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RESEARCH BY CHOICE OF EXCIPIENTS INGREDIENTS OF THE GEL FOR THE THERAPY OF RADIATION LESIONS OF THE SKIN BASED ON RHEOLOGICAL STUDIES

Ksenija Burban, Halyna Kukhtenko, Anna Kriukova, Volodymyr Yakovenko, Ksenia Matsiuk, Halyna Slipchenko, Liliia Vyshnevska

The aim *of this work is to conduct a research analysis of changes in the structural and mechanical properties of the gel from the addition of active substances and surfactants.*
Materials and methods. *In the presented work, model samples of the gel with active substances were studied: freshly obtained stonecrop juice, sea buckthorn oil, rosehip oil, St. John's wort oil and quercetin. As substances for the manufacture of bases hydrocolloids of cellulose derivatives were used: sodium carboxymethylcellulose (NaCMC) and hydroxyethylcellulose (HEC) with a surfactant Lanette SX.*
A study of the rheological properties of the samples was performed using a rheoviscometer Rheolab QC (Anton Paar, Austria) using a system of coaxial cylinders C-CC27/SS. The Rheolab QC rheometer is equipped with RheoPlus software, which allows you to set the necessary experimental conditions (shear rate gradient range, number of measuring points and measurement time of one point).
Results*. The rheological properties of model samples of NaCMC and HEC gels, depending on the used concentration, were studied. With increasing concentrations of both NaCMC and HEC thixotropy of dispersed systems decreases. The change of structural and mechanical parameters of hydrogels from the addition of active ingredients and surfactant is analyzed, and established that adding them into the hydrogels increases the structural and mechanical parameters of model samples.*
A study of gels with a constant concentration of sodium carboxymethylcellulose and hydroxyethylcellulose and different content of surfactant Lanette SX established that as the surfactant concentration increases, the area of the hysteresis loop and the resistance of the dispersed system to the applied mechanical fracture increase.
Conclusions*. According to the results of the obtained structural and mechanical parameters and rheograms of the studied model samples of gels, it is rational to use in further studies of sodium carboxymethyl-cellulose (1.5 %) and hydroxyethylcellulose (1.25 %) stabilized Lannete SX in concentrations of 4–5 % and 3–5 % respectively*
Keywords*: rheological studies, combined gel, phytocomposition, sodium carboxymethylcellulose, hydroxyethylcellulose, Lanette SX*

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1. Introduction

Gels, as a dosage form, are widely used in medical practice due to the good and rapid release and absorption of active pharmaceutical ingredients. The rheological properties of gels are due to the presence of gelling agents in small concentrations and other auxiliary substances that form the base. According to the literature, gels are prescribed for application to the skin and its appendages, wounds, ulcers and mucous membranes, have practically no contraindications, can be used at any age, regardless of the presence of concomitant diseases, and do not have systemic side effects [1–3].

The selection and justification of the component composition of a soft drug is a complex process that requires comprehensive physicochemical, structural-mechanical, biopharmaceutical and biological research methods to ensure the high efficiency and safety of the developed tool [4–6].

Structural and mechanical (rheological) studies allow to evaluate the consistent properties of the tool, analyze the component effect in the viscosity component, predict the behaviour of the dispersed system during machining in industrial production, allow to scientifically substantiate temperature and speed conditions when scaling production, etc. [7–9].

The aim of this work is to conduct a research analysis of changes in the structural and mechanical properties of the gel from the addition of active substances and surfactants.

2. Research planning (methodology)

The design of the experiment to substantiate the composition of excipients was as follows [10, 11] (Fig. 1).

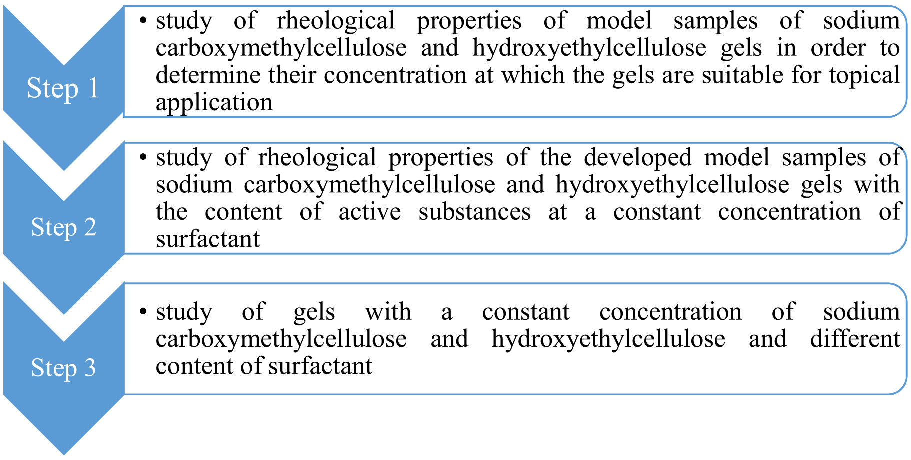

Fig. 1. Research planning scheme

3. Materials and methods

The model samples of gel with active substances were studied: freshly obtained stonecrop juice [12, 13], sea buckthorn oil (manufacturer LLC DKP «Pharmaceutical factory», Ukraine), rosehip oil (manufacturer LLC DKP «Pharmaceutical factory», Ukraine), St. John's wort oil (manufacturer «Aromatika», Ukraine) and quercetin (manufacturer PJSC SIC «Borshchahivskiy CPP», Ukraine) [14]. The choice of oils is determined by their specific pharmacological activity; their presence in the composition gives the drug under study anti-inflammatory, wound-healing and regenerative activity. Pharmacological screening confirmed the therapeutic effect of the developed drug [15–17]. Model samples of gels made on the basis of hydrocolloids of cellulose derivatives, sodium carboxymethylcellulose and hydroxyethylcellulose with the surfactant Lanette SX, which is a mixture of cetostearyl alcohol, sodium lauryl sulfate, sodium cetaryl sulfate (manufacturer BASF SE, Germany) [18]. Butylhydroxyanisole and potassium sorbate were added to the model gel samples to ensure microbiological and oxidative stability of the studied samples [19, 20]. Concentrations of these substances corresponding to the average value of the range of used concentrations were used.

The composition of the studied model samples of gels is shown in Table 1.

Model gel samples were prepared using the following technology: in hot water (50±5) °*C*, add the required amount of sodium carboxymethylcellulose/hydroxyethylcellulose with mixing at 250 rpm, leave until complete swelling during the day. An emulsion is obtained: the required amount of complex emulsifier Lanette SX is heated in a water bath at a temperature (70±5) °C, sea buckthorn oil, rosehip oil, St. John's wort oil are added and mixed with purified water to a homogeneous consistency. Prepare a suspension of quercetin during dispersion with glycerin, followed by dilution with a stonecrop juice. Essential oils of cinnamon and lemon (gel flavours) are solubilized in part of the glycerin. The emulsion of fatty oils is transferred to the reactor with a gel base, and mixed, then the quercetin suspension is added, mixed to a homogeneous consistency and the prepared composition of essential oils is added. Therefore, a combined gel of a homogeneous, viscous consistency, dark yellow colour with a slight specific smell of essential oils was obtained [21, 22].

Table 1

The composition of the drug for the treatment of radiation damage to the skin

Components	The composition of the samples, %										
	The composition of the gels, %				The composition of gels with the addition of surfactants, %						
	1	2	3	4	1	2	3	4	5	6	7
Sea buckthorn oil	15.0				15.0						
Rosehip oil	5.0				5.0						
Stonecrop juice	20.0				20.0						
St. John's wort oil	20				20.0						
Quercetin	4.0				4.0						
Butyloxyanisole	0.05				0.05						
Potassium sorbate	0.1				0.1						
Lanette SX emulsifier (alloy cetostearyl alcohol, sodium lauryl sulfate, sodium cetiarylsulfate)	4.0				0	1.0	2.0	3.0	4.0	5.0	6.0
Sodium carboxymethylcellulose/hydroxyethylcellulose	1.0	1.25	1.5	1.75	1.5/1.25						
Glycerin	5.0				5.0						
Clove essential oil	10 drops				10 drops						
Cinnamon essential oil	10 drops				10 drops						
Water purified up to	100				100						

A study of the rheological (structural-mechanical) properties of the samples was performed using a rheoviscometer Rheolab QC (Anton Paar, Austria) using a system of coaxial cylinders C-CC27/SS. The Rheolab QC rheometer is equipped with RheoPlus software, which allows you to set the necessary experimental conditions (shear rate gradient range, number of measuring points and measurement time of one point). Rheological measurements were performed in three stages:

a) a linear increase in the gradient of the shear rate from 0.1 s^{-1} to 350 s^{-1} with 105 measuring points and the duration of the measurement point 1 s;

b) a constant shift at a shear rate of 350 s^{-1}, one measuring point lasting 1 s;

c) a linear decrease in the shear rate gradient from 3500 s^{-1} to 0.12 s^{-1} with 105 measuring points and the measurement duration of the point 1 s.

The study was performed at 25±0.5 °C, the duration of thermostating of each sample was 30 minutes.

The flow point (boundary) was calculated using software using a mathematical model of the Casson rheological flow.

The coefficient of dynamic rarefaction (flow) was determined at shear rates of 3.45 and 10.2 s^{-1}, corresponding to the shear rate of the palm when distributing the soft dosage form on the surface and the viscosity of the system at shear rates 27 and 1551 s^{-1}, which correspond to speeds at technological processing during its manufacturing. Based on the results obtained, the values of the coefficients of dynamic rarefaction of the system were calculated according to the formulas (1) – (2):

$$K_{d1}=\frac{\eta_{3,45}-\eta_{10.2}}{\eta_{3,45}}\cdot 100\%, \quad (1)$$

$$K_{d2}=\frac{\eta_{27}-\eta_{155}}{\eta_{27}}\cdot 100\%, \quad (2)$$

where K_{d1} i K_{d2} – coefficients of dynamic rarefaction;

η – structural viscosity at appropriate shear rates, Pa·s.

The calculation of mechanical stability (MS) was performed at a shear rate of 3.45 s^{-1},) according to the following formula (3):

$$MC=\frac{\tau_1}{\tau_2}, \quad (3)$$

where τ_1 – shear stress to failure;

τ_2 – shear stress after failure.

4. Research results

The results of rheological studies of hydrogels of sodium carboxymethylcellulose and hydroxyethylcellulose are shown in Fig. 2, 3 and Table 2. The studied hydrogels show pseudoplastic properties, their flow begins at insignificant values of shear stress, and the calculated flow limit according to the mathematical model of the rheological flow Casson I is 0.02 Pa – 0.85 Pa – 7.03 Pa – 10.56 Pa – 10, 98 Pa for samples of NaCMC gels at a concentration of 1.0 – 1.25 – 1.5 – 1.75 – 2.0 %, respectively. Consistency characteristics increase with increasing NaCMC concentration. For samples of NES gels, the calculated flow limit is 1.04 Pa – 6.10 Pa – 10.24 Pa – 17.34 Pa – 17.34 Pa – 17.87 Pa, respectively, for HEC gels at a concentration of 1.0 – 1.25 – 1.5 – 1.75 – 2.0 %. The test samples show the properties of viscoelastic liquids, as evidenced by the low value of the flow limit and pseudoplastic type of flow; the formation of hydrogels occurs because of hydration of the polysaccharide molecule.

As can be seen from Table 3, when testing for colloidal and thermal stability, samples of sodium carboxymethylcellulose gels (1.5 %) with surfactant concentrations of 0, 1, 2 and 3 % did not pass the test. All samples of gels based on hydroxyethylcellulose (1.25 %) were stable. The dependence of the shear stress on the shear rate gradient of gels and the dependence of the structural viscosity on the shear rate gradient are shown in Fig. 4, 5.

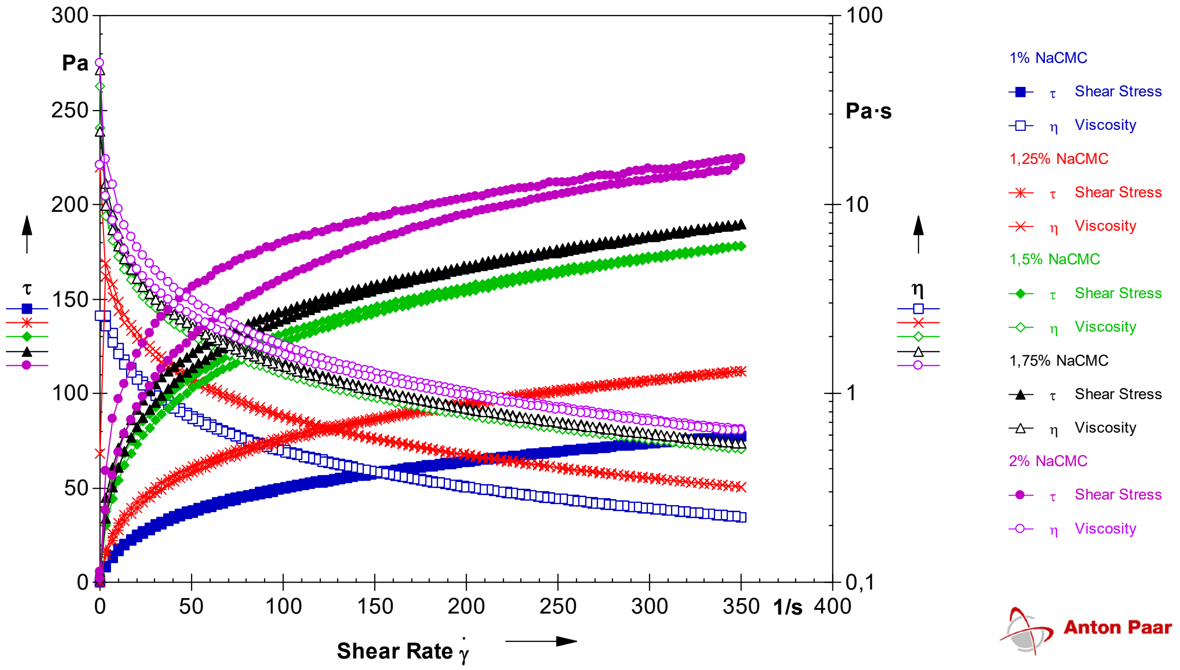

Fig. 2. Rheograms of the flow of sodium carboxymethylcellulose gels

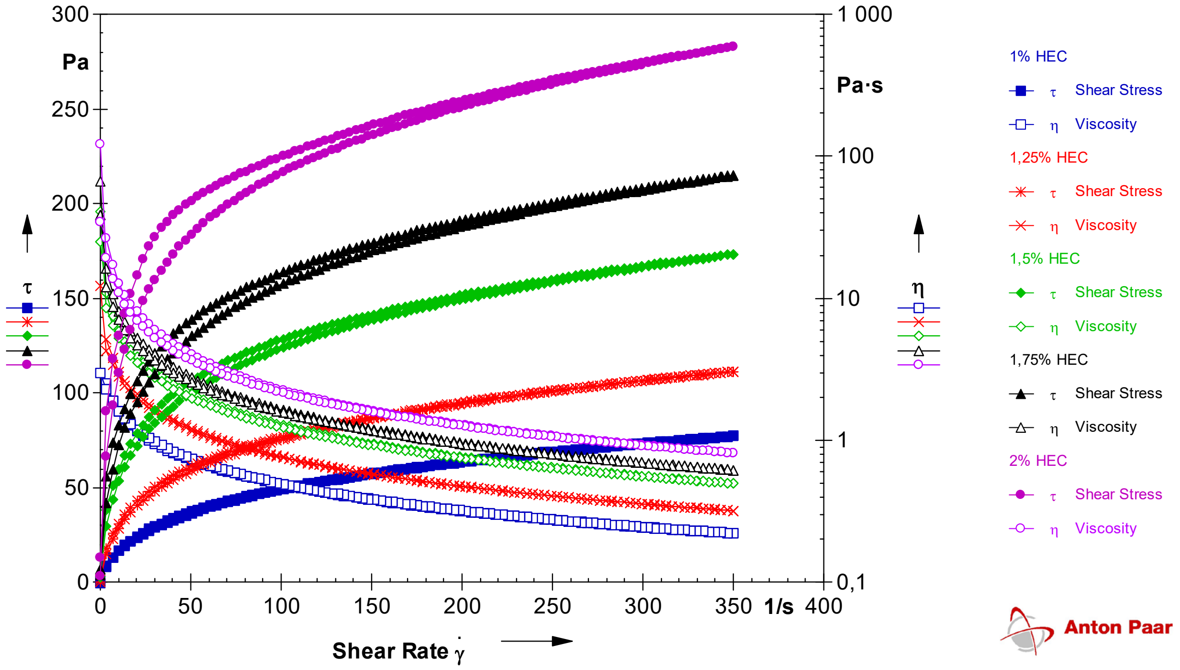

Fig. 3. Rheograms of the flow of hydroxytylcellulose gels

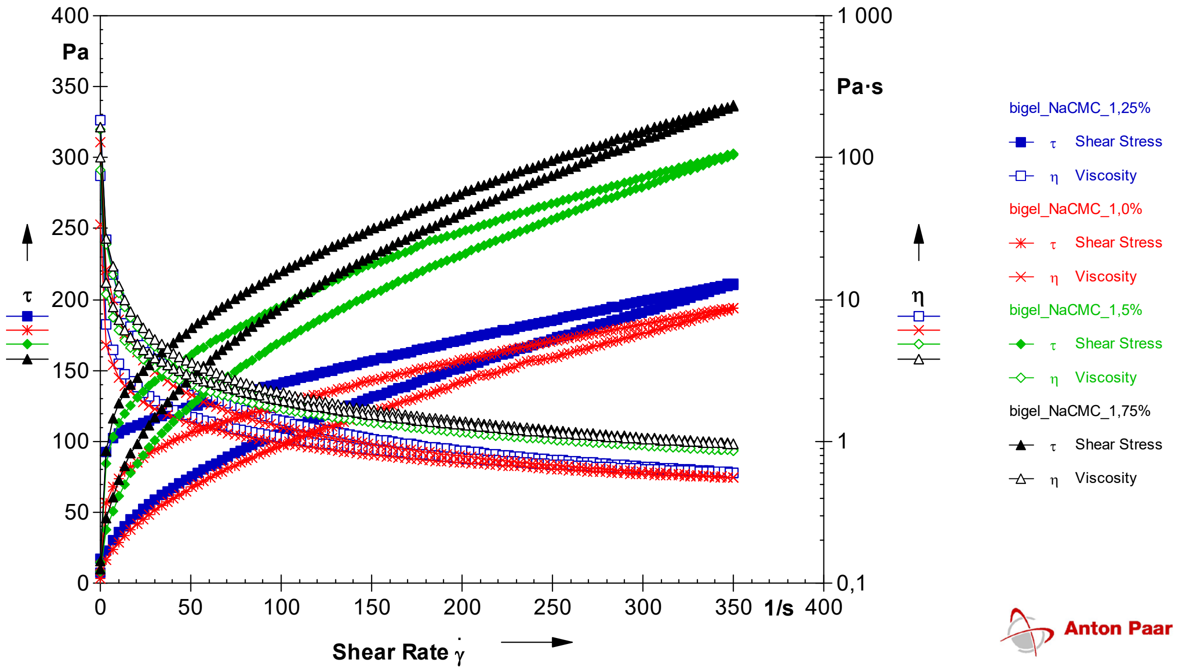

Fig. 4. Rheograms of the flow of gels based on sodium carboxymethylcellulose

With increasing concentration of both NaKMC and HEC thixotropy of dispersed systems decreases; on the rheograms of the flow between the ascending and descending curve there is a certain space (area of the hysteresis loop), from which it is seen that the restoration of the structure in the reverse order (with a decrease in the gradient of the shear rate) is delayed in time, with increasing concentration of the structure-forming substance in the area of the hysteresis loop increases (Table 3).

The next step was to evaluate the rheological properties of gels containing active substances, in which the concentration of sodium carboxymethylcellulose and hydroxyethylcellulose was varied at a fixed concentration of surfactant Lanette SX 4.0 %.

The addition of active substances and surfactants Lanette SX into the hydrogels increases the structural and mechanical parameters. The fabricated gels are heterogeneous dispersion systems stabilized by creating a structural-mechanical barrier in the volume of the dispersion medium and by anion-type surfactants, which are distributed on the interface of the two phases, thereby reducing the surface tension. Gel samples retain the pseudoplastic type of flow, thixotropic properties decrease, i.e., the restoration of the gel structure is delayed in time, which could be explained by the change in the type of dispersed system from homogeneous to heterogeneous and the increase in viscosity of the system. The calculated mechanical stability of the system are renewable, according to the indicators of dynamic rarefaction coefficients suitable for spreading on the skin surface, susceptible to machining during manufacture (Table 3).

For the next stage of substantiation of the composition of excipients, bigels with a concentration of sodium carboxymethylcellulose – 1.5 %, hydroxyethylcellulose – 1.25 % were selected. In the selected gels, the surfactant concentration was varied from 0 to 6 %, in increments of 1 %.

The results of rheological studies are shown in Fig. 6, 7 and Table 4.

The general profile of the rheological flow remains characteristic of previous model samples of gels. As the surfactant concentration increases, the area of the hysteresis loop and the resistance of the dispersed system to the applied mechanical fracture increase.

A sample of HEC gel with 6.0 % Lanette SX at an interval of high shear rates shows instability, the reason for this may be the rupture of elongated at steady flow chains of the polysaccharide molecule. On the other hand, the non-uniformity of the flow, which is recorded on the rheogram, may be a consequence of the Weissenberg effect, i.e. the gel is wound on the shaft and rises along the axis to the top.

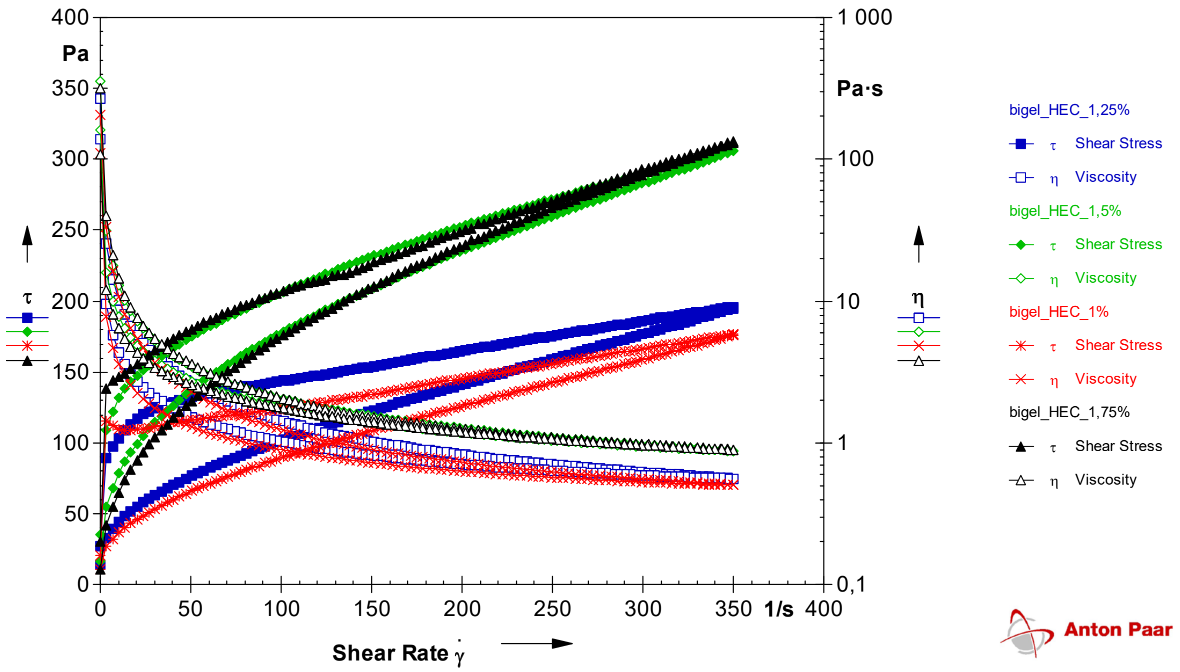

Fig. 5. Rheograms of the flow of gels based on hydroxyethylcellulose

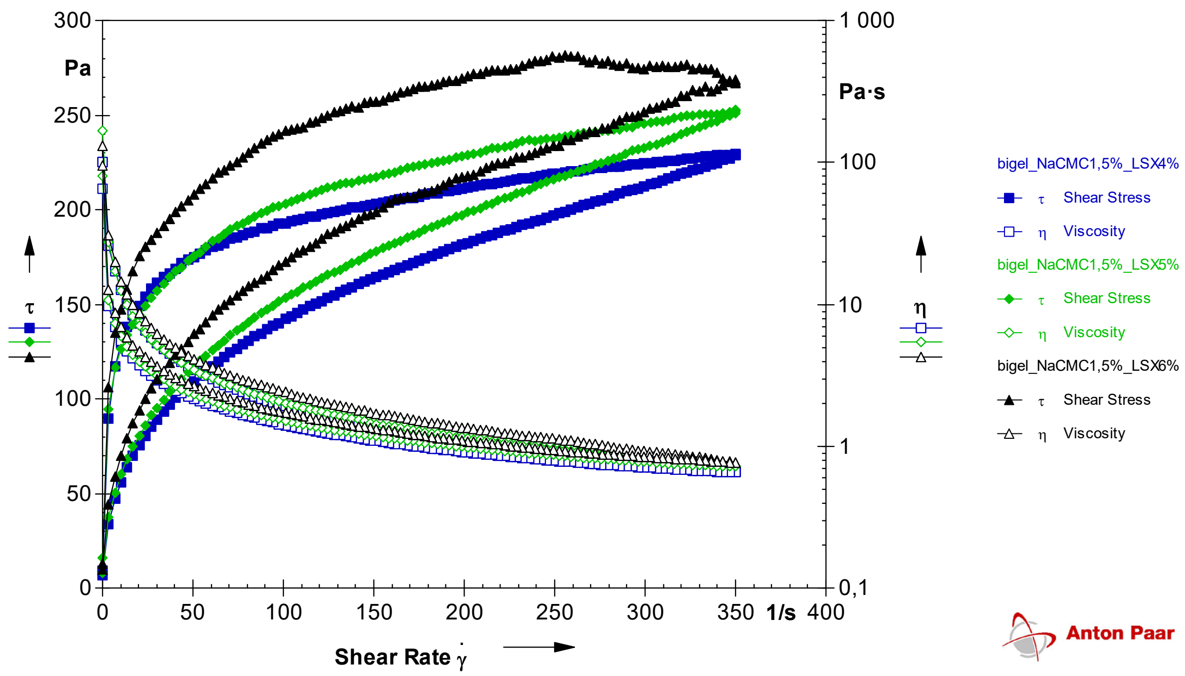

Fig. 6. Rheogram of the flow of gels based on sodium carboxymethylcellulose with the addition of a surfactant

Table 2

Calculated structural and mechanical parameters of model samples of gels

Indicators	1.0 % NaCMC	1.25 % NaCMC	1.5 % NaCMC	1.75 % NaCMC	2.0 % NaCMC	1.0 % HEC	1.25 % HEC	1.5 % HEC	1.75 % HEC	2.0 % HEC	gel_1.0 % NaCMC	gel_1.25 % NaCMC	gel_1.5 % NaCMC	gel_1.75 % NaCMC	gel_1.0 % HEC	gel_1.25 % HEC	gel_1.5 % HEC	gel_1.75 % HEC
Hysteresis loop area, Pa/s	188.48	533.22	1136.3	1217.1	4620.6	–52.54	321.3	1047	1569	2370.1	9200.6	7228.9	6975.8	6705.7	10431	7553	9343.2	7767.9
Boundary layer flow of Casson τ_0, Pa	0.02	0.85	7.03	10.56	10.98	1.04	6.1	10.24	17.34	17.87	11,97	22.19	27.79	32,93	28.18	31.01	35.34	38.62
Coefficient of dynamic rarefaction K_{d1}, %	32.68	37.55	44.72	45.89	45.09	35.34	40.5	46.9	49.94	51.52	55.64	60.9	54.73	53,53	67.58	60.55	58.65	63.89
Coefficient of dynamic rarefaction K_{d2}, %	64.9	68.14	71.3	72.72	74.44	63	67.98	71.43	73.15	76.07	72.48	75.83	71.59	83,16	78.73	78.09	73.6	75.29
MC	1.13	1.18	1,31	1.25	1,56	1.11	1.21	1.28	1.34	1.36	3,45	4	2,24	2,04	4.4	2.71	2,0	3.32

Table 3

The results of the research into colloidal and thermal stabilities of model samples of gels

Colloidal and thermal stability/samples							
Stability indicator	No. 1		No. 2		No. 3	No. 4	
Gels based on sodium carboxymethylcellulose	+/+		+/+		+/+	+/+	
Gels based on hydroxyethylcellulose	+/+		+/+		+/+	+/+	
Colloidal stability							
–	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	No. 7
Gels based on sodium carboxymethylcellulose with the addition of an emulsifier	–	–	–	–	+/+	+/+	+/+
Gels based on hydroxyethylcellulose with the addition of an emulsifier	–	+/+	+/+	+/+	+/+	+/+	+/+

Table 4

Calculated structural and mechanical properties of gels based on hydroxyethylcellulose with the addition of surfactant

Indicators	Gel_1.5 % NaCMC_ LSX0 %	Gel_1.5 % NaCMC_ LSX1 %	Gel_1.5 % NaCMC_ LSX2 %	Gel_1.5 NaCMC_ LSX3 %	Gel_1.5 % NaCMC_ LSX4 %	Gel_1.5 % NaCMC_ LSX5 %	Gel_1.5 % NaCMC_ LSX6 %	Gel_1.25 % HEC_ LSX0 %	Gel_1.25 % HEC_ LSX1 %	Gel_1.25 % HEC_ LSX2 %	Gel_1.25 % HEC_ LSX3 %	Gel_1.25 % HEC_ LSX4 %	Gel_1.25 % HEC_ LSX5 %	Gel_1.25 % HEC_ LSX6 %
Hysteresis loop area, Pa/s	–	–	–	–	12723	12336	18123	821.15	4259.8	5979.2	7918.7	9091.6	11552	14329
Boundary layer flow of Casson τ_0, Pa	–	–	–	–	25.14	31.78	34.96	2.41	3.95	9.92	18.43	29.38	40.69	63.24
Coefficient of dynamic rarefaction K_{d1}, %	–	–	–	–	58.63	58.76	57.3	29.35	39.08	40	47.48	51.15	54.58	53.09
Coefficient of dynamic rarefaction K_{d2}, %	–	–	–	–	75.92	76.76	80.28	59.42	82.89	69.72	71.08	77.44	75.13	75.66
MC	–	–	–	–	2.81	2.4	2.51	0.96	1.48	2.13	1.94	2.64	2.53	2.42

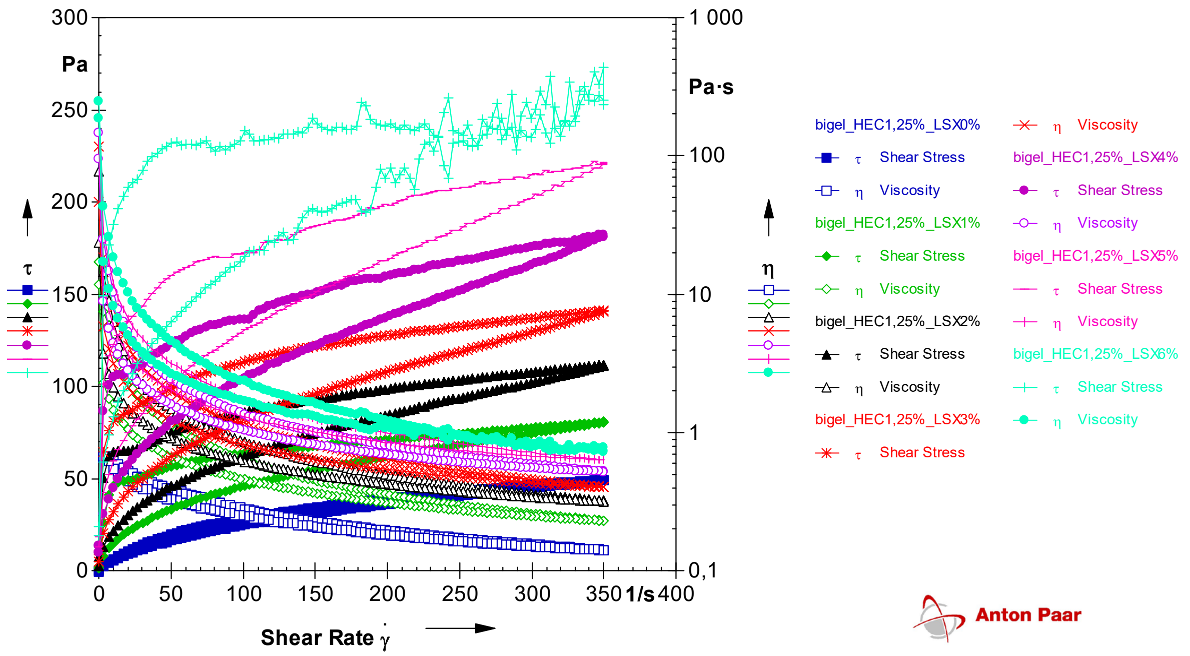

Fig. 7. Rheograms of the flow of gels based on hydroxyethylcellulose with the addition of a surfactant

5. Discussion of research results

The rheological properties of model samples of NaCMC and HEC gels, depending on the used concentration, were studied. With increasing concentrations of both NaCMC and HEC thixotropy of dispersed systems decreases.

Today, the results of rheological studies of gels based on NaCMC and HEC are published [23, 24]. However, these studies were carried out on model gel samples in purpose to select the optimal concentration of gelling agent. The presented studies do not contain information about the effect of active substances and excipients (surfactants) on the structural and mechanical properties of the samples.

We analyzed the change of structural and mechanical parameters of hydrogels from the addition of active ingredients and surfactant is analyzed and established that adding them into the hydrogels increases the structural and mechanical parameters of model samples. A study of gels with a constant concentration of sodium carboxymethylcellulose and hydroxyethylcellulose and different content of surfactant Lanette SX established that as the surfactant concentration increases, the area of the hysteresis loop and the resistance of the dispersed system to the applied mechanical fracture increase.

Study limitations. Studies of structural and mechanical properties were carried out on model samples of the gel of the original composition. The change in the structural and mechanical properties of gels after the addition of active components (freshly obtained stonecrop juice, sea buckthorn oil, rosehip oil, St. John's wort oil, quercetin and surfactant Lanette SX was analyzed.

Prospects for further research. The obtained research results are the basis for further pharmaceutical development of the combined gel «Biosedum Plus» for treating inflammatory and radiation skin lesions.

6. Conclusions

According to the set of structural and mechanical parameters and rheograms of the studied model samples of gels, it is rational to use in further studies of sodium carboxymethylcellulose (1.5 %) and hydroxyethylcellulose (1.25 %) stabilized Lannete SX in concentrations of 4–5 % and 3–5 % respectively. The data obtained can be used in the development of the combined gel «Biosedum plus».

Conflicts 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 article.

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Data availability

Data will be made available on reasonable request.

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