UDC 615.262.1: 615.454.12
DOI: 10.15587/2519-4852.2026.350751

APPLICATION OF THE METHOD OF MATHEMATICAL PLANNING FOR THE SELECTION OF AUXILIARY COMPONENTS FOR THE CREATION OF A FUNCTIONAL-PURPOSE MEDICINAL AND COSMETIC PRODUCT

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The aim of the research: *selection of the optimal complex of excipients and development of technology for a therapeutic and cosmetic cream for the acne treatment.*
Materials and methods*. The following active pharmaceutical ingredients were selected – the dry extract of "Fitoinflam," nicotinamide, salicylic acid, and camphor. Twenty ingredients were used as excipients, acting as a structure-forming agent, emulsifier, emollient, or oil phase. Excipient selection was conducted using a four-factor design based on a 5 × 5 Greco-Latin square. In vitro studies were conducted using equilibrium dialysis through a semipermeable membrane according to Kruvchinsky. Quantification of total flavonoids, expressed as rutin, was determined by high-performance liquid chromatography.*
Results*. Using Duncan's ranking test, the most optimal excipients for the cream under development were determined: aerosil (structuring agent), sodium tetraborate (emulsifier), glycerin (emollient), and castor oil (oil medium). The concentration of citric acid as a pH regulator was selected empirically: according to the data obtained, the optimal concentration was 1%.*
Conclusions*. Based on the results of an experimental design using a 5 × 5 Greco-Latin square layout, a composition for a medicated, emulsion-type anti-acne cream was developed: dry extract of "Phytoinflam," nicotinamide, salicylic acid, camphor, aerosil, sodium tetraborate, glycerin, castor oil, citric acid, tea tree essential oil, and purified water. A technology for producing cosmetic cream was developed based on the physicochemical properties of the active pharmacological substances and excipients*
Keywords*: medicinal and cosmetic cream, method of mathematical experimental design, plant extract "Fitoinflam", in vitro biopharmaceutical studies, total flavonoids, high-performance liquid chromatography, nicotinamide, salicylic acid, camphor, composition, preparation technology*

How to cite:
Karieva, E., Baratova, M., Matazimov, M., Kukhtenko, O. (2026). Application of the method of mathematical planning for the selection of auxiliary components for the creation of a functional-purpose medicinal and cosmetic product. ScienceRise: Pharmaceutical Science, 1 (59), 11–21. http://doi.org/10.15587/2519-4852.2026.350751

1. Introduction

Acne vulgaris is one of the most common chronic inflammatory skin diseases, characterized by blockage of the pilosebaceous follicles. It can manifest externally as various skin rashes, including comedones, papules, and pustules. Although the disease has no geographical limitations, its prevalence varies by country and patient age [1–4]. Skin rashes are observed in patients of all ages, but those aged 15 to 19 are most susceptible (85% of all registered patients). According to statistics, this disease is among the top ten most common skin diseases, affecting 9.79% of the population [5–8].

The rash most often affects the face, with the shoulders and back also at risk. Scarring, pigmentation, and erythema are common symptoms of the disease [9, 10].

According to the literature, four causes of acne are currently identified: sebaceous gland hyperfunction, abnormal proliferation of Cutibacterium acnes bacteria, inflammatory processes, and hyperkeratinization of hair follicles. All these processes are interconnected, and one often triggers the next [3, 5].

Sebaceous gland hyperfunction. Numerous studies confirm a direct correlation between the incidence of acne and the severity of the disease due to increased sebum production in hair follicles, which must be considered when treating patients [11–13].

Pathological proliferation of Cutibacterium acnes bacteria. Cutibacterium acnes is a species of actinobacteria from the *Propionibacteriaceae* family. The growth and proliferation of these bacteria is directly related to the cause – increased sebum production in the follicles – as they primarily feed on sebum and cellular debris. These bacteria thrive primarily on the fatty acids contained in sebum secreted by the sebaceous glands in the follicles. *C. acnes* also cause comedones and inflammation by producing the enzyme lipase, which is involved in the metabolism of sebum triglycerides into the trihydric alcohol glycerol and fatty acids [14, 15].

Inflammatory processes. As described above, inflammation is caused by *Cutibacterium acnes*. This inflammation, in turn, produces lymphocytes, neutrophils, and macrophages. Mechanical damage to the skin (follic-

ular damage, microbial penetration into the dermis, etc.) is also observed, which, along with neutrophils, leads to the formation of papules, pustules, and nodules [16–18].

Hyperkeratinization of hair follicles. In healthy hair follicles, keratinocytes are released into the follicles, which subsequently die and are eliminated. However, in the presence of inflammation, which always accompanies acne, the body mounts a protective response, manifested by increased division and proliferation of keratinocytes. As a result, they accumulate in the hair follicles along with lipids [19, 20].

Genetic predisposition, environmental factors (air pollution, living conditions, humidity and temperature, ultraviolet radiation intensity, etc.), a balanced and "correct" diet, bad habits (smoking, alcohol consumption), a person's psychological state, hormonal status, medication intake, etc., play a significant role in the development of this disease [21–23].

Currently, acne treatment can be carried out either solely topically (for mild to moderate cases) or in combination with systemic methods (moderate to severe cases) [3, 24]. Topical application (solutions, lotions, creams, gels) reduces the absorption of the active pharmaceutical ingredient and primarily enhances the effect on the hair follicles. Acne treatment with topical medications can last for years [25–27].

If the disease is unresponsive to topical therapy or the patient's condition is assessed as moderate, systemic treatment is preferable. In this case, the patient's psychological state is of great importance. In both cases, acne is treated with retinoids [28–30], antibiotics [31–33], and hormonal agents [34, 35].

Thus, the main acne treatment regimens include topical, oral, or systemic anti-inflammatory and antibacterial agents. It is noted that a combination of several drug regimens (topical and oral or topical and systemic) is more effective in the pathogenesis of this disease [11, 36, 37].

However, despite the wide range of drugs for the treatment of acne, many active pharmaceutical ingredients (hormones, antibiotics and retinoids) with prolonged use lead to skin irritation, resistance to antibiotics, and can also cause various allergic reactions [38–40].

Considering the above, manufacturers of functional therapeutic and cosmetic products are increasingly focusing on natural APIs, particularly those of plant origin. The dry extract "Fitoinflam" is developed from a blend of medicinal plant raw materials: oak (*Quercus robur* L.), chamomile (*Matricaria chamomilla* L.), and *Bidens tripartita* L. Pharmacological studies have demonstrated the pronounced anti-inflammatory and wound-healing activity of this combined extract, which, according to the toxicity classification, is classified as virtually non-toxic. It has also been established that the dry extract "Fitoinflam" contains 20 amino acids, 10 of which are essential. The total amino acid content is 14.767 mg/100 mg, of which 38.97% are essential amino acids and 61.03% are non-essential. In addition to amino acids, the presence of 28 micro- and macroelements has been proven, of which seven are essential and four are conditionally essential. High levels of calcium, potassium, sodium, magnesium, silver, and other elements have been detected, which is direct evidence of the high pharmacological activity of the dry extract "Fitoinflam" [41, 42].

The aim of the research: selection of the optimal complex of excipients and development of technology for a therapeutic and cosmetic cream for the treatment of acne.

2. Planning the research methodology

To achieve this goal, the following tasks were formulated:

– select active pharmaceutical ingredients considering their therapeutic action to achieve the most effective complex acne therapy;

– using the method of mathematical experimental design, conduct a scientifically based selection of auxiliary ingredients;

– develop a rational technology for producing cream, considering all key stages of production.

The first stage of the research was conducted based on a review of the scientific literature: APIs were selected based on published clinical trial results, i.e., considering their pharmacotherapeutic effects. A deconstruction method and aspect analysis were used.

In the second stage, the response (*in vitro* study results) was determined to be dependent on the input variables (type of excipient used). The study results demonstrated the superiority of certain input data over others.

The third stage was carried out considering the physicochemical properties of each component, both active pharmaceutical ingredients and excipients.

3. Materials and methods

The active pharmaceutical ingredients selected were dry extract "Fitoinflam," niacinamide, salicylic acid, and camphor.

Dry extract "Fitoinflam" (Extractum siccum "Fitoinflam") (VFS 42 Uz-5712-2024). Due to its tannin content, Cortex Quercus has an astringent effect on the skin, thereby reducing sebum. Herba Bidentis and Flores Chamomillae contain a rich flavonoid composition, which has anti-inflammatory and wound-healing properties; it was added to the cream at a concentration of 10%.

Nicotinamide (Nicotinamidum) is a pyridine-3-carboxamide ($C_6H_6N_2O$) M. m. 122.1 (European Pharmacopoeia 11.0; 01/2017:0047). Nicotinamide (also known as niacinamide), being an amide compound of nicotinic acid, has an anti-inflammatory effect on acne; its topical application helps form a skin barrier and thereby prevents the penetration of infections, reduces sebum production and protects the skin from breakouts, and also exhibits an antibacterial effect [43, 44]. According to the results of numerous studies, niacinamide exhibits a range of the above-mentioned effects at a concentration of 1–5%, however, in cosmetic products applied topically, a content of 2-4% is most often used [45, 46]. Taking this into account, we decided to include it in the composition of the cream under development at a concentration of 3%.

Salicylic acid (*Acidum salicylicum*) is 2-hydroxybenzenecarboxylic acid ($C_7H_6O_3$). M.m. 138.1 (European

Pharmacopoeia 11.0; 01/2017:0366). Salicylic acid has anti-inflammatory, bacteriostatic, and fungistatic properties. It has a moderate keratolytic effect, due to which it can be used in the treatment of acne. Salicylic acid is a common ingredient in several over-the-counter acne products [47, 48]. In accordance with European Commission Regulation (EU) 2019/1966 of 27 November 2019, salicylic acid and its derivatives may be present in cosmetic products for topical use in concentrations of up to 2% [49]. During the study of this issue, we decided to include this API in the cream at a concentration of 0.5%.

Camphor – (*Camphora racemica*) - (1RS, 4RS)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one. ($C_{10}H_{16}O$). M.m. 152.2 (European Pharmacopoeia 11.0; 01/2008:0655 corrected 6.0). Many years of experience in the use of camphor in medicine have revealed such properties as local anesthetic, antiseptic, antispasmodic, antipruritic, anti-inflammatory, anti-infectious, local irritant [50]. It is due to most of these properties that it is used as a prophylactic agent for dermatological infectious diseases and is also a common component of cosmetics and medical products [51, 52].

The US Food and Drug Administration (FDA) permit the inclusion of camphor as an active ingredient in topical products at concentrations ranging from 0.1% to 3% [53]. Health Canada guidelines also prohibit the use of this substance in cosmetic products exceeding 3% by weight [54]. Taking these facts into account, camphor was introduced into the cream being developed at a concentration of 1%.

Considering that the cream being developed, in addition to achieving the desired therapeutic effect, must be stable, have high bioavailability, and meet the required rheological properties, we decided, based on prior information, to use four groups of excipients that most effectively impact the above-mentioned qualities of the finished product. Information on the excipients selected for the experiments is provided in Table 1.

The dynamic growth of the pharmaceutical industry, the wide range of modern excipients, the high-quality requirements for finished products, and the level of competition among manufacturers require the use of advanced approaches to research on formulation selection and the development of pharmaceutical manufacturing processes. The goal of implementing innovative approaches is to reduce the number of experiments, the consumption of starting materials, energy consumption, and time.

Table 1

Excipients and their functions

Ingredients	Functions	DN	Links
Structure-forming agents			
Lignin	Base former, structure former	CAS 9005-53-2	[55, 56]
Na-КМЦ (Na-CMC	Gelling agent, base former, surfactant	CAS 9000-11-7	[57, 58]
Aerosil (Silicon dioxide)	Rheological modifier, stabilizer, gelling agent	CAS 112945-52-5	[59, 60]
PEG -400	Structuring agent, solubilizer, solvent, stabilizer	CAS 25322-68-3	[61, 62]
Bentonite	thickener, structure-forming agent, emulsifier, disintegrating agent, adsorbent	CAS 1302-78-9	[63, 64]
Emulsifiers			
Polysorbat 80	Emulsifying agent, gelling agent, surfactant	CAS 9005-65-6	[65, 66]
Sodium tetraborate	Emulsifier, exfoliant, humectant, preservative	CAS 1303-96-4	[67, 68]
Polysorbat 20	Emulsifier, gelling agent, surfactant	CAS 9005-64-5	[69, 70]
BTMS-50 (Behentrimonium methosulfate)	Cationic emulsifier, surfactant	CAS: 81646-13-1	[71, 72]
Stearic acid	Emulsifier, emollient	CAS 57-11-4	[73]
Emollients			
Vaseline (Petrolatum)	Base former, moisturizing component	CAS 8009-03-8	[74, 75]
Dimeticone	Post-emulsifying component, emollient, silicone	CAS 9006-65-9	[76, 77]
Beeswax	Natural emulsifier, base-forming component, thickener	CAS 8012-89-3	[78, 79]
Glycerol	Humectant, base former	CAS 56-81-5	[80]
Cyclomethicone	Silicone, moisturizing agent, improves t he texture of the cream.	CAS 541-02-6	[81, 82]
Oil phase			
Castor oil	Oil base, wound-healing properties	CAS 8001-79-4	[83, 84]
Grape Seed Oil	Antioxidant, moisturizing agent, oil base	CAS 85594-37-2	[85, 86]
Olive oil	Moisturizing and toning agent, oil base	CAS 8001-25-0	[87, 88]
Argan oil	Moisturizing component, oil base, beneficial effect on the skin microbiome, anti-inflammatory effect	CAS 223747-87-3	[89, 90]
Almond oil	Moisturizing component, oil base	CAS 8007-69-0	[91, 92]

Based on the above, we decided to use a mathematical experimental design method for the scientifically based selection of auxiliary components for the composition of a therapeutic and cosmetic acne cream. The input variables (factors) were the type of structure-forming agent (factor A), emulsifier (factor B), emollient (factor C), and oil base (factor D). Given that we decided to examine the effects of four types of auxiliary ingredients at five levels, it is rational to use a four-factor design based on a 5 × 5 Greco-Latin square, which will reduce the number of experiments by 25 times.

The factors and their levels are presented in Table 2.

The response was determined by the release of total flavonoids into the dialysis medium in *in vitro* biopharmaceutical experiments.

In vitro studies were conducted using the equilibrium dialysis method through a semipermeable membrane according to Kruvchinsky [93].

Table 2

Factors and their levels used in the experiment

Factor and its levels	The importance of the factor	Factor and its levels	The importance of the factor
Structure-forming agent (factor A)		Emulsifier (factor B)	
a_1	Lignin	b_1	Polysorbate-80
a_2	Sodium-CMC	b_2	Sodium tetraborate
a_3	Aerosil	b_3	Polysorbate-20
a_4	PEG-400	b_4	BTMS-50
a_5	Bentonite	b_5	Stearic acid
Emollient (factor C)		Oil base (factor D)	
c_1	Vaseline	d_1	Castor oil
c_2	Dimethicone	d_2	Grapeseed oil
c_3	Beeswax	d_3	Olive oil
c_4	Glycerin	d_4	Argan oil
c_5	Cyclomethicone	d_5	Almond oil

Experimental conditions:

– advantec semipermeable membrane (Ireland), 125–135 μm thick, 0.45 μm pore diameter;

– dialysis medium – methanol (selected based on the solubility of the biologically active substances);

– temperature – 37 ± 10°C;

– the amount of released biologically active substances (total flavonoids calculated as rutin) was determined by high-performance liquid chromatography.

Method for the quantitative determination of total flavonoids expressed as rutin. Quantitative determination of total flavonoids expressed as rutin was performed using high-performance liquid chromatography (Eur.Ph.).

Chromatography conditions. HPLC: SPD-M20A – DIODE ARRAY DETECTOR; column – PerfectSil Targer ODS stainless steel, 250 mm long, 4.6 mm internal diameter, 3.5 μm particle size or equivalent, flow rate – 1.0 mL/min; detection (rutin) – 357 nm, column temperature – 40°C; sample volume – 10 μL; analysis time – 25 min.

Reagents: – HPLC–grade methanol;

– phosphoric acid;

– purified water.

Preparation of the mobile phase. (A) Methanol and (B) phosphoric acid were mixed in a volumetric ratio, filtered through a 0.45 μm filter, and degassed.

Preparation of solution B. 0.3 ml of phosphoric acid was placed in a 1000 ml volumetric flask, and 800 ml of purified water was added. The solution was mixed and made up to the mark with the same solvent.

Preparation of standard solution. An accurately weighed 15 mg standard sample of rutin was placed in a 25 ml volumetric flask. 15 ml of methanol was added, mixed, and the volume was made up to the mark with the same solvent (rutin concentration 0.6 mg/ml).

To determine the quantitative content of total flavonoids released into the dissolution medium, 10 ml of the solution was collected, transferred to a centrifuge tube, and centrifuged at 5000 rpm for 15 minutes. Next, 5 ml of the solution was collected and filtered through a polytetrafluoroethylene (PTFE) filter with a pore size of 0.45 μm.

The amount of total flavonoids, expressed as rutin (X), released into the solution was calculated using the formula:

$$X = \frac{A_1 \cdot m_0 \cdot 100 \cdot P \cdot 100}{A_0 \cdot 25 \cdot 5 \cdot m_1 \cdot 100},$$

where A_1 – peak value of the test solution; A_0 – peak value of standard solution; m_1 – sample of cream taken for analysis, mg; m_0 – standard sample weight, mg; P – rutin content in the standard sample, %.

The following equipment was used in the research: analytical scales "Electronic balance" (China) model PTT-A 1000, technical scales "JAN-5" (Electronic balance, China), high-performance liquid chromatograph (Agilent Technologies (USA) trademark "Agilent 1200 series" with software "Chemstation"), magnetic stirrer "Magnetic stirrer" (China), universal drive of the company "Erweka" (Germany) with a "Planetary stirrer" attachment, Kruvchinsky device, portable pH meter "Five easy" (Mettler Toledo, Switzerland).

4. Research results

Using the mathematical design of experiments method, a 5 × 5 experimental plan was developed. This experimental plan, with three replicates, as well as the results of determining the quantitative content of total flavonoids, expressed as rutin, released after 6 hours of *in vitro* experiments, are presented in Table 3.

Before conducting the ANOVA, we checked for homogeneity of variance using Cochran's test. The uniformity of the experiments was confirmed by the fact that the calculated value of y_{exp} (0.09704) was less than the y_{tab} value of Cochran's test (0.22 for $f1 = 2$ and $f = 25$).

Next, we calculated the sums of squares, and the mean squares were found by dividing the resulting sums of squares by the number of degrees of freedom. The ANOVA results are presented in Table 4.

According to the data obtained, $F_{exp} > F_{tab}$, or all four factors studied, confirming the statistical significance of all variables. The $F_{er.in.c}$ value indicates the presence of interactions between the factors.

For each of the four variables, preference rankings were constructed using Duncan's multiple rank test. It was found that the influence of the structure-forming agent on the response, i.e., the release of total flavonoids, can be arranged in the following order: $a_3 > a_2 > a_1 > a_5 > a_4$. Thus, Aerosil is the optimal structure-forming agent for the cream being developed, followed by sodium carboxymethylcellulose and lignin. The use of PEG-400 and bentonite did not promote intensive release of the biologically active substance.

Since the cream being developed is an emulsion, the choice of emulsifier is an important consideration when selecting the formulation. It is known that the complete release of biologically active substances, as well as the stability of the finished dosage form, depends not only on the uniform distribution of the active ingredients between the two phases (oil and water), but also on the

surfactant, particularly the emulsifier. The influence of the next factor under study, the emulsifier, can be arranged in the following order: $b_2 = b_4 > b_3 > b_5 > b_1$. Thus, sodium tetraborate and BTMS demonstrated the best emulsifying properties. However, considering cost-effectiveness, we decided to select the first component. Multiple comparisons revealed that polysorbate-20, polysorbate-80, and stearic acid were weaker in activity; their use did not ensure complete release of flavonoids, and therefore they were excluded from further studies.

As is well known, emollients, acting as moisturizing components, promote cell turgor, which facilitates better penetration of active pharmaceutical ingredients. The preference order for this factor is represented as follows: $c_5 = c_4 > c_3 > c_2 > c_1$. Thus, cyclomethicone or glycerin proved optimal, while petroleum jelly, dimethicone, and beeswax proved less effective. Given the additional bactericidal and bacteriostatic properties of glycerin, it was decided to retain it as the emollient of choice.

Table 3

Yield of total flavonoids in the extract in a four-factor 5 × 5 design with three replicate experiments, %

Factor A		Factor B					Results
		b_1	b_2	b_3	b_4	b_5	a_i
a_1		c_1d_1	c_2d_2	c_3d_3	c_4d_4	c_5d_5	–
		0.631	0.711	0.587	0.901	0.68	
		0.684	0.696	0.604	0.918	0.716	
		0.661	0.681	0.57	0.934	0.669	
		1.976	2.088	1.761	2.753	2.065	10.643
a_2		c_2d_3	c_3d_4	c_4d_5	c_5d_1	c_1d_2	–
		0.514	0.733	0.809	1.211	0.385	
		0.492	0.681	0.749	1.247	0.422	
		0.54	0.745	0.771	1.184	0.404	
		1.546	2.159	2.329	3.642	1.211	10.887
a_3		c_3d_5	c_4d_1	c_5d_2	c_1d_3	c_2d_4	–
		0.743	1.503	0.918	0.889	0.604	
		0.671	1.433	0.942	0.936	0.628	
		0.687	1.468	0.893	0.912	0.652	
		2.101	4.404	2.753	2.737	1.884	13.879
a_4		c_4d_2	c_5d_3	c_1d_4	c_2d_5	c_3d_1	–
		0.611	0.933	0.391	0.639	0.651	
		0.588	0.981	0.43	0.683	0.718	
		0.639	0.952	0.416	0.661	0.737	
		1.838	2.866	1.237	1.983	2.106	10.03
a_5		c_5d_4	c_1d_5	c_2d_1	c_3d_2	c_4d_3	–
		0.61	0.662	0.792	0.732	0.765	
		0.583	0.715	0.763	0.65	0.749	
		0.645	0.646	0.811	0.673	0.692	
		1.838	2.023	2.366	2.055	2.206	10.488
Results	B_j	9.299	13.54	10.446	13.17	9.472	55.927
	C_k	9.184	9.867	10.182	13.53	13.164	
	D_l	14.494	9.945	11.116	9.871	10.501	

Table 4

Analysis of variance of experimental data for determining the release of total flavonoids in terms of rutin from model cream samples into dialysis medium

Sources of dispersion	Number of degrees of freedom (f)	Sums of squares (SS)	Mean squares (MS)	F exp	$F_{tab\,(0.05)}$	Hypothesis Ho
Factor A	4	1.101582	0.275396	331.8712	2.56	$a \neq 0$
Factor B	4	0.630669	0.157667	190.0003	2.56	$b \neq 0$
Factor C	4	1.077507	0.269377	324.618	2.56	$c \neq 0$
Factor D	4	0.979086	0.244772	294.9671	2.56	$d \neq 0$
Residue	8	0.004142	0.000518	6.2397	2.13	res $\neq 0$
Error inside cell	50	0.0041491	0.000083	–	–	–
Total amount	74	3.834478				

Using Duncan's rank test also helped identify the effect of the oil medium type on the response, and this series can be represented as follows: $d_1 > d_3 > d_5 > d_4 > d_2$. Thus, castor oil is the best option for the therapeutic and cosmetic cream being developed, while almond oil is the least desirable.

Based on the results obtained, the following set of excipients is recommended for the cream being developed: aerosil (a_3), sodium tetraborate (b_2), glycerin (c_4), and castor oil (d_1).

As is well known, the pH of cosmetic products intended for application to the skin should vary between 1.2 and 8.5. However, given that the proposed cream will be used to treat acne, i.e., will be applied primarily to oily skin, its pH should be slightly acidic to achieve the maximum therapeutic effect. Determining the pH of the therapeutic cosmetic cream revealed a value of 7.1, i.e., it is necessary to introduce an auxiliary component into the cream to shift the pH to a slightly acidic environment. The modern chemical industry has a wide range of pH regulators [27], but we decided to opt for citric acid, which, in addition to this function, is also a proven preservative and exhibits mild bleaching properties, which is very important for the treatment of post-acne.

The citric acid concentration was selected empirically. According to literature, citric acid content can reach up to 2%. The relationship between the cream's pH and citric acid concentration is shown in Fig. 1.

According to the data obtained, the optimal concentration of citric acid in the cream is 1%.

To improve the consumer properties of the therapeutic and cosmetic cream being developed, it was decided to include tea tree essential oil, which, in addition to acting as a fragrance, also exhibits anti-inflammatory properties.

Based on the studies conducted, the following composition of the medicinal and cosmetic anti-acne cream is proposed: dry extract "Fitoinflam" (containing at least 2.5% of the total flavonoids in terms of rutin) –

10.0; nicotinamide – 3.0; salicylic acid – 0.5; camphor – 1.0; aerosil – 3.0; sodium tetraborate – 1.0; glycerin – 6.0; castor oil – 15.0; citric acid – 1.0; tea tree essential oil – II gtt (0.06); purified water – up to 100.0.

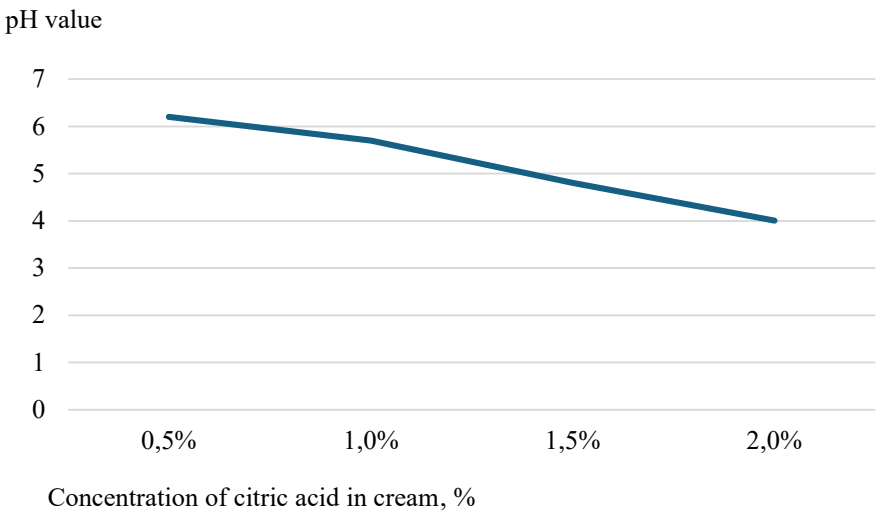

Fig. 1. Change in the pH value of a medicinal and cosmetic cream depending on the concentration of citric acid

Cream technology.

Preparation of the aqueous phase (phase A). Measure 1785 ml of purified water heated to 70–80°C into a "Planetary mixer", add 300 ml of dry "Fitoinflam" extract and 30 ml of sodium tetraborate, and stir until completely dissolved. Next, dissolve 90 ml of nicotinamide and 30 ml of citric acid in the resulting solution. Filter the resulting solution, add 180 ml of glycerin, and stir until smooth. Next, add 90 ml of aerosil and homogenize.

Preparation of the oil phase (phase B). Place 450.0 g of castor oil in a porcelain cup and heat in a water bath to 40°C. Add 15.0 g of salicylic acid and 30.0 g of camphor and stir until completely dissolved.

Add phase B gradually to phase A and homogenize for 5 minutes at 600 rpm. Thirty seconds before the end of homogenization, add 60 drops (1.79 g) of tea tree essential oil. Let sit for 1 hour, then package and label.

5. Discussion of research results

According to educational and scientific literature, creams are the optimal dosage form for skin application for both therapeutic and decorative purposes. The two-phase nature of creams improves the bioavailability of active ingredients and allows for the inclusion of medicinal and auxiliary components with varying physicochemical properties. While creams offer advantages as a dosage form, their required multi-component nature must be considered. Selecting the optimal composition of ingredients empirically is a time-consuming and costly task.

In this regard, a mathematical planning method was applied, the results of which revealed that all types of auxiliary components (structure-forming agents, emulsifiers, emollients, and oil medium) used in the model samples influenced the bioavailability of the developed medicinal and cosmetic cream. The obtained data are consistent with the results of numerous scientific studies conducted in this area [57, 58, 62, 87, 94]. The $F_{er.in.cell}$ value, calculated using the analysis of variance, indicates the presence of interaction between the factors studied. For example, a combination of Aerosil (a structure-forming agent) and sodium tetraborate (an emulsifier) demonstrated the best results in terms of active substance release (1.47% of total flavonoids). However, when using a structure-forming agent such as sodium carboxymethylcellulose, the best result was observed when using BTMS-50 as an emulsifier (1.21% of total flavonoids). This emulsifier was also optimal when using lignin, while when using PEG-400, it was only in third place (0.66% of total flavonoids).

The analysis of the planning matrix also showed a relationship between the type of oil medium and the emulsifier: the highest percentage of total flavonoid release (1.47%) was observed with a combination of castor oil and sodium tetraborate, followed by argan oil with BTMS-50 (0.92%), and in third place were olive oil and polysorbate-20 (0.59%).

Although the emollient was primarily used to improve the consumer properties of the finished product, it also impacted the biopharmaceutical properties of the cream. Glycerin, dimethicone, and cyclomethicone proved to be optimal emollients. The former demonstrated good results when used in combination with lignin (0.92% total flavonoids), aerosil (1.47% total flavonoids), and sodium carboxymethylcellulose (0.78% total flavonoids). Also, according to the matrix data, cyclomethicone incorporated with PEG-400 and dimethicone with bentonite provided flavonoid yields of 0.96% and 0.79%, respectively.

The constructed preference orders for each of the studied factors allowed us to evaluate the contribution of each excipient to the complete release of the active pharmaceutical ingredient in *in vitro* experiments.

Acne-prone skin is characterized by high sebum production, which is produced by the bacteria *Cutibacterium acnes*. The growth and proliferation of these microorganisms is slowed by changes in skin pH from neutral to slightly acidic [15, 39]. Furthermore, at pH below 5.0, the therapeutic activity of nicotinamide, a component of the cream, is reduced. Therefore, it was decided to adjust the pH of the developed cream.

The choice of citric acid as a pH adjuster was based not only on this function, but also on its preservative properties and ability to lighten post-acne pigmentation.

Practical significance of the research is that the developed therapeutic and cosmetic product will help expand the range of domestically produced acne treatment medications. A regulatory document for this cream will be developed and approved, and approval for its production and use in medical practice will be obtained from higher-level organizations. Furthermore, the re-

search and results obtained may be useful for young scientists in developing their own experimental methods.

Study limitations. The objectives of this study were fully met. All methods used are reproducible, and accompanying experiments can be conducted in an academic or research laboratory.

Prospects for further research. At subsequent stages of the research, it is advisable to study the rheological properties, storage conditions and shelf life of the developed medicinal and cosmetic cream.

6. Conclusions

Based on the results of planning an experiment using a 5 × 5 Greco-Latin square plan, a composition of a medicinal and cosmetic anti–acne cream was developed: dry extract "Fitoinflam" – 10.0, nicotinamide – 3.0, salicylic acid – 0.5, camphor – 1.0, aerosil – 3.0, sodium tetraborate – 1.0, glycerin – 6.0, castor oil – 15.0, citric acid – 1.0, tea tree essential oil – II gtt (0.06), purified water – up to 100.0. Based on the physicochemical properties of the active pharmacological substances and excipients, a technology for obtaining this cream was developed.

Conflict of interest

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this paper.

Funding

The study was performed without financial support.

Data availability

Data will be made available on reasonable request.

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies in creating the submitted work.

Authors' contributions

Ekut Karieva: Conception and design, Acquisition and data, Analysis and interpretation of data, Drafting of the manuscript, Critical revision of the manuscript for important intellectual content, Administrative, Technical or material support, Supervision; **Malika Baratova:** Acquisition and data, Analysis and interpretation of data, Drafting of the manuscript, Statistical analysis; **Mukhammadjon Matazimov:** Acquisition and data, Drafting of the manuscript, Statistical analysis; **Oleksandr Kukhtenko:** Analysis and interpretation of data, Critical revision of the manuscript for important intellectual content, Administrative, Technical or material support.

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Received 10.12.2025
Received in revised form 05.01.2026
Accepted 26.01.2026
Published 03.02.2026

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