

RESEARCH ARTICLE

Development and Rheological studies of gels with Essential oil of Chamomile (*Chamomillae recutita* L.)

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ABSTRACT:

The article presents the results of research on the development of dosage forms with essential oil of chamomile (*Chamomillae recutita* L.) for dental use. The object of study was hydrophilic gel base under the code name "Chamazulenogelum". **Materials and Methods.** Rheological studies were carried out on a rotational viscometer Visco Star Plus (Fungilab, Spain). The study of the structural and mechanical properties of the "Chamazulenogelum" ointment was carried out at temperatures of 25, 40, 55 and 70°C. The shear stress and dynamic viscosity of the gels were measured. Based on the obtained results, graphs are constructed that characterize the change in the logarithm of the effective viscosity on the shear flow rate gradient and the dependence of the shear flow rate gradient on the shear stress. The results of rheological studies showed the absence of structural changes in the shear field with destruction or the appearance of new compounds; the thixotropic properties of the hydrophilic gel bases "Chamazulenogelum" were also established. **Results and Discussion.** As a result of studying the antimicrobial and antifungal activity of dosage forms with chamomile essential oil, it was found that the gels inhibit the growth of test cultures in vitro to some extent. High-intensity antimicrobial activity was shown by the hydrophilic gel "Chamazulenogelum" against *Staphylococcus aureus* and *Escherichia coli*. **Conclusion:** The investigated samples of "Chamazulenogelum" gels do not undergo strong structural changes in the shear field, that is, there are no intrasystem rearrangements with destruction or with the formation of new compounds. The thixotropic properties on the hydrophilic gel base "Chamazulenogelum" have been established, which characterize good smearability and the ability to extrude from the tube. The pronounced antimicrobial activity of the developed gels "Chamazulenogelum" for topical use provides a basis for further tests included in the drug development cycle.

KEYWORDS: *Chamomillae recutita*, rheology, structural and mechanical properties, dynamic viscosity, shear stress, thixotropic properties, biological activity.

INTRODUCTION:

The modern market of preparations for external use in the world is represented very widely. These funds, according to the ingredients included in the composition, can be divided into two large classes: synthetic and vegetable origin.

Despite significant advances in the field of creating synthetic drugs of a new generation, in the last decade there has been an ever-increasing interest in herbal remedies.

In Kazakhstan, its own pharmaceutical industry is extremely poorly developed, and is able to meet the needs of the Republic in the amount of no more than 4-8%. A significant proportion of medicines is purchased in near and far abroad¹⁻⁴.

At present, the pharmaceutical markets do not have enough anti-inflammatory and wound-healing herbal remedies that are comparable in strength to synthetic

drugs and, at the same time, are economically accessible to the general population⁵.

Studies conducted in Kazakhstan have shown that a promising, industrially significant domestic raw material for the isolation of biologically active compounds such as chamazulene, 1,8 - cineole from essential oil can be a plant - chamomile (*Chamomillae recutita* L.) from the *Asteraceae* family. The essential oil of this plant has anti-inflammatory, antimicrobial, fungicidal and wound healing effects⁶⁻⁹.

Given the above, the current problem today is to obtain new phytochemical substances based on essential oils and carbon dioxide extracts that have anti-inflammatory and wound healing effects and to develop the technology of soft dosage forms¹⁰⁻¹¹.

The rational combination of herbal preparations with various excipients, as well as the use of the optimal technological scheme for the manufacture of soft dosage forms for external use, significantly expands the therapeutic possibilities of herbal preparations for the treatment and prevention of dermatological and gynecological diseases.

As dosage forms, phytopreparations for external use are represented by oils, drops, ointments, solutions, films and suppositories. The most widely represented dosage form among them are ointments (58%), followed by suppositories (15%), oils account for about 10%, solutions, drops and films are in approximately equal proportions - 6% and 4%, respectively. The "Miscellaneous" group includes such dosage forms as sticks and patches, accounting for about 3%.

Of interest is the arsenal of phytopreparations for external use as wound healing and anti-inflammatory agents in the form of ointments, oils, tinctures, solutions and various phytocompositions currently used for medical practice.

MATERIALS AND METHODS:

Raw materials: The object of the study is the above-ground parts of *Chamomillae recutita* L. collected on the territory of the Turkestan region of the Republic of Kazakhstan.

Study design:

The work was performed on the basis of the School of Pharmacy, the Department of Clinical Immunology, Allergology and Microbiology of the Non-Commercial Joint Stock Company "Medical University of Karaganda" (NCJSC MUK).

Development of the composition of gels with essential oil of *Chamomillae recutita* L.

To develop the optimal composition of the ointment, several gel compositions were developed, which are investigated for biological activity and pharmaceutical accessibility.

The physico-chemical and structural-mechanical indicators of the foundations used, melting temperature, acid, peroxide, iodine numbers are determined¹².

As auxiliary ingredients, we composition of the compositions of the ointment include substances such as sodium carboxymethyl cellulose, glycerin, dimexide, emulsifier Twin-80, PEO-400, PEO-1500 and purified water.

Study of the antimicrobial activity of gels with essential oil of *Chamomillae recutita* L.

The objects of study were gel samples consisting of the following bases: sample No. 1 (essential oil of chamomile 1.0, dimexide 10.0; polyethylene glycol (PEG) 1500 19.0; polyethylene glycol 400 to 100.0), sample No. 2 (EMRA 1.0, Tween 80 2.0; sodium carboxymethylcellulose 5.8; purified water 81.48; glycerin 0.7), sample No. 3 (EMRA 3.0, polyethylene glycol 1500 27.0; (PEG) 400 to 100.0). To obtain essential oils, the dried aerial parts of the plant were separately subjected to hydrodistillation (Ph. Eur. IV, 2008) for 3 hours on a Clevenger apparatus. The resulting essential oils were stored at +4°C in the dark until use.

Gel samples were tested for antimicrobial activity. The study of the antimicrobial activity of the above samples was carried out by diffusion into agar.

Museum strains of gram-positive bacteria of the species *Staphylococcus aureus* 6538, *Bacillus subtilis* 6633 were taken as test cultures; Gram-negative bacteria *Escherichia coli* 8739, *Pseudomonas aeruginosa* ATCC 9027, and yeast-like fungi *Candida albicans* 10231. As reference drugs, the ointment form of drugs was used: Levosin (Levosin®) for bacteria and nystatin for the culture of *C. albicans* fungi. Samples of ointment bases were used as control.

The cultures were grown on a liquid medium (pH 7.3±0.2) at a temperature of 30 to 35°C for 18-20 hours. The cultures were diluted 1:1000 in a sterile 0.9% isotonic sodium chloride solution, 1 ml was added to cups with the appropriate elective nutrient media for the test strains under study.

After drying, 6 mm wells were formed on the surface of the agar, into which the test samples of the ointment, reference preparations, and control were added. The inoculations were incubated at 37⁰C, the results were recorded after 24hours.

The study of the rheological properties of the gel with the essential oil of *Chamomillae recutita L.*

The thixotropy of the substrate under study was established by the method of continuous, increasing destruction of the structure, as a function of shear stress. The determination was carried out in accordance with the provisions of the State Pharmacopoeia of the Republic of Kazakhstan using a rotational viscometer Visco Star plus L. The kinetics of structure formation in the studied bases was studied in the range of strain rates from low to high (0.5-200rpm) and from high to low at temperatures of 25, 40, 55 and 70⁰C. As the temperature increased, the sample was kept in an electric dry-air thermostat TS-80 M for 24 hours.

RESULTS AND DISCUSSION:

Selection of the optimal composition of the hydrophilic gel base:

The choice of bases for the preparation of an ointment is an important problem, since it was necessary to use both lipophilic and hydrophilic bases that do not have

allergic, irritating properties and release the drug from the gel form well¹³⁻¹⁴.

In a study on the choice of the optimal composition of the hydrophilic gel base, the ability of the base to swell is important due to the fact that when using a hydrophilic ointment in the 1st phase of wound healing, the wound field absorbs liquid contents. The ability of hydrophilic bases to swell was studied; for this, the bases were mixed with water in a ratio of 1:2 to 1:10 and observed during the day.

The selected bases for all the studied indicators met the requirements of the SP RK for the bases for the preparation of ointments.

When studying the release of the active substance chamazulene by direct diffusion into agar, hydrophilic bases were the most effective. Therefore, in the process of research work, compositional models of ointments on hydrophilic bases were compiled.

For an objective assessment, 9 compositions of gels with different contents of the active substance were prepared. The concentration of biologically active substances in the gels varied from 0.5 to 5% (Table 1).

Table 1: Prescriptions of the investigated gels with essential oil of *Chamomillae recutita L.*

No.	Ingredient, g	Base numbers											
		3a	3b	3c	3d	2a	2b	2c	2d	1a	1b	1c	1d
1	2	3	4	5	6	7	8	9	10	11	12	13	14
1	Essential oil of <i>Chamomillae recutita L.</i>	0,5	1,0	3,0	5,0	0,5	1,0	3,0	5,0	0,5	1,0	3,0	5,0
2	Twin-80	-	-	-	-	2,0	2,0	2,0	2,0	-	-	-	-
3	Sodium carboxymethyl cellulose	-	-	-	-	5,85	5,82	5,7	5,58	-	-	-	-
4	Glycerol	-	-	-	-	0,75	0,7	0,5	0,3	-	-	-	-
5	Dimexide	-	-	-	-	-	-	-	-	10,0	10,0	10,0	10,0
6	Purified water	-	-	-	-	81,9	81,48	79,8	78,12	-	-	-	-
7	PEO - 400	29,5	29,0	27,0	25,0	-	-	-	-	19,5	19,0	17,0	15,0
8	PEO - 1500	before 100,0	before 100,0	before 100,0	before 100,0	-	-	-	-	before 100,0	before 100,0	before 100,0	before 100,0

Therefore, for further studies, a gel was prepared according to the selected composition. Based on the above, the biological activity of the gels was investigated.

Antimicrobial activity of gels with essential oil of *Chamomillae recutita L.*

The antimicrobial activity of the samples was determined by the diameter of the growth inhibition zones of the test strains (mm). The diameter of growth inhibition zones less than 10mm and continuous growth in the cup was assessed as the absence of antibacterial

activity, 10-15mm - weak activity, 15-20mm-moderately pronounced activity, more than 20mm-pronounced. Each sample was tested in three parallel experiments.

Static processing was carried out using the methods of parametric statistics with the calculation of the arithmetic mean and standard error¹⁵⁻²³.

The results of the study of the antimicrobial activity of the samples are shown in Table 2.

Table 2: Antimicrobial activity of gels based on essential oil of *Chamomillae recutita* L.

No.	Call number	<i>S. aureus</i>	<i>Bacillus subtilis</i>	<i>E. coli</i>	<i>Ps. aeruginosa</i>	<i>Candida albicans</i>
1	2	3	4	5	6	7
1	Sample No. 1 (1% essential oil of <i>Chamomillae recutita</i> L. gel form)	13,0±0,92	15,0±1,1	12,0±1,0	11,0±0,91	11,0±1,0
2	Base No.1	-	-	-	-	-
3	Sample No.2 (1% essential oil of <i>Chamomillae recutita</i> L. gel form)	14,0±1,2	15,0±0,93	11,0±0,91	11,0±1,0	11,0±1,1
4	Base №2	-	-	-	-	-
5	Sample No.3 (3% essential oil of <i>Chamomillae recutita</i> L. gel form)	15,0±0,5	15,0±0,91	12,0±0,92	11,0±1,1	11,0±1,2
6	Base No.3	-	-	-	-	-
Ointment levosin		13,0±1,1	14,0±1,0	12±1,1	-	-
Nystatin ointment		-	-	-	-	22,0±1,0

In soft dosage form technology, the most important is the gel base used, which contains only polyethylene glycol (PEG-400 and PEG-1500), since sample No. 3 has a moderately pronounced activity against Gram-positive bacteria of the species *Staphylococcus aureus*, *Bacillus subtilis*, against gram-negative species of *Escherichia coli*, *Pseudomonas aeruginosa*, as well as yeast-like fungi *Candida albicans*, while samples No. 1 and No. 2 are selectively active only against *Bacillus subtilis*.

Rheological properties of essential oil gels with essential oil of *Chamomillae recutita* L.

The dependence of shear stress (τ) and effective viscosity ($\ln\eta_{eff}$) on the shear flow rate gradient (D) at different temperatures was studied for a gel sample with chamomile essential oil 3.0%, where polyethylene oxide with a molecular weight of 400 and 1500 in a ratio of 3:2. Graphs of the dependence of the average values of shear stress and dynamic viscosity on the applied velocity gradient were plotted, which were used to judge the type of system flow and the presence of thixotropic properties (Figures 1, 2).

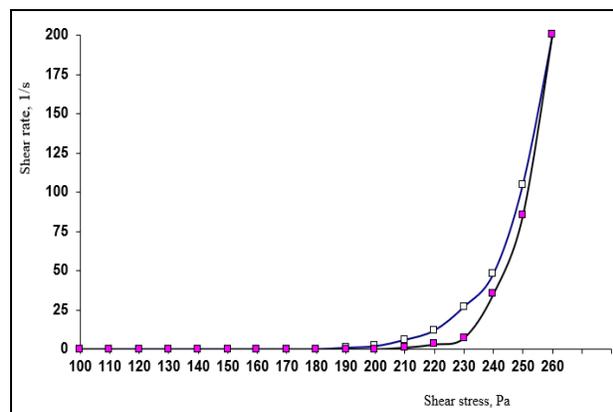


Fig. 1: Rheogram of the kinetics of deformation of a sample gel with essential oil of *Chamomillae recutita* L. 3.0% based on PEO at 25 °C

At a temperature of 25°C, the descending curve is located from the ascending curve to the left, which indicates that the destruction of the structure with a decrease in loads somewhat prevails over its restoration (Figure 1). The width of the loop indicates a low degree of destruction of the structure. A further increase in temperature leads to a fairly rapid destruction of the structure and a decrease in the area of the hysteresis loop. Obviously, this is due to the fact that the effect of temperature contributes to the destruction of the structure.

The degree of destruction of the structure of the ointment was judged by the value of mechanical stability (MS)²⁴⁻²⁶. The calculated MS value for the gel, equal to 1.08, indicates the predominance of coagulation bonds in the system and possible stability during long-term storage.

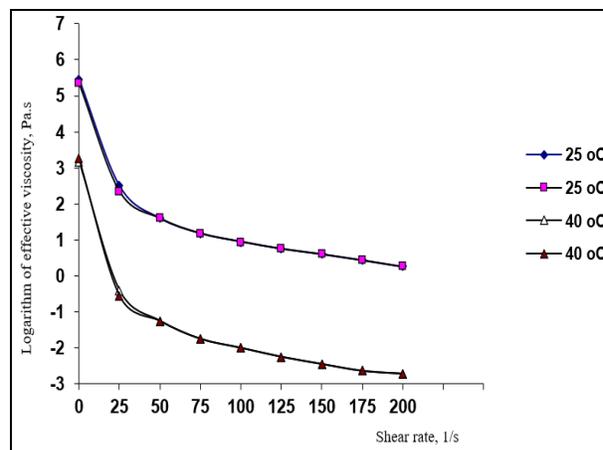


Fig. 2: Dependence of effective viscosity ($\ln\eta_{eff}$) on shear flow rate gradient (D_r) at different temperatures for a sample of *Chamomillae recutita* L. 3.0% gel based on PEO

As can be seen from Figure 2, at low shear rates, the structure of the ointment is destroyed and completely restored (in this case, the system has the highest viscosity). As the shear rate increases, the destruction of the structure begins to predominate over the recovery, and the viscosity decreases. At high shear rates, the

structure is completely destroyed, and the system begins to flow.

It is known that structure formation in dispersed systems largely depends on temperature. With an increase in temperature from 25 to 55°C, the viscosity of the ointment based on polyethylene oxide decreases from 214.9 to 26.2 Pa.s, which indicates a high sensitivity of the ointment to temperature changes. The direct and reverse process of changing the velocity gradient slightly changes the value of viscosity, which indicates the absence of strong internal system rearrangements and the formation of a new phase in the temperature range from 25 to 55°C. However, the presence of a hysteresis loop indicates that a noticeable deformation ordering occurs in the ointment.

Figure 3 shows the nature of the change in dynamic viscosity with increasing temperature for the test ointment. As can be seen from the graph, an increase in temperature leads to a change in the fluidity of the gel. There is no fundamental difference in the course of the curves with an increase and decrease in the shear flow rate of the test sample. Heating the base leads to a decrease in its structural viscosity, and consequently, to a loss of thixotropy.

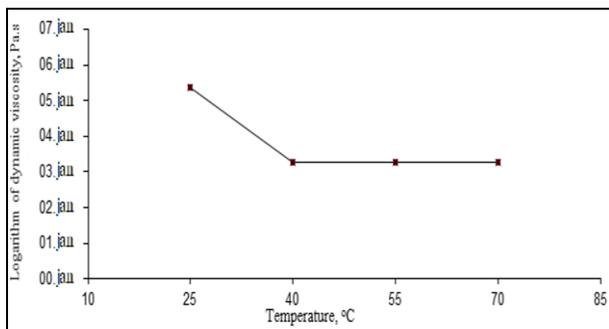


Fig. 3: Decrease in dynamic viscosity ($\ln\eta$) with increasing temperature (T) for a sample gel with essential oil of *Chamomilla recutita* L. 3.0 % based on PEO

As can be seen from Figure 3, the logarithm of the effective viscosity of the gel shows an inverse relationship with temperature. The lower the temperature, the faster and deeper are the processes of structure formation. The basis under study gives a sharp increase in the limiting shear stress with decreasing temperature. This property of the proposed base is of great practical importance, which will allow the gels prepared on it to be easily squeezed through the pipes during the production process and squeezed out of the tubes when they are used under various temperature conditions with decreasing temperature.

Figure 4 shows the dependence of the effective viscosity of the gel on the reciprocal temperature.

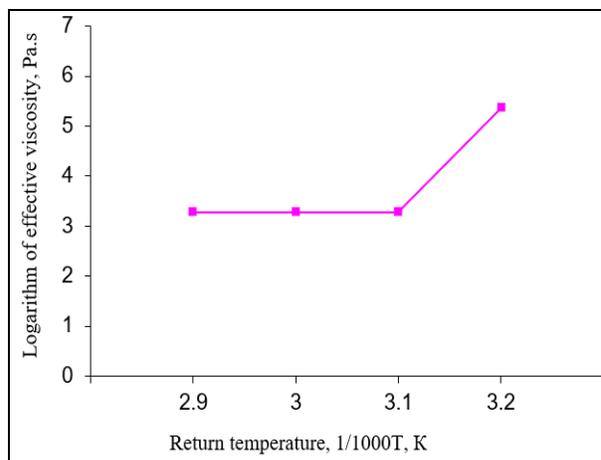


Fig. 4: Dependences of effective viscosity ($\ln\eta_{eff}$) on reciprocal temperature ($1/10^3 T$) for a sample gel with essential oil of *Chamomilla recutita* L. 3.0% based on PEO

From the studies carried out, it can be concluded that the gel base obtained on the basis of polyethylene oxides has a pronounced thixotropy and low values of ultimate shear stress and plastic viscosity at different temperatures. This means that the structure of the base is easily destroyed, allowing you to freely squeeze it out of the tubes and spread it painlessly on the skin, but quickly recovers if the base is left alone, which is essential when storing gels based on this base.

CONCLUSIONS:

Thus, the studied samples of "Chamazulenogelum" gels do not undergo strong structural changes in the shear field, that is, there are no intrasystem rearrangements with destruction or with the formation of new compounds. The thixotropic properties on the hydrophilic gel base "Chamazulenogelum" have been established, which characterize good smearability and the ability to extrude from the tube. The pronounced antimicrobial activity of the developed "Chamazulenogelum" gels for topical use provides a basis for further tests included in the drug development cycle.

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CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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