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DEVELOPMENT OF THE CREAM COMPOSITION WITH GEORGIAN THERMAL WATER AND HERB EXTRACTS

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Thermal mineral waters contain a certain amount of mineral substances. They are widely used around the world to develop pharmaceuticals and cosmetics. Georgia is rich in thermal mineral water and plant resources, but Georgian mineral waters and medicinal plant raw materials have not been used together in any of the dermato-cosmetic products produced in Georgia.

***The aim of this work** is to develop the cream composition with mineral waters from Georgian hot springs and herb extracts.*

***Material and methods. T**he objects of the study were Georgian thermal waters and herb extracts. Thermal waters of various degrees of mineralization were used: Sulori (mineralization – 182.6 mg/L), Tskaltubo (mineralization – 0.8 g/L) and Borjomi (mineralization – 5–7 g/L). For the study, the main methods for developing dosage forms, experimental and technological studies, physical, physico-chemical, biopharmaceutical and other methods were used.*

***Research results.** Based on preliminary tests, preference was given to highly mineralized water "Borjomi" and its dilutions. This allowed us to develop a general strategy for creating a formula for creams containing thermal mineral water and herb extracts. The experiments were conducted with different dilutions of Borjomi. A model system suiTable for mineral waters of any degree of mineralization was developed. Preliminary tests determined the ratio of the main components, with the use of which ten versions of cream were developed, and their physicochemical properties, sterility and toxicological safety were studied.*

***Conclusions**. The critical analysis of thermal waters of Georgia was carried out and the more mineralized thermal water of Borjomi was used in the model systems. A methodological approach to the development of this type of medical and cosmetic creams for the use of selected thermal waters and plant raw materials was substantiated. The cream formulation was developed using Georgian thermal water and plant extracts. The conditions of their stability and safety were studied*

***Keywords**: Georgian hot springs, cream base, dermato-cosmetic cream, Borjomi, Sulori, herb extracts*

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1. Introduction

Georgia has huge natural thermal water sources and a long history of using them because of its geographic location. There are currently 250 natural thermal springs with water temperatures ranging from 30 to 108 degrees, as well as spring clusters. Consequently, the nation's geothermal potential is a valuable resource [1]. Natural mineral water may possess curing properties and favourably affect human health [2].

Recently, thermal mineral water has been widely used for the production of pharmaceuticals and cosmetics. It is possible to use thermal waters as an active and inactive ingredient in the treatment of a variety of skin ailments, and they may play a significant role in pharmaceutics and cosmetics due to the effect they have on the skin and the lack of adverse effects that have been recorded in numerous studies [3, 4]. The name thermal mineral water signifies mineral water with different degrees of mineralization and temperature over 20–25. Mineralization of waters is based on the dissolution of mineral substances in water in the water passage zone under the influence of relatively high temperatures and often high pressure.

Mineral waters, especially thermal waters, contain a certain amount of mineral substances necessary for the normal functioning of the human body and are noTable for particular activity [5]. This is what determines their effectiveness in pharmaceuticals and cosmetics for treating various skin diseases. Many thermal mineral waters in the world are already being used for the preparation of various lotions, creams, pastes and other products [6, 7]. Georgia is rich in thermal mineral waters, the composition of which is not inferior to the well-known waters in the world. There are more than 2,000 mineral and thermal waters of 730 different types registered on the territory of Georgia. The most famous of them are: Borjomi, Tskaltubo, Nabeglavi, Sairme, Lugela, Zvare, Tbilisi, Nunisi, Akhaldaba, Sulori, Dzuguri, hot sulfur spring Nokalakevi, sulfur pool in Dikhashkho, Lailashi, etc. All of them are used as Table waters or in balneotherapy (spa treatment) [8, 9]. Waters have a wide variety of major ions, distinct physical and chemical properties, physiologically active substances, and microelements. Up to 1200 of these springs are currently recognized. There are over 700 cases of mineral waters with distinct medical benefits that are given [10]. None of the waters described here have been used in the preparation of dermato-cosmetic dosage forms.

Georgia is also rich in medicinal plants. Plant raw materials used for medicinal and cosmetic purposes contain biologically active organic compounds: fatty and essential oils, flavonoids, carotenoids, alkaloids, various phenolic compounds, etc. In many countries of the world, they have been used in a combination with thermal waters to develop effective dosage forms [11, 12]. Thermal waters and medicinal plant raw materials of Georgia have not been used together in any of the products produced in Georgia.

The task of modern pharmaceutical technology is to develop effective pharmaceutical products containing natural, biologically active substances, which will display a wide range of action thanks to micro- and macroelements, various natural factors, multi-component composition, will be easily included in the metabolic processes of the body, will have a gentle effect, less toxicity and fewer side effects, and will be more affordable if produced from local raw materials. Hence the need for scientific research using Georgia's thermal mineral waters and medicinal-plant raw materials for the development of pharmaceutical products containing them.

In view of the above, **the aim of this study** is to develop the cream composition with mineral waters from Georgian hot springs and herb extracts, which can significantly contribute to the economic growth of the country.

2. Planning (methodology) of research

Step 1. Critical analysis of a number of thermal waters in Georgia and selection of the most suiTable for use.

Step 2. Development of a methodological approach to the study, since in the joint use of thermal waters and plant materials, various obstacles may arise, which must be taken into account in advance.

Step 3. Sample preparation: creating samples of creams and ensuring the rational conduct of experimental studies.

Step 4. Interpretation of the results and drawing conclusions.

3. Materials and methods

The research methodology is based on the main methods for the development of dosage forms – the strategy of experimental technological research. Physical, physico-chemical, biopharmaceutical research methods were used, and account was taken for the basic requirements of the GOST 33506-2015 Methods for determination and assessment of toxicological safety indicators [13]. Interpretation of findings was done and conclusions were made.

Georgian thermal waters, herb extracts, creams, and their emulsifying bases were the study's objects. In particular: Distilled monoglyceride (NMGK group of companies, *Nizhny Novgorod*, Russia), Gallic acid ethyl ether and Gallic acid methyl ether (HearNature, Xi'an, China), Olive oil (Aromatica, Ukraine), Shea butter (Ataman Kimya, Istanbul, Turkey), Stearin (Ataman Kimya, Istanbul, Turkey), Wax Emulsion (Ataman Kimya, Istanbul, Turkey), Cetyl palmitate (Ataman Kimya. Istanbul, Turkey), Carbomer 940 (Ataman Kimya, Istanbul, Turkey), Glycerin (JSC Halychpharm, Lviv, Ukraine), Grapeseed oil (Basso, Italy), Walnut oil (Golden kings, Ukraine), Dog rose oil (Mirrolla, Russia), Castor oil (Arterium, Kiiv, Ukraine), Apricot oil (Aromatica, Ukraine), Sea buckthorn oil (Neopharmi, Tbilisi, Georgia), Caffeine sodium benzoate (National Analytical Corporation, Mumbai, Maharashtra, India), Salicylic acid (Ataman Kimya Anonim Sirketi, Turkey), Purified sulfur (Hatkim Kimya Sanayi ve Dış Tic.A.Ş. Üsküdar/İstanbul, Turkey). At the Department of Stomatology and Pharmacy of the Akaki Tsereteli State University in the laboratory of pharmaceutical technology, glycerin extracts of green tea, sage herb, peppermint, calendula and motherwort herb were prepared by percolation method from raw materials collected in the Imereti region, near Kutaisi, Georgia), bentonite clay (mwvane-aftiaqi.com/ Askana Deposit, Ozurgeti region, Georgia), Borjomi water (IDS Borjomi beverages company, Georgia), Sulori and Tskaltubo waters (from deposit Sulori, Tskaltubo, Georgia).

We purchased glycerin extracts of medicinal plants from different companies:

1. Green tea glycerin extract: https://beurre.ua/cosme-phytamis-zelenyj-chaj.

2. Motherwort herb glycerin extract: https://www.amazon.com/Motherwort-Alcohol-FREE-Leonurus-Glycerite-Supplement/dp/B01BI98UAS?th=1 3. Calendula flower glycerin extract https://kazenina.ru/catalog/kalendula_ekstrakt/kalendula_tsvetok_vodno_glitserinovyy_ekstrakt/.

4. Sage herb glycerin extract Salvia officinalis Salvia Officinalis (sage) derived from the leaves and whole plant of sage. Contains 20 **%** extract dissolved in water and glycerin. https://makingcosmetics.com/BOT-SAGE-01.html?lang=en_US.

5. Peppermint leaf extract is produced from the leaves of peppermint dissolved in water and glycerin https://makingcosmetics.com/Z-BOT-PEPMINTLEAF-01.html?lang=en_US.

To achieve the set goal, it was necessary to solve the following objectives:

First, conducting a critical analysis of a number of thermal waters of Georgia and selecting the most suiTable ones for use. We singled out three of them: Borjomi with high mineralization, Tskaltubo with medium mineralization, and Sulori with low mineralization. It is worth noting that due to the processes occurring in nature, over period of time, some mineral waters undergo slight changes in chemical composition, so the critical review was preceded by a study to find out the chemical composition of mineral waters.

Borjomi. 9 production wells of Borjomi water are at a depth of 200 to 1500 meters. The natural temperature of thermal water is +38–40 °C. It is used as drinking mineral water. Mineralization is 5.0–7.5 g/L. It is close to the so-called hypertonic waters, it is worth noting that the chemical composition of Borjomi water in nature does not change over time; pH 5.5–7.5 [14].

Table 1

The chemical composition of Borjomi mineral water, mg/L

Ions	mg/L
HCO_3^-	3500—5000
SO_4^{2-}	<10
Cl^-	250—500
Ca^{2+}	20—150
Mg^{2+}	20—150
Na^+	1000—2000
K^+	15—45
F^-	80,0
Total mineralization	5500–7500 mg/L

Tskaltubo waters are low-radon waters. They are heated to +30–35 °C. Tskaltubo waters contain biologically active trace elements, such as: iodine, bromine, manganese, lithium, boron, zinc, strontium, and copper. They play a big role in the vital activity of the body. Tskaltubo waters belong to low-radon waters (1–2.7 nano curies/l or 7.5 trap units. 1 trap=3.64·10−10 curies/L). The average mineralization of the springs is 0.8 g/L [9, 15].

Table 2

The chemical composition of Tskaltubo mineral water

Chemical elements	Grams	mg equivalents	Equivalents %
Cations			
Na+K	0.0534	2.32	20.33
Mg	0.0341	2.84	24.89
Ca	0.1250	6.25	54.78
Fe	0.0011	–	–
Total amount	0.2136	11.41	100.00
Anions			
Cl	0.1012	2.85	24.98
SO_4	0.2237	4.66	40.84
HCO_3	0.2079	3.90	34.18
Total amount	0.5628	11.41	100.00
SiO_2	0.242	–	–
$Al_2O_3F_2O_3$	0.0029	–	–
Total mineralization	0.8	–	–
CO_2	0.088	–	–
A dry residue, 110 °C	0.764	–	–

Sulori spring is located on the historical territory of ancient Colchis, 30 km from Kutaisi. It is close to the so-called isotonic waters. Sulori subthermal and thermal waters (35–37 °C) are sulphide, sulfate-carbonate sodium waters (mineralization 300–400 mg/L) [16]. The mineral composition of water is presented in Table 3.

The second objective is to develop a methodological approach to the research, because in the joint use of thermal waters and plant raw materials, various obstacles may appear, which have been taken into account in advance.

One of these obstacles could be the chemical interaction between the minerals of thermal waters and organic substances in the plant extracts, forming a complex compound and a sTable sediment as a result of the reactions. This reaction most often occurs in solutions. In this case, it is advisable to include auxiliary substance in the dosage form, which will either inhibit or lead the reaction to the formation of soluble complex compounds with metal cations. In the first case it was more appropriate to use glycerin, while in the second case – EDTA.

Table 3

The chemical composition of Sulori mineral water

Sulori Spring No. 3	pH 9,9		
	mg	mg/equiv/%	mg/equiv/%
Cations			
Na	76	3.304	99.5181
K	0.1	0,0002	0.0602
Ni	0.013	0.0004	0.0133
Fe (total)	0.175	0.0092	0.2831
Cu	0.001	0.00003	0.0009
Pb	0.01	0.0003	0.009
Total amount	76.3	3.32	99.88
Anions			
Cl	10.64	0.3	6.39
HCO_3	42.7	0.7	14.92
CO_3	78	2.6	55.43
SO_4	16.5	0.34	7.25
NO_2	0.021	–	–
H_3SiO_4	71.7	0.75	15.99
H_2SiO_4	1.28	0.03	15.99
Total amount	274.74	4.69	99.98 %
Undissociated molecules			
H_4SiO_4	53.9	–	–
Mineralization	351.04		

Another main problem was the instability of the emulsion system, which is caused by the presence of mineral salts in thermal mineral waters. Based on our previous studies [17], in order to obtain sTable creams, we had to use either low-mineralized thermal waters or introduce a sufficient amount of gelling agent into the system. We took the second path.

4. Research results

The next objective was the development and study of formulations of creams with Georgian hot spring and herb extracts.

We have developed a model system to study the possibility of using Georgian thermal waters with different content of mineral substances: waters differing not only in the degree of mineralization, but also in the content of mineral components were used: low-mineralized Sulori, medium-mineralized Tskaltubo, and highly mineralized Borjomi.

Preference was given to highly mineralized Borjomi water, considering that this allowed us to create a general strategy for the development of formulation of thermal mineral waters and creams containing substances of plant origin. Experiments were conducted on its various dilutions.

Based on literary sources and experiment results, the active and inactive ingredients in the emulsifying base and cream are chosen. In the preliminary tests, we used a cream base containing distilled monoglycerides 6.6 %, glycerin 7.0 %, cetyl palmitate 3.5 %, emulsion wax 3.5 %, stearin 3.0 %, shea butter 3.5 %, olive oil 10.5 %, gallic acid methyl ether 1.5 %, gallic acid ethyl ether 1.5 %, Borjomi mineral water – up to 100.0 g [17, 18].

The stability of obtained creams was evaluated according to the existing requirements: the emulsion system is considered stable if, after centrifugation in test tubes, no more than 1 drop of aqueous phase or a layer of oily phase no more than 0.5 cm high is observed. Due to the different degrees of mineralization of thermal waters, the emulsion system may become unstable. To prevent this, we introduced the gelling agent into the system. The use of carbomer 940 guarantees emulsion and colloidal stability of the cream.

Experiments were conducted to determine stability of the emulsion system at different dilutions of Borjomi water (mineralization: 5.54 g/L; mineralization 4.83 g/L and mineralization 3.14 g/L) in the presence of gelling agent. These dilutions of thermal mineral water were used as the aqueous phase of the o/w type emulsion. Increasing the amount of gel-forming carbomer 940 to 2 % has already given us a stable system. We used this result in the course of the following experiments.

The second factor of compromising the stability of the emulsion system could be the replacement or addition of the components used in the development of pharmaceutical and cosmetic creams. One such option could be changing/adding components of the oil phase, adding extracts, other active pharmaceutical ingredients. At this time, the ratio of oil and thermal water would change, but the stability of the emulsion should not be compromised even when we used highly mineralized (5.54 g/L) water. Carbomer 940 showed better results among different emulsifying agents. Since we included various active pharmaceutical substances in the cream, we considered it necessary to increase the amount of Carbomer 940 by 3 % [17]. Carbomer is safe for the skin and can be used in products in the concentrations up to 50 % [19].

The list of the main components used in the development of the emulsifying bases and cream formulation with indication of concentration is presented in Table 4.

Table 5 shows 10 versions of the cream that we developed containing vegeTable fatty oils and plant extracts. Concentrations of their use are limited both by the sensory properties (especially for the products used in cosmetology) and by specific biological activity.

Many different substances can be used in this kind of dosage form. The Table shows the versions of the cream for different supposed problems and skin types, where salicylic acid, bentonite clay (Askane bentonite clay. Georgia), purified sulfur, caffeine sodium benzoate and so on are added to the cream. Possible incompatibilities of the ingredients have been studied: caffeine sodium benzoate may be incompatible with salicylic acid in liquid dosage forms, but in the composition of the cream, and even in small doses, cases of incompatibility have not been known.

Table 4

The main components used in the development of the cream formulation

No	List of components and weight % concentration respective to 100 g of cream
1	Cream base ingredients
1.1	Distilled monoglycerides 6.6
1.2	Gallic acid ethyl ether 1.5
1.3	Gallic acid methyl ether 1.5
1.4	Olive oil 10,5
1.5	Shea butter 3.5
1.6	Stearin 3.0
1.7	Emulsion wax 3.5
1.8	Cetyl palmitate 3.5
1.9	Carbomer 940–3.0
1.10	Glycerin 7.0
2	Oils and extracts
2.1	Grape-seed oil 2–5.0
2,2	Walnut oil 1–3.0
2.3	Dog-rose oil 1–3.0
2.4	Castor oil 2–5.0
2.5	Apricot oil 2–4.0
2.6	Sea buckthorn oil 1–3.0
3.1	Green tea glycerin extract 1–4.0
3.2	Sage herb glycerin extract 1–2.0
3.3	Peppermint glycerin extract 1–2.0
3.4	Calendula flower glycerin extract 1–2.0
3.5	Motherwort herb glycerin extract 1–5.0, etc.
4	Borjomi water up to 100.0 g

The fourth task was to study some qualities of the developed formulations. The ability of biologically active substances to diffuse from the cream samples into skin layers was studied by *in vitro* testing. For the case of our study, we have proceeded the method of working on Petri dish with a gelatinous mass/method of diffusion in agar gel: a hole was made in gelatinous or agar gel, which was filled with cream, the temperature of the experiment was 37.0–37.2 °C. The speed of movement of the colored zone was determined. The obtained data are presented in Table 6. As can be seen from the table, the colored zone moves quite quickly. This speed as well as the spot sizes prove that the pharmaceutical substances from the creams diffuse quite well in gelatinous and agar gel, which allows us to make a logical conclusion that they also will diffuse well in the skin layers.

Spreadability of cream was determined in accordance with a diameter of spreading 2 grams of cream. A sample of cream was placed between the two glass slides with dimensions of 10×10, and 100 g of weight was placed on the glass slide for 5 min to compress the sample to a uniform thickness. Then we measured the diameters of the resulting spots in millimeters. The obtained results are presented in Table 7. Conclusion: cream has good spreadability.

Creams may be used both as a dermato-cosmetic product and for wound cleansing. The osmotic activity of the cream versions was studied, and the results are presented in Table 8. Based on the obtained results, it can be said that the osmotic activity of the cream versions is at an appropriate level.

Table 5

Formulations of 10 versions of developed cream

No.	Components	% content of components in 100 grams of cream									
		1	2	3	4	5	6	7	8	9	10
1	Distilled monoglyceride	6.6	6.6	6.6	6.6	6.6	6.6	6.6	6.6	6.6	6.6
2	Gallic acid ethyl ether	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
3	Gallic acid methyl ether	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
4	Olive oil	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5
5	Shea butter	–	–	–	3.5	3.5	–	3.5	3.5	3.5	3.5
6	Stearin	3.0	3.0	3.0	3.0	3.0	3.0	–	3.0	3.0	3.0
7	Emulsion vax	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
8	Cetyl palmitate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
9	Carbomer 940	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
10	Glycerin	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0
11	Grape-seed oil	3.0	–	–	3.0	–	3.0	–	–	–	–
12	Walnut oil	5.0	–	–	5.0	3.0	–	–	3.0	3.0	3.0
13	Dog rose oil	–	5.0	–	3.0	–	–	5.0	–	–	–
14	Castor oil	–	5.0	–	–	–	–	–	–	–	–
15	Apricot oil	–	5.0	–	3.0	–	–	5.0	–	–	–
16	Sea buckthorn oil	–	–	3.0	–	5.0	5.0	5.0	5.0	–	5.0
17	Green tea glycerin. extract	3.0	3.0	3.0	–	3.0	–	4.0	3.0	3.0	3.0
18	Sage herb glycer. extract	1.0	1.0	1.0	–	–	2.0	2.0	–	–	–
19	Spearmint glycer. extract	–	–	1.0	1.0	–	2.0	–	–	–	–
20	Calendula glycer. extract	–	–	1.0	–	2.0	2.0	–	2.0	2.0	2.0
21	Motherwort herb glycer. extract	–	–	–	5.0	1.0	–	1.0	1.0	1.0	1.0
22	Bentonite clay (Askane)	–	–	–	–	–	–	–	–	1.5	1.5
23	Caffeine Na benzoate	–	–	–	–	–	–	–	–	–	1.5
24	Salicylic acid	–	–	–	–	–	–	–	–	–	0.7
25	Purified sulfur	–	–	–	–	–	–	–	–	–	0.5
26	Borjomi water 5.54 g/L	Up to 100.0									
	Quality of cream	Satisfactory									

Table 6

The speed of movement of the colored zone

Time, hr	The length of the spot displacement zone, cm									
	Spot number									
	1	2	3	4	5	6	7	8	6	7
2.0	0.29	0.25	0.20	0.30	0.20	0.27	0.24	0.20	0.18	0.19
4.0	0.55	0.52	0.44	0.59	0.46	0.55	0.51	0.42	0.40	0.41
6.0	0.83	0.78	0.67	0.79	0.69	0.78	0.72	0.66	0.73	0.72
9.0	1.39	1.30	1.02	1.46	1.1	1.42	1.35	0.92	0.90	0.90
12.0	1.44	1.4	1.13	1.46	1.12	1.43	1.38	1.10	1.05	1.05

Table 7

Spreadability test result

Name	Spot diameter, mm
Base spreadability	40.0
Cream version 1	52.6
Cream version 2	51.7
Cream version 3	48.2
Cream version 4	52.9
Cream version 5	52.2
Cream version 6	48.5
Cream version 7	53.1
Cream version 8	51.9
Cream version 9	50.0
Cream version 10	50.3

Note: The spot diameter is the arithmetic mean of three measurements

Table 8

Osmotic activity of creams, *%*, 12 hours later

Cream version	Osmotic activity, *%*
Cream version 1	125.0
Cream version 2	129.0
Cream version 3	130.0
Cream version 4	132.0
Cream version 5	130.0
Cream version 6	130.0
Cream version 7	135.0
Cream version 8	132.0
Cream version 9	135.3
Cream version 10	135.7

Note: The osmotic activity is the arithmetic mean of three measurements

As can be seen from the tables, the use of the base that we developed for cream allows us to obtain the versions of creams containing Borjomi water with a wide range of ingredients. They can be used for different skin types, including dry and sensitive skins.

Glycerin, glycerin extract of green tea leaves, caffeine 1.0–1.5 %, sulfur 0.4–0.7 %, salicylic acid 1.0–1.5 %, finely dispersed bentonite clay powder 1.0–1.5 % were introduced in cream, which, together with other pharmacological effects, reduce the amount of skin fat and make it possible to use cream for the treatment of problematic skin. It was the use of purified sulfur or finely dispersed bentonite clay that led to an increase in the amount of carbomer 940 in cream to 3 %.

We conducted centrifugation tests to determine the emulsion and colloidal stability of cream. Neither water nor fat phase were separated during testing. The final formulation was mainly developed using highly mineralized undiluted thermal water. Similar results were obtained when using other thermal waters of different mineralization in semi-solid dosage form.

However, it should be said that in order to achieve the colloidal and emulsion stability of cream in the new proportions of the above-mentioned substances, it will be necessary to study the correlation between Carbomer 940 and the amount of these substances in specific cases.

Studies were also conducted on the sterility/microbial stability [20] of the prepared dosage form: Number 3 sample of cream was made for the study. The studies were conducted in the microbiological laboratory of the Imereti Division of the National Center for Disease Control and Public Health of Georgia. Soybean broth and blood agar were used. The developed samples were introduced in the sterile culture media. Growth of microorganisms, predominantly bacteria, was not observed. Cream that we prepared was sterile.

In addition, in the learning-experimental laboratory of physiology of the Biology Department of Akaki Tsereteli State University, studies were conducted on 5 laboratory white rats for the purpose of evaluating the toxicological safety of the developed dosage form, which is stipulated by the standard [13]. In parallel, a control testing was conducted. The standard stipulates the determination and evaluation of the allergenic index – skin irritating effect on laboratory animals. According to the change in the functional state of the skin of the laboratory animal (erythematous reactions and/or swelling) after applying a specified amount of the test sample, a conclusion should be made on the presence and severity of the skin irritating effect of the test products.

We used rats weighing between 180 and 220 g. The requirements of the standard were met: the temperature in a sTable that housed the test animals was (20±2) °C; relative humidity range (50–65 %); artificial lighting with a following regime: 12 hours in light, then 12 hours in darkness; The feeding and water regimes of the laboratory rats were observed.

Table 9

Conclusion of the microbiological laboratory on the sterility of No. 3 cream

Date	Analysis number	Name of sample – cream Number 3	Used culture medium	The growth of bacteria	Result
1	2	3	4	5	6
29.06.2022	3	Cream prepared by Irma Kikvidze	Soybean broth and blood agar	No observed	Sterile

Five animals were shaved: the so-called “windows” of the dimensions 2×2 cm^2 were made on the skin of the sides.

The version 3 of cream that we prepared was applied to the “windows” by the open application method and distributed evenly without dilution. With the assumption that 1 square centimeter accounted for 0.02 g, it was accurately distributed on the surface of the “window” of the skin. The thickness of the rat’s skin was determined before the test and 24 hours and 48 hours after the start of the study – as accurately as possible. The other side of the same rat was used as a control. Distilled water in the amount of 0.02 ml/1 cm^2 was also evenly distributed on the control “window”. After 24 and 48 hours, the functional state of the skin was observed on the control and test areas: whether there was an erythematous reaction – a clear visual picture of redness, and the thickness of the skin fold was measured at the application site.

Observations revealed that the thickness of the skin folds did not increase during this time. The severity of the erythematous reaction was visually assessed according to the standard: no erythema (0 point). Experiments have shown the safety of developed dosage forms.

5. Discussion of research results

The thermal waters of Georgia have undergone a thorough study. Model system to investigate the viability of employing Georgian hot waters with various mineral compositions was created. Low-mineralized Sulori, medium-mineralized Tskaltubo, and highly mineralized Borjomi were used. The more mineralized thermal water of Borjomi was used in the model system. The obtained results can be used in the preparation of dosage forms from other thermal waters.

A methodological approach to the development of this type of medical and cosmetic creams for the use of selected thermal water and plant raw materials was substantiated. The cream formulation was developed using Georgian thermal water and plant extracts. When developing pharmaceutical and medical cosmetic products, the process of selecting inactive ingredients and their concentrations, in particular an emulsifier, is extremely important to ensure the creation of a stable final product. In the developed compositions, the best result was given by carbomer 940 at a concentration of 2–3 %, depending on the mineralization of thermal water. This emulsifier in this concentration provided colloidal and emulsion stability of the developed creams. The proposed model will be useful in developing a new semi-solid product creams for different qualitative and quantitative composition of the oil phase components to achieve the desired stability of the emulsion system. The model system will also allow the researcher to change both the oil phase and the variety of emulsifier components, changing their weight percentage in the emulsion. The model system will significantly reduce the number of technological experiments. The research results can be applied to highly mineralized thermal waters and their various dilutions, and any mineralization. Adding pharmaceutical substances and herbal extracts to the composition will not affect the stability of the system. However, it should be said that in order to achieve the colloidal and emulsion stability of cream in the new proportions of the above-mentioned substances, more research will be required to improve or deepen the results of studying the correlation between Carbomer 940 (or other gelling agent) and the amount of these substances in specific cases.

Study limitation. It is recommended to use spring water for research within a few days of collecting it. It is preferable to conduct experiments after comparing the mineral composition of water with available literature data because the mineral content of waters can occasionally alter over time [21].

Prospects for further research. Georgian hot springs are one of the most promising raw material to find dermato-cosmetic pharmaceuticals. The improvement of cream technology and in-depth biopharmaceutical research will be the main areas of future study. Future study might assess the efficacy of the developed dermato-cosmetic product using clinical trials and other tests, as well as develop other soft dosage forms based on Georgian hot springs.

6. Conclusions

1. A critical *analysis* of Georgia's thermal waters was carried out. Borjomi with high mineralization, Tskhaltubo with medium mineralization, and Sulori with low mineralization were singled out. Borjomi thermal water was chosen as the most mineralized for use in the model system for all thermal waters. Experiments were conducted using various dilutions.

2. When thermal waters, plant extracts and other active pharmaceutical ingredients are used together, various difficulties may arise, such as incompatibility of cream components and instability of the emulsion system. With the addition of excipients such as glycerin or EDTA and carbomer 940 to the formulations, we substantiated a *methodical approach* to the production of this type of dermato-cosmetic cream.

3. The emulsion base's composition was developed, and mass concentrations of the components were determined. Using the Georgian thermal water Borjomi, plant extracts, and other active ingredients, ten cream types for various skin and cosmetic problems were developed.

4. The conditions of stability and safety of the developed creams were studied. Studies have shown positive results: including emulsion and colloidal stability, the speed of movement of the colored zone of active ingredients (spreadability), osmotic activity, preliminary tests for sterility, evaluation of toxicological safety, etc.

5. Clinical studies and other testing can be used in future research to evaluate the effectiveness of the created dermato-cosmetic product.

Conflict of interests

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

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Data availability

Manuscript has no associated data.

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