deryagin) and thoroughly mixed and the remaining amount of the base that has not cooled down yet is gradually added. Stir the cream until cooled to room temperature. At the end, the liquid extract "Diabderm" is introduced and mixed until a homogeneous mass is obtained. The cream is homogenized for 2-3 hours in the MI-2 mixer. This forms a cream of yellowish soft consistency.

Method III (emulsion base according to E.N. Kutumova). Vaseline and emulsifier T-2 are fused in a water bath (at a temperature of 50 ± 5°C). Then menthol is introduced into the melted base (at a temperature of 30-35°C), thoroughly mixed until the menthol is completely dissolved.

Boric acid is dissolved in hot water, carbamide is dissolved in water at room temperature and filtered.

Then, solution boric acid is added little by little to the melted base, in which menthol was dissolved (solution temperature is 50-60ºC), the mixture is stirred down until it reaches to the room temperature. Next, the carbamide solution is added and mixed thoroughly.

At the end, the liquid extract "Diabderm" is added to the cream and mixed thoroughly. The cream is homogenized for 2-3 hours in the MI-2 mixer. This forms a cream of yellowish soft consistency.

Method IV (hydrophilic base, bentonite). To prepare a cream on a hydrophilic basis, bentonite is preliminarily crushed and sifted through a sieve with a hole diameter of 100 microns, then the bentonite is calcined in a dry oven at a temperature of 200-250°C for an hour. After cooling, carbamide, boric acid are added to the bentonite, thoroughly mixed, and a glycerin solution of menthol is added to the dry mass, mixed again. Purified water is added little by little to the mass and mixed thoroughly. The resulting cream is homogenized using an MI-2 mixer for 3 hours until a homogeneous plastic-viscous mass is formed.

After quality assessment, all four cream samples were packaged in aluminum tubes (according to GOST 11069-64) covered with polyvinyl chloride film (according to GOST 25250-88), dark glass jars (according to OST 64-2-71-80 or GOST 5717) with a screw-on plastic lid (according to OST 64-2-218-84) and in plastic jars (according to TSh 64-17490735-01:2001) with a screw-on plastic lid (OST 64-2-218-84) 50.0 g each.

In preliminary studies, the intercompatibility of selected medicinal substances and bases were studied by obtaining various model compositions of creams and storing them for 30 days at room temperature, as well as under "stress conditions" - in a thermostat (45±2°C).

The compatibility of the components and the quality of the cream were determined by appearance, homogenenity, pH indicators, thermo- and colloidal stability, using the methods described in the literature.

Determination of appearance (organoleptic characteristics - smell and color) was carried out visually according to the properties of the medicinal substances included in the ointment and from the used ointment bases. To determine the appearance, cream samples were applied in a thin layer on a slide or a sheet of white paper.

The smell of cream samples was evaluated by organoleptic method in the sample after determining the appearance.

The homogeneity of the creams (the absence of lumps or grains) was determined by touch by lightly rubbing the sample between the fingers.

To determine the size of the particles of the dispersed phase, a biological microscope was used, equipped with an MOB-1 ocular micrometer with an eyepiece magnification of 15x and an objective of 8x. The division value of the ocular micrometer was verified by the object-micrometer for transmitted light (TLM).

The average sample of the ointment was taken according to the article "Sampling of medicines" (not less than 5.0 g). A sample of 0.05 g was taken from the average sample of the ointment and placed on the untreated side of the glass slide.

The samples of the "Diabderm" cream were examined on a piece of glass, in the middle on one side, which had a square with a side of 15 mm and diagonals applied with an abrasive material, and the lines were outlined with a pencil on the glass. Slides with applied cream samples were placed in a water bath until the base melted, a drop of 0.1% Sudan III solution was added for cream samples prepared on hydrocarbon, fat and emulsion bases of the V / M type (according to the methods I, II, III), or 0.15% methylene blue solution for hydrophilic bases (according to method IV) and mixed. The samples were covered with a cover slip (24 x 24 mm) and fixed by slight pressure and viewed in four fields of view of the segments formed by the

diagonals of the square. For the analysis of one sample of the drug, 5 determinations of the average sample are carried out.

The pH value of the aqueous extract of the cream "Diabderm" was determined potentiometrically, on a pH-meter SevenEasy laboratory, designed to determine pH from 0 to 14., (Manufacturer Mettber Toledo, commissioning year 2007). For determination, 50 ml of purified water (pH–6.2–7.0) was added to 2.0 g of the test cream, the mixture was thoroughly mixed for 5 minutes, and the pH was measured by the potentiometric method (according to GP XI, issue 1, pp. 113–115) [12].

The thermal stability of the manufactured samples of the cream "Diabderm" was determined in accordance with GOST 29188.3-91 under conditions of sharply changing temperatures. To do this, the samples were thermostated for 7 days at 40–42°C, after which they were placed in a refrigerator with an average temperature of 8°C for 7 days, and then kept at room temperature (20°C) for another 3 days. Thermal stability was assessed visually. The samples of creams were considered stable during the tests, no phase separation and separation of the aqueous phase were observed during the entire period of the experiment. It is allowed to separate a layer of the oil phase no more than 0.5 cm.

The colloidal stability of the manufactured samples of the cream "Diabderm" was determined in accordance with GOST 29188.3-91 "Cosmetic products. Methods for determining the stability of emulsions" by centrifuging samples in a laboratory centrifuge "ЦУМ-1", Russia. To determine the glass test tube 2 parts out of 3 filled with cream. Then the test tube with the cream is placed in a thermostat and incubated: for thick emulsions - 20 minutes at a temperature of 42 to 45 °C. The test tube is removed from the thermostat, wiped dry and placed in the centrifuge socket. Centrifugation is carried out for 5 minutes at a speed of 2000 rpm. The tube is then removed from the centrifuge and the stability of the cream is determined. If there is no clear stratification of the system, then the contents of the test tube are carefully poured onto a sheet of white thick paper and the presence or absence of stratification of the cream is noted. An emulsion cream is considered colloidally stable if no separation of the system is observed after centrifugation. It is allowed to release on the surface of the emulsion cream in a test tube no more than 1 drop of the aqueous phase or a layer of the oil phase no more than 0.5 cm.

Determination of the structural and mechanical properties of the cream "Diabderm" was carried out on a rotational viscometer "Rheotest 2.1.", using a cell which consists of a system of cylinders S/S1 with a constant Z = 5.6. At the same time, such indicators as: effective viscosity, shear stress limit and plastic viscosity of the prototype samples of the drug were studied.

Determination of effective viscosity(η_{eff}) at different velocity gradient (γ) for the drug was carried out in a shear flow at 25^0C. The instrumental reading of the device α was fixed in mode II at different values of the experimental numbers.

The bioavailability of the cream "Diabderm", prepared on various bases was studied in experiments in vitro - by the method of equilibrium dialysis

(L. Kruwchinsky, Poland) to release boric acid into the dissolution medium.

To optimize the composition and technology of the anti-inflammatory cream "Diabderm", the method of mathematical planning of the experiment was used - three-factor fractional plans of Latin squares 4x4, which allowed using statistical methods to select the most suitable composition and technology, and also reduce the number of experiments.

Results: according to the results of preliminary studies conducted on the intercompatibility of medicinal and excipients by storing cream samples for 30 days under various conditions, it was found that under "stress conditions" samples of hydrophilic-based creams (according to the fourth method), packaged in plastic jars with screw-on plastic lids and stored in a thermostat (in a thermostat at

45 ± 2°C), on the 7th day colour slightly changed (the color from light grayish-beige became dark gray-brown), however, the smell and consistency remained benign. Other samples of the cream, prepared on hydro-visible bases and packaged in other types of packages, did not change colour. The remaining samples of the cream "Diabderm", prepared on various bases and packaged in glass containers and aluminum tubes, covered with a polyvinyl chloride film, remained in a good quality under all storage conditions.

In the tests carried out to analyze the colloidal stability of the cream, they were stable throughout the entire observation period and no separation of the aqueous phase was observed.

In all samples stored at room temperature, it practically did not change and corresponded to the normalized skin pH - 5.5-6.5.

To optimize the composition and technology of the cream "Diabderm" by the method of mathematical planning of experiments, three-factor fractional plans of Latin squares 4x4 were used, where the following factors affecting the quality indicators of the finished cream were studied: factor A - type of base; factor B - method of preparing the cream; factor C - type of packaging. Each factor chosen for optimization was studied at four varying degrees - output indicators: Y_1 - appearance (1-5 points), Y_2 - particle size of the dispersed phase (μm), Y_3 - effective viscosity (Pa*s) Y_4 - release of boric acid, % .

The characteristics of the changing factors, affecting the quality indicators of the cream "Diabderm" are given in table 2.

Table 2.
Characteristics of the changing factors, affecting the quality indicators of the cream "Diabderm"

Degree	Factors		
	Base type (A)	Making method (B)	Type of packaging (C)
1	Vaseline 1	№1 (4) in 1	3 Tubes from half measure s1
2	Vaseline/lanolin anhydrous (6:3) a2	№2 (2) in 2	2 Glass jars with plastic screw cap s2
3	Emulsion consistent a3	№3 (1) in 3	4 Polymer jars with screw cap s3

4	Hydrophilic (bentonite) base a4	№3 (3) in 4	1 Aluminum tube with PVC polymer coating s4

According to the experiment planning matrix, 16 experiments were carried out under standard conditions. The experiment planning matrix and the results obtained during the optimization of the composition and technology of the "Diabderm" cream are shown in Table 3.

Table 3

Experimental planning matrix and results of optimization of the composition and technology of the cream "Diabderm"

Number of experiments	Factors			U1, appearance(1-5 points)	U2, particle size of the dispersed phase (μm)	U3, effective viscosity (Pa*s)	U4, release of boric acid,%	D
	A	B	C					
1	a_1	b_1	c_1	2	95	24,02	30	0,35
2	a_2	b_1	c_2	3	60	18,16	16	0,60
3	a_3	b_1	c_3	3	55	11,16	12	0,50
4	a_4	b_1	c_4	3	50	28,09	14	0,45
5	a_1	b_2	c_4	4	35	22,02	27	0,70
6	a_2	b_2	c_3	3	60	17,30	14	0,60
7	a_3	b_2	c_1	4	40	12,25	11	0,78
8	a_4	b_2	c_2	4	65	27,15	13	0,65
9	a_1	b_3	c_2	4	60	21,07	25	0,62
10	a_2	b_3	c_1	4	40	16,02	13	0,76
11	a_3	b_3	c_4	5	25	11,02	9	0,85
12	a_4	b_3	c_3	3	60	26,05	12	0,58
13	a_1	b_4	c_3	2	90	22,06	28	0,33
14	a_2	b_4	c_4	4	40	17,11	16	0,79
15	a_3	b_4	c_2	4	45	12,07	10	0,80
16	a_4	b_4	c_1	3	60	27,03	14	0,63

The significance of factors affecting the quality of the "Diabderm" cream was evaluated using a dispersion analysis (Table 4).

Table 4
Results of dispersion analysis

Studied indicators	Source of dispersion	Number of degrees of freedom	Sum of squares	Medium square	$F_{exper..}$	F_{table}	Hypothesis
Appearance (1-5 points)	Factor A	3	191,25	63,75	0,005	4,76	α_i =0
	Factor B	3	192,75	64,25	0,006	4,76	β_j =0
	Factor C	3	192,75	64,25	0,006	4,76	γ_k=0
	Residue	6	64130	10688	-	-	-
	Total sum	15	64706	-	-	-	-
The size of the particles of the dispersed phase (μm)	Factor A	3	50212,5	16737,5	2,114	4,76	α_i =0
	Factor B	3	12315,6	4105,2	0,518	4,76	β_j =0
	Factor C	3	50212,5	16737,5	2,114	4,76	γ_k=0
	Residue	6	47497,6	7916,26	-	-	-
	Total sum	15	65243,02	-	-	-	-
Effective viscosity (Pa*s)	Factor A	3	6637,8	2212,6	121,7	4,76	α_i =0
	Factor B	3	6113,3	2037,7	0,051	4,76	β_j =0
	Factor C	3	6107,6	2035,8	2,137	4,76	γ_k=0
	Residue	6	22177,7	3696,29	-	-	-
	Total sum	15	41036,46	-	-	-	-
Half-release period, (boric acid, minutes)	FactorA	3	5038,5	1679,5	0,2941	4,76	α_i =0
	Factor B	3	4378,5	1459,5	0,255	4,76	β_j =0
	Factor C	3	4358	1452,6	0,254	4,76	γ_k=0
	Residue	6	34264	5710,6	-	-	-
	Total sum	15	48039	-	-	-	-

Note. For each taken optimization parameter, the average values of the responses of two repeated determinations are given.

The results of the dispersion analysis were compared with the table values of Fisher's micro-test: Due to the insignificant influence of factors on the quality indicators of the cream "Diabderm", the linearity of the model was preserved. Next, multiple repeated comparisons of factors were carried out. At the same time, for factor A, the degree of desirability was distributed in the following sequence: a3>a2>a4>a1; for factor B: b3>b2>b4>b1; for factor C: c4>c2>c1>c3.

To optimize the quality indicators of ointments, it is convenient to use the combined desirability function. The desirability function is the geometric average of individual properties with different units of measurement and is calculated using the following equation:

$$D = \sqrt[4]{d_1 d_2 d_3 d_4} \quad (1)$$

where,

D is the index of the combined desirability function;

d_1 – appearance (1-5 points, U_1);

d_2 is the size of the particles of the dispersed phase (μm, U_2);

d_3 – effective viscosity (Pa*s, U_3)

d_4 is the degree of bioavailability (U_4, %).

To build a desirability scale, quantitative indicators of desirability values were used in the range from 0 to 1 (Figure 1), where the value D=1 corresponds to the values of indicators with positive properties, D=0 – negative indicators. Intermediate indicators of the degree of desirability for the cream "Diabderm": 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).

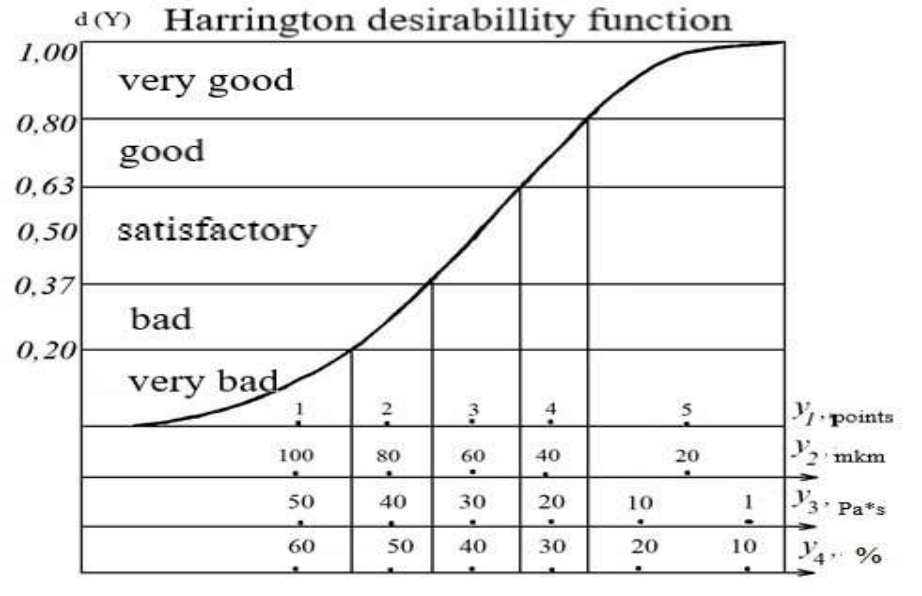

Figure 1. Generalized desirability function of optimization parameters

Values (Y) of having a specific numerical expression in units of measurement can be converted to a generalized partial value limited to one-sided values $Y=Y_{max}$ or $Y=Y_{min}$using the following equation:

$$d = \exp[-\exp(Y')], \quad (2)$$

where $y'=b_0+b_{1y}$, b_0 and b_1 coefficients with the help of which calculate two or more desirability values (d), located in the interval $0.2<d<0.8$, and apply a distributed value d calculated by the equation of the desirability function, Y' on the coordinate axis of the desirability function curve (Figure 1). In this case, the values of Y_{max} and Y_{min} on the scale of the desirability function should be equal to "0", on the dimensionless scale they should be equal to Y'. The desirability scale gives partial values of the desirability of the optimization parameters Y_i.

Using the graph of the desirability function, indicators of the degrees of desirability (Y1, Y2, Y3, Y4) are found and the values are converted to dimensionless, i.e. Unitless desirability

function indicators (d1, d2, d3, d4). Using equation 1, find the indicators of the generalized desirability function (D).

As a result of optimization, the scientifically based composition of the cream "Diabderm" was selected. The process flow diagram is shown in figure 2.

Composition: 100 g of ointment contains active ingredients:

"Diabderm" liquid extract 5.0

Boric acid 1.0

Carbamide 10.0

Menthol 0.1

Auxiliary substances - the basis of the emulsion consistency:

Vaseline 50.0

Emulsifier T-2 8.4

Purified water 25.5

Total weight 100.0

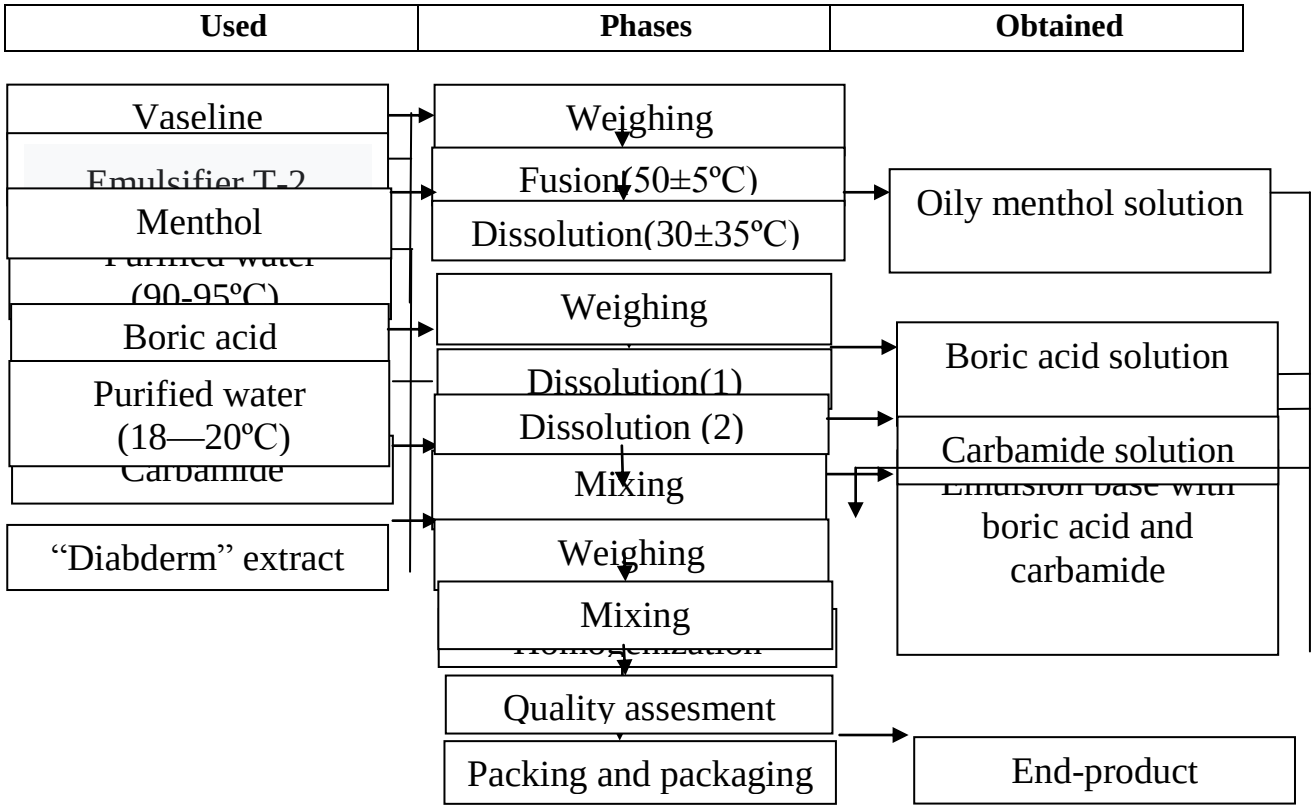

Figure 2. The scheme of the technological process for the preparation of the cream "Diabderm", prepared on an emulsion-based basis according to E.N. Kutumova

The results of the research of rheological properties of the cream "Diabderm". The results of the research of rheological parameters of the cream "Diabderm" are presented in Table 5. Based on the data obtained, two graphs were built: the first one to determine the effective viscosity of the sample, Figure 3, the second to determine the shear stress limit of the sample, Figure 4.

Table 5

The results of the research of rheological properties of the cream "Diabderm"

Instrumental reading		Shear stress, $\tau = \alpha*Z$, Pa	Gradient velocity, γ, c^{-1}	Effective viscosity, $\eta_{eff.} = \tau/\gamma$, Pa*s	Logarithm of effective viscosity, $\ln\eta_{eff.}$, Pa*s
№	α				
1a	5	28	3,0	9,3	2,23
2a	7	39,2	5,4	7,2	1,98
3a	10	56	9,0	6,2	1,83
4a	14	78,4	16,2	4,8	1,58
5a	20	112	27,0	4,2	1,42
6a	29	162,4	48,6	3,3	1,21
7a	41	229,6	81,0	2,83	1,04
8a	60	336	145,8	2,30	0,83

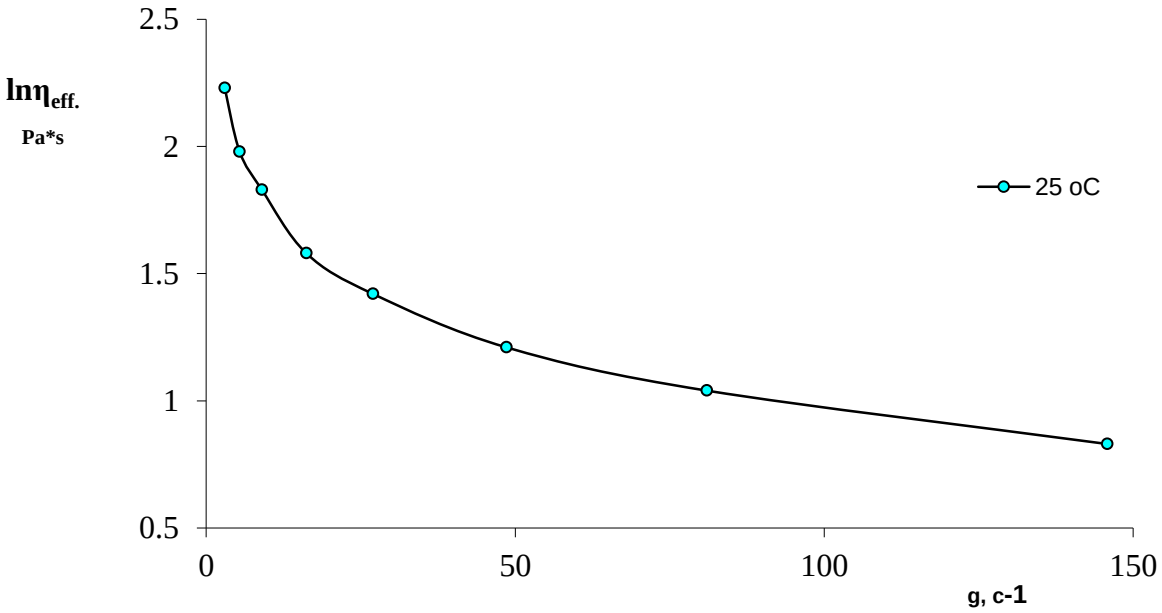

Figure 3. Dependence of the effective viscosity($\ln\eta_{eff.}$) from gradient velocity(γ) of the sample at a temperature of 25^0C.

As can be seen from Figure 3, when $\gamma \rightarrow 0$ the logarithm of the effective viscosity of the drug is equal to $\ln\eta_{eff.}$ = 2,4 Pa*s or the effective viscosity of the drug is equal to $\eta_{eff.}$ = 11,02 Pa*s.

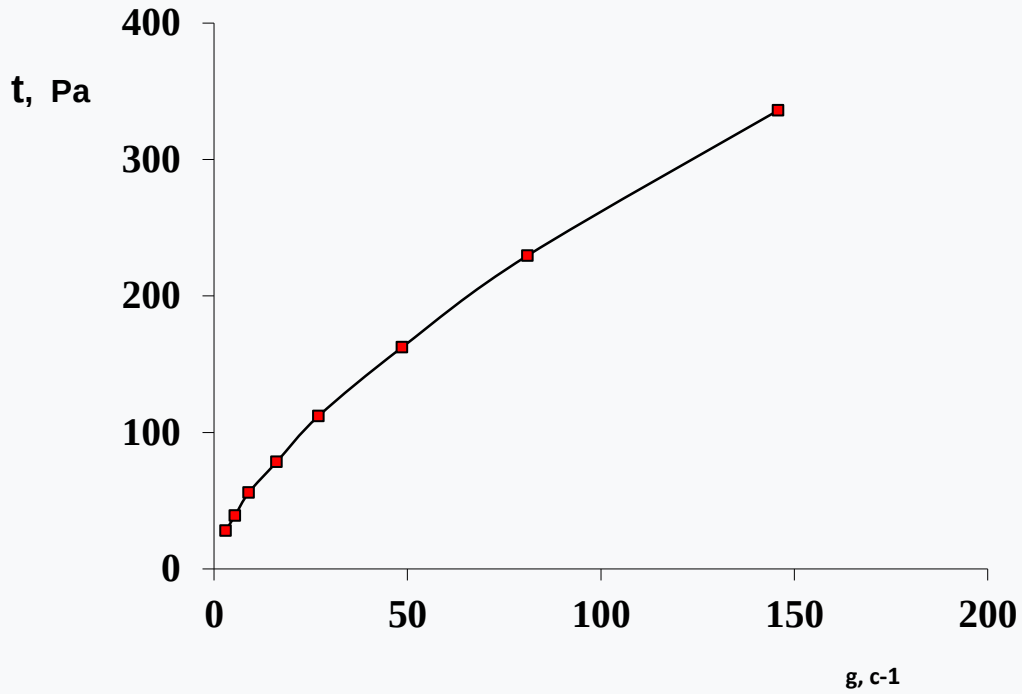

Figure 4. Shear stress (τ) from the gradient velocity (γ) for the sample

From figure 4 with $\gamma \rightarrow 0$ the limiting shear stress of the preparation is equal to

$\tau_{sam.} \approx 25$ Pa. For determination of plastic viscosity (plasticity) (η_p) we applied the Shvedov-Bingham formula:

$\tau = \tau_{sam.} - \eta_p \gamma$

$\eta_p = (\tau - \tau_{sam.})/\gamma = (78{,}4 - 25)/16{,}2 = 3{,}3$ Pa*s.

The study of bioavailability of the cream "Diabderm" by "in vitro" method. The bioavailability of boric acid from the composition of the cream was determined by the method of equilibrium dialysis, for which a dialysis tube with a diameter of 2.5 cm and a length of 25-30 cm was used, a semi-permeable membrane was used as a membrane (cellophane with a diameter of 65 mm, with a pore size of 0.025 mm), purified water was used as a dialysis substance. Samples of cream "Diabderm", prepared in different bases by four methods, 5.0 g each, were applied in even layers on a cellophane film and attached to the end of a dialysis tube. Next, the dialysis tube with the ointment sample was immersed 2 mm into a thermostatically controlled (37 ± 0.5 °C) beaker with purified water with a volume of 50 ml. The dissolved substance was stirred from time to time and every 30 minutes a sample of 5 ml was taken from the dialysate so that the volume of the dialysis substance did not decrease; after sampling, 5 ml of purified water was added to the substance. The content of boric acid released into the dialysis substance was determined in the sample selected for analysis.

To the selected sample, 10 ml of glycerin, previously neutralized with phenolphthalein, was added and titrated with 0.01 M sodium hydroxide until a pink colour appeared.

Next, another 5 ml of neutralized glycerol is added to the titrated solution, and if the colour disappears, then titration is continued. 1 ml of 0.01 M sodium hydroxide is equivalent to 0.0006183 boric acid. The quantitative content of boric acid was calculated by the formula:

$$C = \frac{K * T * V_1 * 25}{V_2 * a} * 100\ \%$$

where,

K - correction factor = 1.04;

T -titer of 0.01M sodium hydroxide solution for boric acid (0.0006183);

V1 is the volume of 0.01 M sodium hydroxide solution used for titration, ml;

25 – total volume of dialysate, ml;

V2 - volume of dialysate taken for analysis, ml;

a - quantitative content of boric acid in the cream, g.

Table 6

The results of determining the bioavailability of boric acid from the cream "Diabderm" in experiments "in vitro"

Studied compositions with basics	Boric acid release time, minutes					
	30	60	90	120	150	180
I (vaseline)	0,25	0,30	0,35	0,40	0,50	0,55
II (vaseline/lanoline)	0,35	0,40	0,45	0,50	0,60	0,65
III (emulsion-consistency)	0,5	0,6	0,65	0,70	0,75	0,80
IV (bentonite)	0,4	0,5	0,60	0,60	0,65	0,70

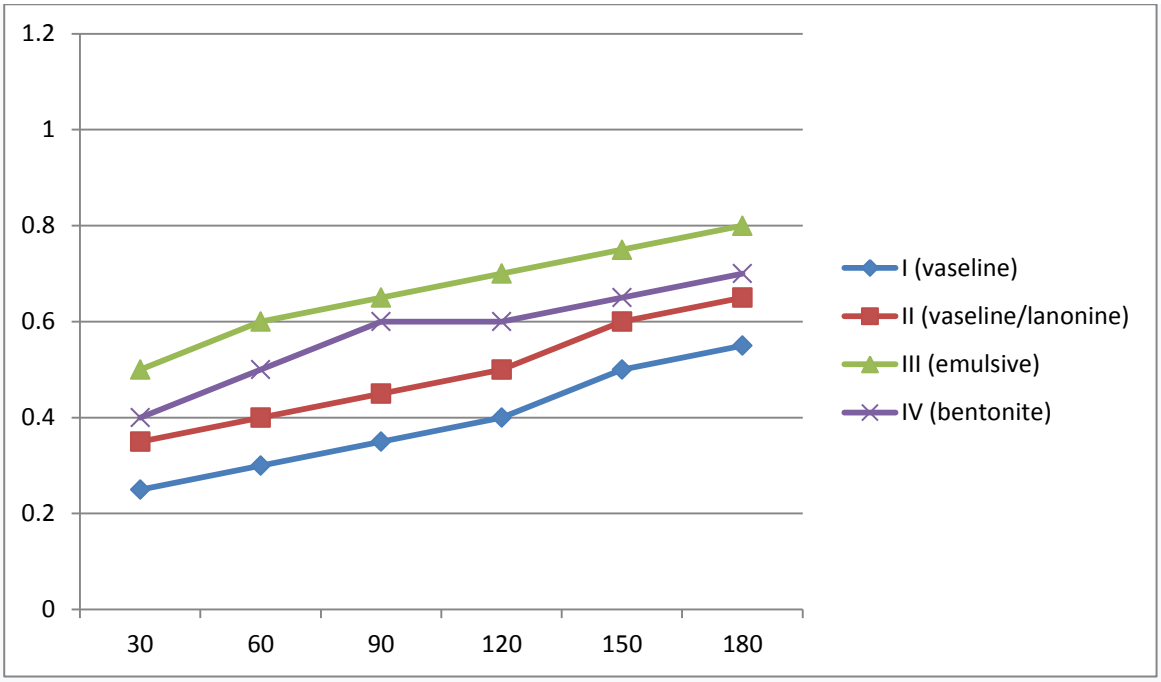

Figure 5. Kinetics of the release of boric acid from samples of cream "Diabderm", prepared on various bases.

As the results of studying the bioavailability of the cream "Diabderm" showed, in "in vitro" experiments, the highest result in the release of boric acid was shown by samples prepared on an emulsion consistent basis. The quality indicators of the cream "Diabderm" were also studied (Table 7).

Table 7

The results of the study of the quality indicators of the cream "Diabderm", prepared on an emulsion basis

Studied indicators	Quality standards in accordance with regulatory documents	Results
Appearance	Homogeneous mass, soft consistency, without impurities, colour and odour corresponds to the components used	Homogeneous mass, soft consistency, without impurities, light greenish-beige colour, with a characteristic odor of the components
Uniformity	Homogeneous mass	Corresponds
Authenticity	Cyanidin reaction: place 2–3 ml of an alcohol solution of	Corresponds

	the drug is placed in porcelain cup, add magnesium powder and 5–6 drops of concentrated hydrochloric acid on top, then heat for 1–2 minutes in a water bath, a red colour (flavones) is formed. Add hydrochloric acid to the aqueous solution and apply a few drops of the mixture on turmeric paper;	
Stability: - colloidal, (centrifugation at 2000 rpm) - Thermal (thermostatting at 40±2 0C)	Should not delaminate and precipitate	stable stable
pH value (water extract, 1:10)	6,5-7,5	6.5-6.8
Mass loss during heating, %	14	4,38%
Dispersity, μm	No more than 50	≤50,0

Discussion: According to the scientific works of A.A. Arkusha, I.M. Pertsev, V.G. Gunko by determining the rheological optimum for ointments, the optimum of hydrophilic ointments (at 20°C) is characterized by a yield strength 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 a yield strength of 35–140 Pa and an effective viscosity of 0.32–93.3 Pa*s.

The effective viscosity of the preparation satisfies the requirements, however, the values of the shear stress limit turned out to be slightly lower than those described in the literature, despite the fact that the experiment was carried out at 25°C. However, the higher the value of this value, the more difficult the preparation is to spread. But another important indicator, like plasticity, turned out to be very high, which indicates the strength of the cream structure, namely, the drug is significantly stable, and therefore, in general, the drug has an optimal consistency from a consumer point of view.

The rheological parameters of the composition are quite stable over time, which determines the good quality of the sample during long-term storage.

In order to select the optimal composition of the "Diabderm" cream, samples were prepared on various bases, and their bioavailability was also studied in "in vitro" experiments - the method of equilibrium dialysis according to the kinetics of boric acid release. The following

bases were used to prepare the samples: method I (Vaseline), method II (Vaseline/Lanoline, 6:3), method III (emulsion-consistent base), IV (hydrophilic, bentonite base). Studies have shown that the lowest release of boric acid was observed in the composition prepared on petroleum jelly. It is well known that Vaseline has a good consistency, does not irritate the skin and mucous membranes. However, it is not absorbed by the skin and mucous membranes, slowly releases medicinal substances, therefore it is used for topical ointments, disrupts heat, gas and moisture exchange of the skin, is poorly washed off the skin, and sometimes causes allergies. The composition of the cream, prepared on a vaseline-lanolin basis, had better bioavailability because of the introduction of lanolin into the composition of the ointment. It is well absorbed into the skin, added to the ointment bases as a hydrophilizing component that can increase the absorption of medicinal substances. However, with the addition of lanolin, the viscosity of the cream increased.

Samples of the cream "Diabderm", prepared on a hydrophilic bentonite basis and an emulsion basis, had a more pronounced bioavailability. However, samples of cream on bentonite dried quickly and did not have high quality indicators due to high adsorbing capacity. As shown by the results of determining the bioavailability of the cream, the best base was an emulsion consistent base (water / oil type), where emulsifier T2, an ester of triglycerol and stearic acid, was used as an emulsifier.

Next, the quality indicators of the cream "Diabderm" prepared on an emulsion consistent basis were studied: appearance, uniformity, authenticity, colloidal and thermal stability, pH (water extract, 1:10), mass loss during heating, dispersion), rheological properties. All the studied indicators of the cream "Diabderm" once again proved the feasibility of the selected composition and the developed technology.

Conclusion: Based on the liquid extract "Diabderm", the composition technology of the treatment-and-prophylactic cream of complex composition "Diabderm" was developed, intended for the prevention and treatment of diabetic dermatopathies. In order to optimize the composition and technology of the "Diabderm" cream, the method of mathematical planning of the experiment - three-factor fractional plans of Latin squares 4x4 was used, which allows statistical methods to select the most appropriate composition and technology, and also reduce the number of experiments. As a result of the research, the composition and technology of the cream "Diabderm" on an emulsion consistent basis were developed, quality indicators were studied (appearance, uniformity, authenticity, colloidal and thermal stability, pH value (water extract, 1:10), mass loss during heating, dispersion), rheological properties and bioavailability by the "in vitro" method - the method of equilibrium dialysis according to the kinetics of boric acid release. The results of the research of quality indicators of the Diabderm therapeutic and prophylactic cream gave satisfactory results.

List of used literature:

1. Diabetes prevalence (% of population ages 20 to 79) - World Bank [https://translated.turbopages.org/proxy_u/en-ru.ru.].

2. Tarasenko N.A. Diabetes mellitus: actuality, forecasts, prevention // Modern problems of science and education. - 2017. - No. 6.- P. 14-22.

3. Ibragimova N.S., Kamalov T.T., Shokirov K.S., Kokoreva L., PlatonovaO.Yu. The incidence of diabetic foot syndrome in the patients with type 2 diabetes mellitus in Uzbekistan. Problems of

Endocrinology. 2012;58(4, вып. 2):24-25. (In Russ.) [https://www.probl-endojournals.ru/jour/article/view/13023/10165].

4. Antsiferov M.B., Tokmakova A.Yu., Galstyan G.R., Udovichenko O.V. Diabetic foot syndrome: Atlas for endocrinologists.- M.: Papasha Grizli, 2002.- 80p., ill. ISBN 5-88661-027-8.

5. Tikhonov V.N., Kalinkina G.I., Salnikova E.N. Medicinal plants, raw materials and phytopreparations - Tomsk, 2004.-p.148.

6. Korsun V.F., Trumpe T.E., Ershov N.V., Ogrenich N.A. Phytotherapy against diabetes. Herbs of life / Edited by d.m.s., acad. RANS, prof. V.F.Korsun- M.: Centerpolygraph, 2016.- 390 p. ISBN 978-5-227-06323-6.

7. Kobzar A.Ya. Pharmacognosy in medicine. - Kiev: Medicine, 2007. - 543 p.

8. Khusenova Sh.Sh., Fayzullaeva N.S. Development of technology for liquid extract-concentrate "Dermostop" and quality assessment//Pharmaceutical Journal.-Tashkent, 2017.-N1.- P.89-94.

9.KhusenovaSh.Sh,UmaralievaN.R.,FayzullaevaN.S.Technologyandevalutionofqualityof"Dermostop" ointment/TopicalissuesofnewdrugsdevelopmentAbstractsofXXIVInternationalScientificAndPracticalConferenceOfYoungScientistsAnd Student(April20,2017)in2vol.,Vol.1.–Kh.:PublishingOfficeNUPh,2017.–P.253.

10. Khusenova Sh.Sh. Development of the composition of the collection "DIABDERM" for external therapy of inflammatory skin diseases / Sat. materials of the international scientific and practical conference "The current state of the pharmaceutical industry: problems and prospects." - November 13–14, 2020,

11. KhusenovaSh.Sh., Fayzullaeva N.S. Development of "Diabderm" assembly technology//Pharmaceutical journal.-Tashkent, 2022.-N1.- S.89-96.

12. Groshovyi T.A., Markova E. V., Golovkin V.A. mathematical planning of experiment in pharmaceutical technology. Plans for analysis of variance. - Kyiv: High school, 1992. - 187 p.

13. Quality control and production of soft drugs in the light of the requirements of the Govermental Pharmacopoeia of Ukraine / I. M. Pertsev, S. A. Gutorov, G. V. Zagoriy, E. L. Khaleyeva // Pharmacist. - 2002. - No. 8. -p.42-49. [DOI: https://doi.org/10.31838/ijpr/2020.12.04.545]

14. Kartalov M.G., Dmitruk S.E., Dmitruk V.S., Romanenko T.V. Study of the structural and mechanical properties of the Kartalin ointment.//Bulletin of Siberian Medicine. -2009.-№8 (3).-S.48-52. [https://doi.org/10.20538/1682-0363-2009-3-48-52]

15. Karieva E.S., Maksudova F.Kh. Use of Mathematical Planning Methods for Selecting Optimum Combined Gel Compositions // Pharmaceutical Chemistry Journal. - August 2017.- Vol. 51.- Issue 5. – P. 411–415.v(DOI 10.1007/s11094-017-1624-1)

16. Karieva E.S., Gaipova N.N., Maksudova F.Kh. The utilization of the strategy of mathematical planning of the experiment in the selection of auxiliary substances for a gel based on dry extract «Fitoinflam» // nternational Journal of Pharmaceutical Research.-2020.-Vol.12.-Issue 4.-P.3968-3973

17. Govermental Pharmacopoeia XI. Issue 2. General methods of analysis. Medicinal plant material. M.: Medicine, 1989.- S.160-161.

18. Khoruzhaya T. G., Chuchalin V. S. Biopharmacy - a scientific direction in the development and improvement of drugs: Textbook. - Tomsk: Laboratory of operational printing. Siberian State Medical University, 2006. - P. 40.