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RESEARCH ARTICLE

Development of the composition and research of soft dosage forms with carbon dioxide extract from *Scabiosa ochroleuca* L.

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ABSTRACT:

The article presents the research results on the development of dosage forms with carbon dioxide extract from *pale yellow scabious* (*Scabiosa ochroleuca* L.) for topical use. The lipophilic and hydrophilic ointments bases under the conditional name "Scabiol" were taken as objects of research. Rheological studies were carried out using a rotary viscometer of the "Reotest-2" type (Germany) using a cell consisting of systems of coaxial cylinders (S/S1). The speed of rotation of the inner cylinder was regulated by changing the gap between the cylinders, as well as the speed of rotation, and the tangential shear stress was determined. The study of the structural and mechanical properties of the "Scabiol" ointments was carried out at temperatures of 25, 40 and 55 ^{o}C. The shear stress and dynamic viscosity of the ointments were measured. Based on the obtained results, graphs were constructed that characterize the changes in the logarithm of the effective viscosity from the gradient of the shear flow rate, and the dependence of the gradient of the shear flow rate on the shear stress. The results of rheological studies showed the absence of structural changes in the shear field with the destruction or appearance of new compounds; the thixotropic properties of lipophilic and hydrophilic «Scabiol» ointments bases were also established. As a result of the study of the antimicrobial and antifungal activity of dosage forms with carbon dioxide extract of pale yellow scabious, it was found that to some extent, ointments inhibit the growth of test cultures in vitro. High-intensity antimicrobial activity was shown by lipophilic ointment "Scabiol" against Staphylococcus aureus, and Escherichia coli.

KEYWORDS: Ointment, rheology, Dynamic viscosity, Shear stress, Hysteresis loop, Thixotropic properties, Biological activity.

INTRODUCTION:

In recent decades, preparations based on plant raw materials have become increasingly relevant. The basis of this direction is the advantages of drugs of natural origin in comparison with drugs containing chemically synthesized substances as the active principle. So, for the most part, herbal preparations are developed on the basis of extracts that contain not only the main but also other accompanying biologically active substances; respectively, a complex effect is exerted on the body[1-2]. It is also necessary to note the smaller spectrum of side effects, the low cost of plant raw materials and the possibility of combining them or synthetic drugs[3-5].

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Previously, we obtained a carbon dioxide extract from the herb *pale yellow scabious* (*Scabiosa ochroleuca* L.) and determined its component composition[2]. The main components of the carbon dioxide extract of *Scabiosa ochroleuca* L. were: a-santonin (21.8%), 1.8-cineol (14.9%), n-hexadecanoic acid (5.6%), campesterol (5.0), a - thujone (4.8%), as well as a component, presumably a steroid (7.3%). The carbon dioxide extract exhibits antiradical and cytotoxic activity[6-7]. We also studied the antimicrobial and antifungal activity of the above extract. According to the results of the study, the carbon dioxide extract of pale yellow scabious showed pronounced antimicrobial activity against *Staphylococcus aureus*, and moderate antimicrobial activity against strains of *Escherichia coli*, *Bacillus subtilis*, *Candida albicans*[8]. In the future, on the basis of this extract, we developed the composition of lipophilic and hydrophilic ointments bases under the conditional

name "Scabiol"[9-10].

Since the application of dosage forms is intended to be applied on the skin and mucous membranes, their rheological properties determine the ease of use, the severity of the therapeutic effect and affect such therapeutic and consumer properties of ointments such as the release of drugs from the ointment, packability and extrusion from tubes, convenience and ease of application. The smearing properties of ointments are a function of their consistency properties, which can be objectively characterized by the corresponding rheological parameters. In the light of modern concepts of physical and colloidal chemistry, ointments can be considered as structured dispersed systems. Comprehensive rheological studies are necessary for:

- Development of the optimal composition of soft drugs (evaluation of the effect of excipients on the plastic-viscous properties of systems);
- Development of production technology (behavior during mixing, dispersion, degassing);
- Transportation and packaging (behavior during pumping, filling into tubes);
- Evaluation of consumer properties (squeezing out of the tube, stability, spreadability, softness and tenderness of sensation on the skin, predestination of arbitrary flow out of the tube);
- System stability assessments (long-term storage stability, transport stability)[11]. The concept of "consistency" is one of the most important properties of gels, creams, and ointments belonging to the group of soft dosage forms. The consistency has a significant impact on numerous technological processes of production, and the main properties such as: squeezability from tubes, smearing on the problem area, which ultimately affects the therapeutic effect of the drug, etc.[12-13]. The viscosity of the material determines the quality of the final product and affects the nature of the technological process. Therefore, viscosity measurements can be carried out both on samples in the laboratory and directly during technological operations[14]. The term "thixotropy" means "sensitive to touch", and the thixotropic effect is usually understood as a relatively slow change-usually a decrease - in viscosity (or, more generally, any rheological properties) caused by the deformation of the medium and rest after the external load is removed. The difference between "non-Newtonian" and "thixotropic" behavior is the difference in the time scale: by definition, non-Newtonian behavior consists of an immediate change in viscosity as a function of the strain rate, while the viscosity of a thixotropic medium changes slowly over time[15, 16, 17].

MATERIALS AND METHODS:

The work was carried out on the basis of the School of Pharmacy and of the Department of Clinical Immunology, Allergology and Microbiology of the "Medical University of Karaganda» Non-commercial joint-stock company («MUK» NCJSC). Determination of rheological properties was carried out on the basis of the Institute of Chemistry and Physics of Polymers of the Academy of Sciences of the Republic of Uzbekistan.

Development of dosage forms for topical use with carbon dioxide extract of pale yellow scabious:

Development of the optimal composition of the hydrophilic ointment base "Scabiol":

Soft dosage forms (ointments) - a collective group of medicines for external use with a plastic-elastic-viscous medium of different consistency, which are represented by ointments, pastes, creams, gels and liniments. Ointments occupy a leading position among the preparations of the application effect on the tissues of the skin and mucosa[18].

For the development of the composition of the ointment, we decided to use clay minerals as a hydrophilic base, which are widely used in the technology of ointments. In our study on the choice of the optimal composition of the hydrophilic ointment base, the ability of the base to swell is important due to the fact that when using a hydrophilic ointment at the 1st phase of wound healing, clay minerals absorb the liquid contents of the wound field. We studied the ability of clay minerals to swell, for this we mixed clay minerals with water in a ratio of 1:2 to 1: 10 and observed for 24 hours.

Experimental:

Preparation of model samples:

Clay minerals were mixed with purified water and left to swell for 4 hours. The stabilized horse fat was mixed with tween-80, then glycerin was added and mixed. To this mixture, the "Solid" emulsifier (T-2), swollen with a part of the purified water, and the swollen clay minerals were added, mixed until a homogeneous mass was obtained using a mechanical mixer at a speed of 450-500 revolutions per minute. All the obtained model samples are homogeneous, of a soft consistency, the color corresponds to the used ingredients. The prepared models were left for storage under normal conditions. For select the optimal composition of the base for the ointment, we conducted studies of models for organoleptic properties and resistance to microbial damage, for elasticity, for colloidal stability, for thermal stability, and for resistance to drying. Studies on changes in organoleptic properties and microbial spoilage were carried out after a week of storage of the model compositions. The colloidal stability of the obtained bases was studied on a centrifuge according to the State

standard (SS) 7142-54 method. The centrifuge timer was set for 10 minutes at the appropriate rotation speeds. At the end of the time, the test tubes were removed and the contents were checked for delamination in sufficient light. For determine the thermal stability of the obtained model samples, we used the effects of low and high temperatures. On electronic scales, 5g (grams) of ointment base from each model were weighed, and they were placed in test tubes. Test tubes were installed:

1. In the drying cabinet and for 3 hours the temperature was raised to 100°C.
2. In the freezer at-14-12ºC for 48 hours.

Then the model samples of the ointment were checked for delamination. To establish the drying resistance, we determined the water loss using the following method: the model samples were placed in a single layer in Petri dish and left open for 48 hours and weighed every 6 hours, then the relative water loss was calculated as a percentage.

2.1.2 Development of the optimal composition of the lipophilic ointment «Scabiol:

For development of the optimal composition of the lipophilic ointment base "Scabiol" on the model samples of the ointment, we selected the components that provide the therapeutic effect and technological properties[19].

Carbon Dioxide extract of pale yellow scabious provides a therapeutic effect. Stabilized horse fat is the basis for the ointment, cocoa butter is a structure-forming component, lanolin and wax are plasticizers, and mint oil is a flavoring agent[20-21]. The model compositions of the lipophilic ointment base "Scabiol" are presented in (Table 1).

Table 1. Models of lipophilic ointment base "Scabiol"

S. No	Ingredients	Model samples, g						
		1	**2**	**3**	**4**	**5**	**6**	**7**
1	Carbon dioxide extract of *pale yellow scabious*	1.0	1.0	1.0	1.0	1.0	1.0	**1.0**
2	Cacao-butter	10.0	-	-		10.0		-
3	Lanolin	-	10.0 not molten	10.0	10.0	10.0	-	-
4	Wax	10.0		10,0	-	-	10.0	
5	Mint oil	2.0	2.0	2.0	0.2	2.0	2.0	2.0
6	Stabilized horse fat:lanolin, 6:4	-	-	-	-	-	-	up to 100.0
7	Stabilized horse fat	up to 100.0	up to 100.0	up to 100.0	up to 100.0	up to 100.0	up to 100.0	-

Preparation of model samples:

Preparation of models 1, 2, 3, 4, 5, 6: wax, cocoa butter and lanolin were melted sequentially, and then stabilized horse fat, mint oil and carbon dioxide extract were added to the alloy mixture and the mass was homogenized with a mechanical mixer at a rotation speed of 150-250rpm (the proper revolution per minute) for 2-3 minutes. For preparing the model 7, a pre-prepared ointment base of the following composition was prepared: stabilized horse fat: lanolin 6:4, for this purpose, lanolin was melted, stabilized horse fat was added, and mixed until a homogeneous mass was obtained. Next, we took the appropriate amount from this base; added mint oil and carbon dioxide extract to it, and homogenized it by the above method.

All model compositions were left for storage under normal conditions. For determining the colloidal stability of the model compositions, we conducted a study of all models in a centrifuge at different rotational speeds. The study of thermal stability was carried out with all model samples of lipophilic ointment base "Scabiol". The model samples were heated by raising the temperature up to 100 °C for 3 hours. The samples were frozen for 48 hours at a temperature of-14-12ºC.

Rheological properties:

The lipophilic and hydrophilic ointments bases under the conditional name "Scabiol" were taken as objects of research. The composition of lipophilic ointment base "Scabiol" (in grams)is as follows: carbon dioxide extract of *pale yellow scabious* -1.0, mint oil-2.0, stabilized horse fat: lanolin 6:4-up to 100.0 (Sample 1). The composition of the hydrophilic ointment base "Scabiol" (in grams) is as follows: carbon dioxide extract of *pale yellow scabious* -1.0, sorbent-15.0, stabilized horse fat-12.5, glycerin-4.0, twin-80-1.0, emulsifier "Solid" (T-2) - 1.0, mint oil-2.0, purified water-up to 100.0 (Sample 2)[9-10].

To remove the rheological parameters, a rotary viscometer of the "Reotest-2" type (Germany) was used with a cell consisting of systems of coaxial cylinders (S/S1). The speed of rotation of the inner cylinder was regulated by changing the gap between the cylinders, as well as the speed of rotation. Moreover, the tangential shear stress was determined. The study of the structural and mechanical properties of «Scabiol» ointments was carried out at temperatures of 25, 40 and 55ºC. The shear stress (τ) was calculated using the formula:

$\tau = Z * \alpha$ ----------(1)

Where,

τ - shear stress, Pa;

Z - cylinder constant equal to 5.59 Pa;

α - readings of the measuring device.

The dynamic viscosity was calculated by the formula:

$$\eta = \frac{\tau}{\gamma} \quad \text{----------(2)}$$

Where,

η - dynamic viscosity, Pa*s;

τ - shear stress, Pa;

γ - the gradient of the shear flow velocity, s^{-1}.

Biological activity:

Testing of antibacterial and antifungal activity was carried out by diffusion into agar with test cultures: *Staphylococcus aureus; Bacillus subtilis; Escherichia coli; Candida albicans*[22-23]. The concentrations of the tested drugs were 1mcg (microgram) for the antibacterial activity and 1mcg for the antifungal activity. The concentration of the comparison drugs was 1mg (milligrams). Dilution was performed at the rate of 1mg of the substance per 1ml of solvent. The crops were sown by the lawn culture method on nutrient media. Then the Petri dishes were incubated for a day at 37°C, for mushrooms at 28°C. The antimicrobial activity of the samples was evaluated by the diameter of the growth delay zones of the test strains (mm). Zone diameters less than 10mm (millimeter) and continuous growth in the cup were evaluated as the absence of antimicrobial activity, 10-15mm - low intensity activity, 15-20mm - moderate intensity activity, over 20mm - high intensity activity. Each sample was tested in three parallel experiments. Statistical processing was carried out using parametric statistics with the calculation of the arithmetic mean and standard error.

RESULTS AND DISCUSSION:

Development of dosage forms for topical use with carbon dioxide extract of pale yellow scabious

Development of the optimal composition of the hydrophilic ointment base "Scabiol".

The results of the study of the ability of clay minerals to swell are presented in (Table 2).

Based on the results of the study, we selected bentonite and sorbexin for further research.

Table 2. The results of the study of the ability of clay minerals to swell

No.	Clay minerals	Amount of mineral in g.	Amount of absorbed water in ml (milliliter)	Swelling time in hours	Degree of swelling
1	Bentonite	1,0	10,0	24	10 times
2	Sorbexin	1,0	10,0	24	10 times
3	Egyptian clay	1,0	2,0	4	2 times
4	Smektit	1,0	2,0	4	2 times

Next, we compiled 10 models of combined bases with different quantitative ratios of ingredients (Table 3).

The components included in the composition of the ointment models provide an optimal therapeutic effect and technological properties. Carbon dioxide extract of pale-yellow scabious provides a therapeutic effect. Bentonite and sorbexin are introduced to ointments on a hydrophilic basis due to their ability to swell. We included the stabilized horse fat in order to increase the resistance to drying and taking into account its ability to impart elasticity, flexibility and softening properties of the ointment. Glycerin retains moisture in the base. The inclusion of stabilized horse fat in the base determines the heterogeneity of the base, that is, the formation of an oil-type emulsion in water and the need for the introduction of an emulsifier.

Table 3. Models of hydrophilic ointmen base «Scabiol»

Ingredients	Model samples									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Carbon dioxide extract of pale yellow scabious, g	0.5	0.5	**0.5**	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Sorbexin, g	20.0	21.0	**15.0**	23.0	24.0	-	-	-	-	-
Bentonite, g	-	-	-	-	-	20.0	21.0	22.0	23.0	24.0
Stabilized horse fat, g	7.5	7.5	**12.5**	10.0	10.0	2.5	5.0	7.5	10.0	2.5
Glycerin, g	4.0	4.0	**4.0**	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Twin-80, g	1.0	1.0	**1.0**	-	1.0	1.0	1.0	1.0	-	1.0
"Solid" emulsifier (T-2), g	1.0	-	**1.0**	1.0	-	1.0	-	1.0	1.0	-
Mint oil, ml	2.0	2.0	**2.0**	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Purified water, ml	up to 100.0	up to 100.0	up to **100.0**	up to 100.0	up to 100.0	up to 100.0	up to 100.0	up to 100.0	up to 100.0	up to 100.0

The emulsifying ability of clay minerals does not provide stable emulsions, after one month of storage; they delaminate, so in order to increase the colloidal stability of the emulsion, we introduced twin-80 and Solid T-2 emulsifier into the model compositions of ointments. We used peppermint oil as a flavoring agent. Purified water was used as a formative component. When observing changes in the external features of the

model compositions, we did not find any changes in their color, smell, or mass stratification. On the surface of none of the model compositions, we did not find the appearance of mold and an unpleasant smell, which confirms the absence of microbial spoilage. The model compositions were easily applied to a soft surface. At the same time, the model compositions: 1, 2, 3, 4, 5 on the basis of sorbexin, a layer of sufficient thickness was formed, showed good elastic properties, maintaining these properties for a day, no cracks appeared on the surface of the smeared layer. Model compositions: 6, 7, 8, 9, 10 when lightly applied to a soft surface, a thin layer was formed, dried quickly, and cracks appeared on the surface of the layer of models. We decided to leave all the model samples for further research. The results of the study of model samples for colloidal stability are presented in (Table 4).

Table 4. Colloidal stability of models of hydrophilic ointment base "Scabiol"

Model samples	Centrifugation time, min	The level of liquid layers on the surface of the ointment, mm (millimeter)			
		Speed of rotation, rpm			
		1000	2000	3000	3500
1	10	-	-	1	1
2	10	-	-	2	2
3	10	-	-	-	-
4	10	-	-	0.5	0.5
5	10	-	-	0.5	0.5
6	10	2	6+2	12+2	13+2
7	10	4	7+1	12+2	14+2
8	10	5	5+3	11+2	11+2
9	10	-	2	3	3
10	10	2	5+1	9+1	13+2

According to the results of the study (Table 4), models 6, 7, 8, 10 showed the lowest colloidal stability. At a speed of 1000rpm, water layers of different thickness were found on the surface of the ointment only of these models, and at a speed of rotation from 2000 to 3500 rpm, water and oil layers were formed, while with an increase in the speed of rotation, the thickness of the layers also increased. Low colloidal stability was characteristic of the model 9. In models 1, 2, 4, 5, at 3000 and 3500rpm, there were small layers. Model 3 showed the highest colloidal stability. We decided to conduct further research with all the model samples.

When determining the thermal stability of the obtained model samples, both in the first and second experiments, models 1, 2, 3, 4, 5 remained unchanged, and on the surface of 6, 7, 8, 9, 10 models, when exposed to high temperatures, liquid layers with a thickness of 2-3mm were formed, when frozen, the model compositions had an uneven structure, with characteristic patterns of different shades of color. We decided not to take model samples 6, 7, 8, 9, 10 for further research, due to the indicators of low stability. The results of the study of model samples for drying are presented in (Table 5). As the results of the study showed, model 4.5 is the least resistant to drying, the average values for water loss are characteristic of models 1.2; model 3 is the most resistant to drying.

Thus, as a result of research on the development of the optimal composition of the hydrophilic ointment base "Scabiol", we selected model 3 (Table 3).

Table 5. Resistance of model compositions to drying

Model samples	Relative water loss, % (percentage) after … hours							
	6 hours	12 hours	18 hours	24 hours	30 hours	36 hours	42 hours	48 hours
1	1,0	4,5	9,1	14,2	20,9	31,7	42,7	55,0
2	1,7	3,0	11,1	17,8	25,2	36,8	46,9	61, 4
3	0,5	1,5	4,5	9,0	11,0	15,0	18,0	25,0
4	2,4	5,8	15,3	23,9	30,6	47,2	56,8	72,5
5	3,3	9,1	18,4	29,0	41,7	52,9	64,8	81,3

Development of the optimal composition of the lipophilic ointment «Scabiol».

All lipophilic-based model formulations showed no changes after 5 days. The results of the study of the colloid stability of the models of the lipophilic ointment base «Scabiol» are presented in Table 6.

According to the results of the study, at a rotation speed of 1000rpm, the liquid layer appeared only in model 6-0.6 mm, the lowest colloidal stability at a rotation speed of 2000rpm was shown by models 3, 4: the thickness of the liquid layer was 25mm and 10mm, respectively, in model 2 a layer with a thickness of 3mm was formed, in models 1 and 6 a liquid layer with a thickness of 2 mm was formed, models 5 and 7 remained unchanged.

Table 6. Colloidal stability of models of lipophilic ointment base «Scabiol»

Model samples	Time centrifugation, min	Liquid layer thickness, mm		
		Rotation speed, rpm		
		1000	2000	3000
1	10	-	2	25
2	10	-	3	6
3	10	-	25	30
4	10	-	10	15
5	10	-	-	-
6	10	0,6	2	20
7	10	-	-	-

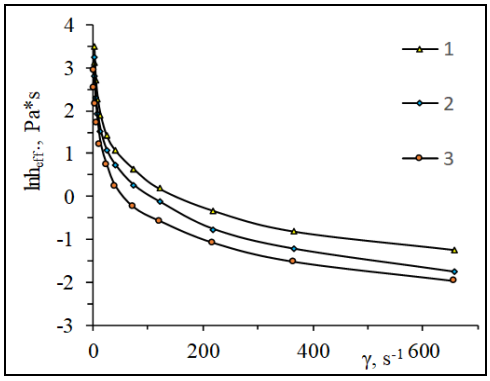
At a rotation speed of 3000rpm in models 1, 2, 3, 4, 6, a liquid layer with a thickness of 6 to 30mm was formed. We found the highest colloidal stability in models 5 and 7, in which no liquid layer was formed at all.

The study of thermal stability showed that when the model samples were heated, raising the temperature to 100°C for 3 hours, models 1, 2, 7 remained unchanged, and a liquid layer with a thickness of 2-3mm appeared on the surface of models 3, 4, 6. Model 5 from 25°C gradually assumed a liquid state and by 100°C completely melted into a mobile liquid. Model 5 did not restore the soft structure of the ointment during the day. When frozen for 48 hours at a temperature of-14-12°C, all models did not delaminate, they retained their colloidal structure. Thus, as a result of the tests, the model 7 was not subjected to any changes, so we selected the model 7 as the optimal composition of the lipophilic ointment base "Scabiol" (Table 1).

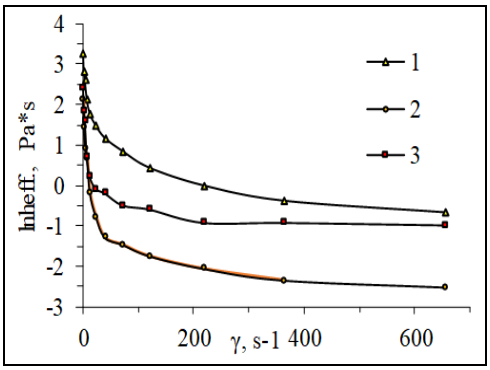
Rheological properties:

Based on the obtained results, graphs were constructed that characterize the changes in the logarithm of the effective viscosity ($\ln\eta_{eff.}$) from the gradient of the shear flow velocity (γ). Figures 1 show graphs of the dependence of the logarithm of the effective viscosity ($\ln\eta_{eff.}$) on the gradient of the shear flow velocity (γ) at different temperatures (figure 1).

From the data in Figures 1, we observe that with an increase in the gradient of the shear flow rate, namely, the deformation rate, a gradual decrease in the viscosity of the test ointment is observed. At the same time, the temperature of the experiment has a great influence on the decrease in viscosity, that is, the increase in temperature shifts the graphs to the region of small values of viscosities. The sharpest decrease in the viscosity of the ointment under study under all three temperature conditions occurred up to a gradient of the shear flow rate equal to γ=200 s^{-1} (Sample 1) and γ=150 s^{-1} (Sample 2), then the process slowed down, i.e. the systems were transitioning to an almost stable fluid state. The obtained data confirms the presence of structure formation in the studied ointment samples, and also allows us to assume that the samples as a whole do not undergo structural changes in the shear field, strong intra-system rearrangements with the formation of new compounds or destruction during the flow in these temperature regions. Figures 2 show graphs of the dynamic viscosity versus temperature. As can be seen from Figures 2, the graphs show an inversely proportional dependence of the dynamic viscosity on temperature, that is, they characterize a decrease in viscosity with an increase in temperature, and this shows an increase in fluidity.

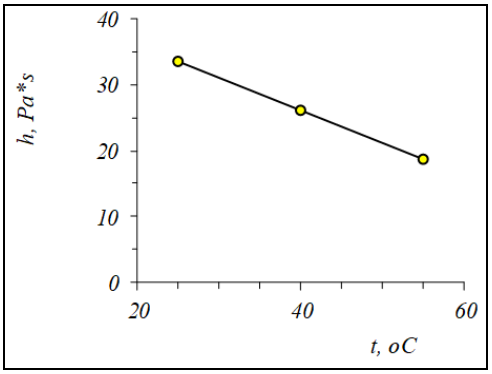


Sample 1

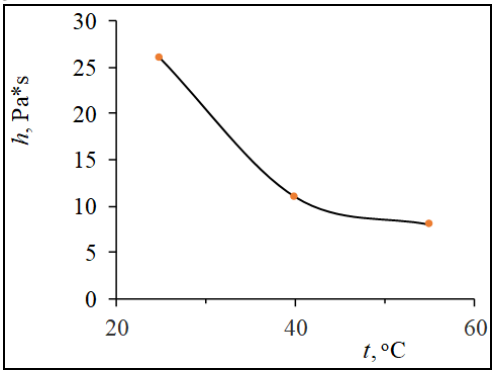


Sample 2

Figure 1. Dependence of the logarithm of the effective viscosity ($\ln\eta_{eff.}$) from the gradient of the shear flow velocity (γ) at 25°C (1), 40°C (2); 55°C (3) for the ointment of Sample 1 and Sample 2



Sample 1



Sample 2

Figure 2. Dependence of the dynamic viscosity (η) on the temperature (t) for the ointment of Sample 1 and Sample 2

The graphs 3 for calculating the activation energy of the viscous flow are constructed. The value of the activation energy of the viscous flow was found with the calculation based on the Eyring-Frenkel formula:

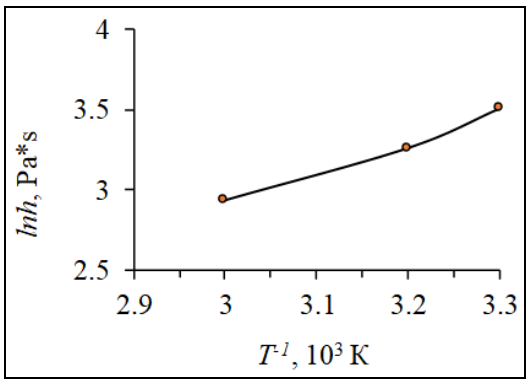
$$ln\eta = lnA + (E_a/R)*(1/T) \quad (3)$$

Where, A is the coefficient;
R =8.31 – universal gas constant;
Ea - activation energy of the viscous flow.
The calculation results for Sample 1 showed that the value of Ea = 16.1 kJ/mol.
$E_a/R = (ln\eta_1 – ln\eta_2)/[(1/T)_1 – (1/T)_2] = (3.51 – 2,93)/(3,3 – 3,0)*10^{-3} = 1,93*10^3$
$E_a = 1,93*10^3$ R = $1.93*10^3$ * 8,31 = $16,1*10^3$ J/mol = 16,1 kJ/mol
The calculation results for Sample 2 showed that the value of E_a = 31,6 kJ/mol.
$E_a/R = (ln\eta_1 – ln\eta_2)/[(1/T)_1 – (1/T)_2] = (3,26 – 2,12)/(3,3 – 3,0)*10^{-3} = 3,8*10^3$
$E_a = 3.8*10^3$ R = $3.8*10^3$ * 8,31 = $31,6*10^3$ J/mol = 31,6 kJ/mol.
Thus, the value of the activation energy of the viscous flow is determined for Sample 1 - 16.1 kJ/mol, for Sample 2 - 31.6 kJ/mol. The energy of hydrogen bonds Ea = 3-50 kJ/mol.

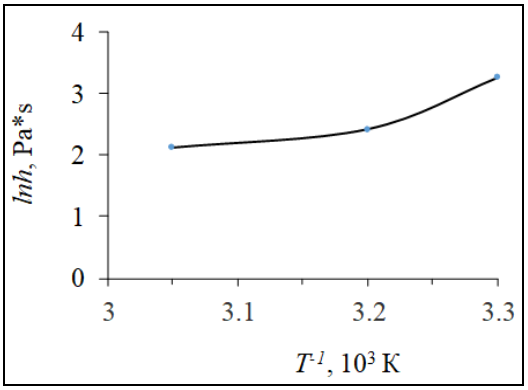
The parameters of Ea in all models are actually equal to ΔG - the Gibbs free energy, which characterizes the interaction energies of the system components when they are mixed relative to each other in the shear flow.

The value of the activation energy of the viscous flow is positive, which indicates the need to supply additional energy (mechanical or thermal) equal to the activation energy for the flow of samples.

It is found that with increasing temperature, the dynamic viscosity decreases, which means an increase in fluidity. The decrease in the activation energy parameter showed an ordered structure of the organization of components during the flow.



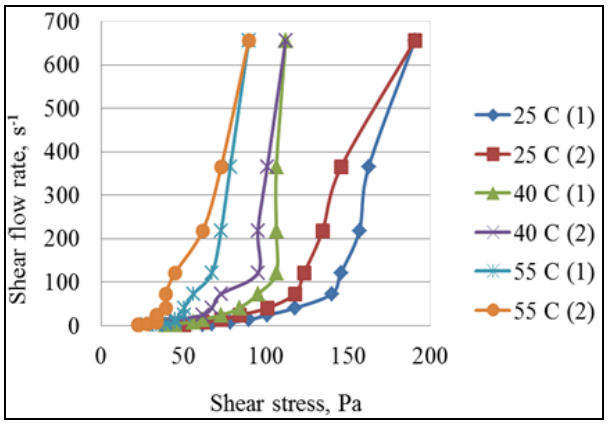
Sample 1



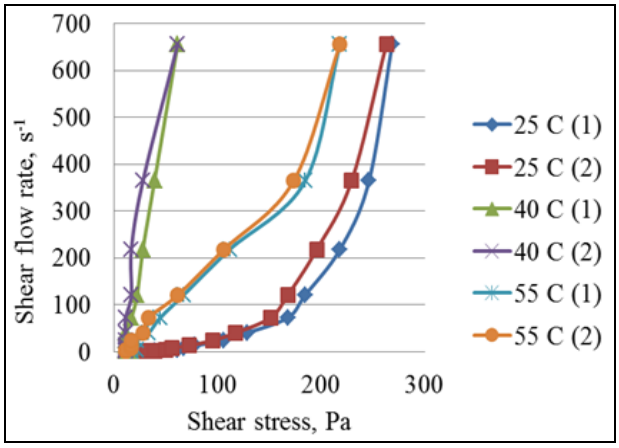
Sample 2

Figure 3. Dependence of the logarithm of the dynamic viscosity (*lnη*) on the temperature (*t*) for the Sample 1 and Sample 2

Figures 4 show graphs for estimating the hysteresis effects that occur during forward and reverse changes in the velocity gradient, depending on the shear stress. In the graphs, the descending curves together with the ascending curves form hysteresis loops, which confirm the thixotropy of the studied systems at different temperatures.



Sample 1



Sample 2

Figure 4. Hysteresis effects as a function of the velocity gradient (γ) on the shear stress (τ) of the shear flow for Sample 1 and Sample 2

The presence of thixotropic properties in the studied objects is characterized by good smearing and the ability to extrude from the tubes. This behavior of the thixotropic system is commonly called hysteresis, and the rheogram reflecting these processes is called a "hysteresis loop" - a graphical proof of the presence of the thixotropy phenomenon for the objects under study[24-25]. The width of the hysteresis loops can serve as a relative estimate of the structure-forming processes in dispersed systems. Comparing the hysteresis loops for the same systems at different temperatures, you can see that their character is the same, but the width is different. At low temperatures, the loops are wider; at high temperatures, they are narrower. This fact allows us to conclude that the processes of structure formation differ at high and low temperatures. The hysteresis loops confirm the absence of any significant changes in the samples during the flow in the shear field at different temperatures. The shift of the hysteresis graphs to the region of small values of the velocity and shear stress gradients is caused by a decrease in the viscosity of the samples with increasing temperature.

Biological activity:

The results of the detected growth retardation on the media are shown in Table 7. As a result of the study of the antimicrobial and antifungal activity of dosage forms with carbon dioxide extract of pale yellow scabious, it was found that ointments to some extent inhibit the growth of test cultures *in vitro*. High intensity antimicrobial activity was shown by lipophilic ointment base "Scabiol" against *Staphylococcus aureus, Escherichia coli.*

Table 7. Antimicrobial and antifungal activity of topical dosage forms " Scabiol»

Research objects	Strains of microorganisms			
	Staphylococcus aureus	***Bacillus subtilis***	***Escherichia coli***	***Candida albicans***
Hydrophilic ointment base "Scabiol"	16±1.0	18±1.0	21±1.0	16±1.0
Lipophilic ointment base "Scabiol "	25±1.0	18±1.0	23±1.0	16±1.0
Benzylpenicillin sodium salt	17±1.0	15±1.0	12±1.0	-
Nystatin	-	-	-	22±1.0
Ethanol 96%	9±1.0	9±1.0	9±1.0	8±1.0

CONCLUSION:

Thus, the studied samples of Scabiol ointments do not undergo strong structural changes in the shear field, that is, there are no intra-system rearrangements with destruction or with the formation of new compounds. The thixotropic properties of on lipophilic and hydrophilic «Scabiol» ointments bases have been established, which characterize good smearing and the ability to squeeze out of tubes. The pronounced antimicrobial activity of the developed «Scabiol» ointments for topical use provides the basis for further tests included in the drug development cycle.

CONFLICT OF INTEREST:

The authors have no conflicts of interest regarding this investigation.

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