

Study of rheological behaviour of hydroxyethyl cellulose gels in the development of the composition and technology of the medicine with anti-inflammatory activity

Vladyslav Postoy¹, Halina Kukhtenko¹, Liliia Vyshnevskaya¹, Ievgenii Gladukh¹,
 Kateryna Semchenko¹

¹ National University of Pharmacy, Kharkiv, Ukraine

Corresponding author: Liliia Vyshnevskaya (liliavyshnevskaya@gmail.com)

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Abstract

The aim of the research was to investigate the rheological behaviour of hydroxyethyl cellulose gels, which are used in the development of the composition and technology of the medicine with anti-inflammatory activity. The objects of research were hydroxyethyl cellulose gels in the concentration of 1.0%; 1.5%; 2.0%; 2.5% and 3.0%. Investigation of the rheological behavior of HEC gels (structural and mechanical properties) was performed using the Rheolab QC rheometer from Anton Paar (Austria) using the C-CC27 / SS Coaxial Cylinder System. The obtained results showed that excipients influence on the rheological behaviour in the following way: propylene glycol and polyethylene oxide 400 reduce rheoparameters, while PEG 40 hydrogenated castor oil increases these parameters. The further study of the rheological properties in comparison with medicines “Troxeutin” and “Thiotriazolium” showed that the developed gel fully corresponds to technological and consumer requirements.

Keywords

rheological paramets, gel, hydroxyethyl cellulose

Introduction

Rheumatic diseases all over the world are considered as one of the most common pathologies of modern society, which significantly reduces the quality of life. Connective tissue diseases, systemic vasculitis, seronegativespondyloarthropathies, and microcrystalline arthritis are among the most severe chronic diseases in humans, and their pharmacotherapy remains one of the most complex pro-

blems of modern clinical medicine (Brooks 1998; Nasonov 2001, Shuba2006).

In the elimination of inflammation, the leading place belongs to non-steroidal anti-inflammatory medicines (NSAIDs), reflecting their efficacy and clinical significance. They exhibit anti-inflammatory, analgesic and antipyretic properties. However, there is a risk of gastroin-

testinal and thromboembolic complications, as well as a limited period of their usage (Shuba 2007).

However, the necessity for prolonged use of NSAIDs is always associated with the risk of side effects, the frequency of which ranges from 26% to 62%, of which up to 30% and higher belongs to gastropathy (Kovalenko and Bortkevich 2003). NSAIDs usage in the form of dosage forms for local therapy, primarily gels, can significantly reduce the systemic effect of these medicines and, therefore, the development of side effects. This type of therapy provides the maximum effect at the site of application, reduces the severity of the inflammatory reaction, swelling of the periarthritic tissues and pain with the practical absence of systemic side effects and low probability of medicines interactions (Gurevich 2004, Nasonova and Vunchuk 2001).

In this regard, the development, study and creation of effective dosage forms of NSAIDs for local application is of practical interest.

The study of structural-mechanical or rheological properties is necessary for the development and maintenance of optimal conditions of the technology of preparation of the medicine in gel form.

In order to develop the rational technology of the combined gel based on the dry extracts of white willow bark and sage leaves and methyl salicylate for the treatment of inflammatory diseases of the joints the aim of this research was to study the rheological behaviour of HEC gels samples: pure, with excipients and active pharmaceutical ingredients.

Materials and methods

Materials

As objects of research the following samples were studied: pure hydroxyethyl cellulose (HEC) gels in the concentration of 1.0%; 1.5%; 2.0%; 2.5% and 3.0%, HEC gels with such excipients as propylene glycol (PG), polyethylene oxide-400 (PEO-400), PEG-40 hydrogenated castor oil, HEC gel with test composition in comparison to finished medicines gel Troxerutin (series 300816) and Thiotriazolium (series 010316) of CHPhP "ChervonaZvezda", Ukraine production.

The choice of excipients is due to the necessity to introduce dry extracts of white willow bark and sage leaves and methyl salicylate into the final composition, which requires a solvent (PG or PEO-400) and a solubilizer (PEG-40 hydrogenated castor oil) studied (Gladukh et al. 2017, Anisimov et al. 2015).

Gel with test composition includes dry extract of white willow bark, dry extract of sage leaves, methyl salicylate, HEC, PEG 40 hydrogenated castor oil, nipagin and purified water. The technology of its preparation consists of the following stages:

- the raw materials for gel preparation is weighed;
- PEG-40 hydrogenated castor oil is placed in a steam jacket reactor and heated at 40 °C. With constant stir-

ring, methyl salicylate is added. Stirring is continued for 10–15 min.;

- in parallel, an aqueous solution is prepared. Part of the purified water is placed in the reactor and, under constant stirring and room temperature, dry extracts of sage leaves and willow bark and nipagin are added. Then the solution from the previous stage is added.
- separately, the rest of the purified water is loaded into the reactor. It is heated to 60 °C and then HEC is added, with constant stirring, to obtain a gel. The gel is cooled to 25–30 °C and is introduced with constant stirring for 10–15 min to the previously prepared mixture of active pharmaceutical ingredients.

Methods

Investigation of the rheological behaviour of HEC gels (structural and mechanical properties) was performed using the rheometer Rheolab QC by Anton Paar (Austria) using the C-CC27 / SS Coaxial Cylinder System. The device meets the requirements of ISO 3219. The rheometer Rheolab QC is equipped with RheoPlus software, which allows setting the necessary conditions for the experiment (range of shear rate, number of measuring points and duration of measurement of one point). Measurement of the rheological curve was carried out in three stages:

- a) linear increase of the gradient of the displacement rate from 0,1 s⁻¹ to 150 s⁻¹ with 45 measuring points and the duration of measuring point 1 s;
- b) a constant displacement at a shear rate of 150 s⁻¹, one point of duration measurement 1 s;
- c) the linear decrease of the gradient of the shear rate from 150 s⁻¹ to 0.1 s⁻¹ with 45 measurement points and the duration of measuring point 1 s.

The temperature of the study for the samples was 25 ± 0.5 °C, each sample was thermostatically stained for 20 min.

The software determined the point (boundary) of the current using the mathematical model of Casson, and also calculated the area of the hysteresis loop.

The coefficient of dynamic dilution (flow) was determined at displacement rates of 3.4 and 10.3 s⁻¹, corresponding to the rate of displacement of the palm in the distribution of a soft dosage form on the surface and viscosity of the system at displacement rates of 27.4 and 150 s⁻¹, which correspond to the speeds of technological processing in the process of its manufacture. On the basis of the obtained results, the values of the coefficients of dynamic rigidity of the system were calculated according to the formulas:

$$K_{d1} = \frac{\eta_{3,4} - \eta_{10,3}}{\eta_{3,4}} \cdot 100\%$$

$$K_{d2} = \frac{\eta_{27,4} - \eta_{150}}{\eta_{27,4}} \cdot 100\%$$

where K_{d1} i K_{d2} – coefficients of dynamic dilution; η – structural viscosity at appropriate shear rates, Pa · s.

For a more complete characterization of the studied samples, mechanical stability (MS) indexes were calculated. It is known that the optimal value of MS is 1. The value of MS is defined as the ratio of the value of the shear stress to fracture (τ_1) to the value of the shear stress after the destruction (τ_2) at a shear rate of 3.4 s⁻¹ by the formula:

$$MC = \frac{\tau_1}{\tau_2}$$

Results and discussion

Fig. 1 shows the results of rheological studies of HEC gels of different concentrations: 1.0%; 1.5%; 2.0%; 2.5% and 3.0%. The flow boundary calculated by the Casson mathematical model is 1.2 Pa; 3.6 Pa; 14.3 Pa; 40.9 Pa; 77.3 Pa, respectively. HEC gels of concentrations 1.0% and 1.5% can be attributed to structured disperse systems that do not reveal the flow boundary and show the insignificant value of this indicator, that is, the system inherent spontaneous flow. The increase in the HEC concentration leads to rise of the flow boundary, the structural viscosity of the gels, and the area of the hysteresis loop.

It should be noted that HEC 1.0% and 1.5% gels exhibit reopectic properties over the entire range of shear rates. Rheopexy systems exhibit an antithixotropic or rheopexy nature of the stream, characterized by increasing viscosity with a long deformation effort. In a state of rest, such systems

restore pseudoplastic, that is, low viscosity. The rheopexive disperse systems can, from an infinite number of times, pass from a state with increased viscosity with a long deformation effort to a state with reduced viscosity in a resting state. The transition to this or that state also depends on the time.

Thixotropy and rheopexy are the opposite rheological characteristics. This can be observed on the location of the “upper curve” in relation to the “lower curve”. In rheopexy fluids, the inverse of the curves of the flow (counterclockwise) is observed: the curve imprinted with a decrease in the shear rate is located above the curve obtained by increasing the shear rate (Kuhtenko and Gladukh 2017, Kukhtenko et al. 2017).

Gels at concentrations of 2.0%, 2.5% and 3.0% exhibit rheopexy properties at low shear rate values (0.1 s⁻¹). Accordingly, in such systems, the index of mechanical stability is less than 1, which cannot be in thixotropic systems, the area of the hysteresis loop is reflected in the negative sense. The dynamic dilution factor of all HEC gels, calculated in the range of shear rates of 27.4 and 150 s⁻¹, exceeds that in the range of 3.4 and 10.3 s⁻¹, which is characteristic of all structured disperse systems.

Taking into account the above data, for the development of gel with a combination of methyl salicylate and dry extracts of white willow bark and sage leaves, the gel with HEC concentration of 2.5% was chosen.

In view of the further usage of PG, PEO-400 and PEG-40 hydrogenated castor oil as the possible excipients in the technology of the test composition gel it is important to study the effects of these substances on the rheological behaviour of the HEC gel.

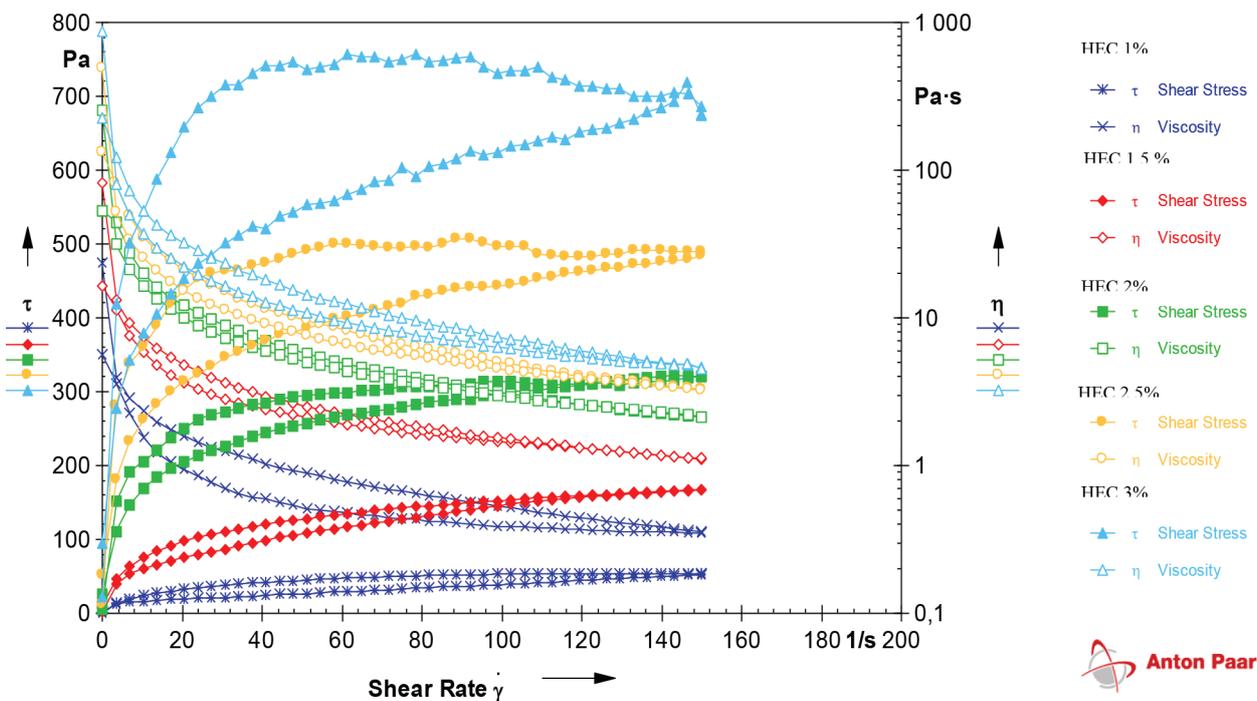


Figure 1. The dependence of the shear stress (τ , Pa) of the HEC gel on the gradient of the shear rate (γ , s⁻¹) and the dependence of the structural (dynamic) viscosity (η , Pa s) on the gradient of the shear rate (τ , Pa).

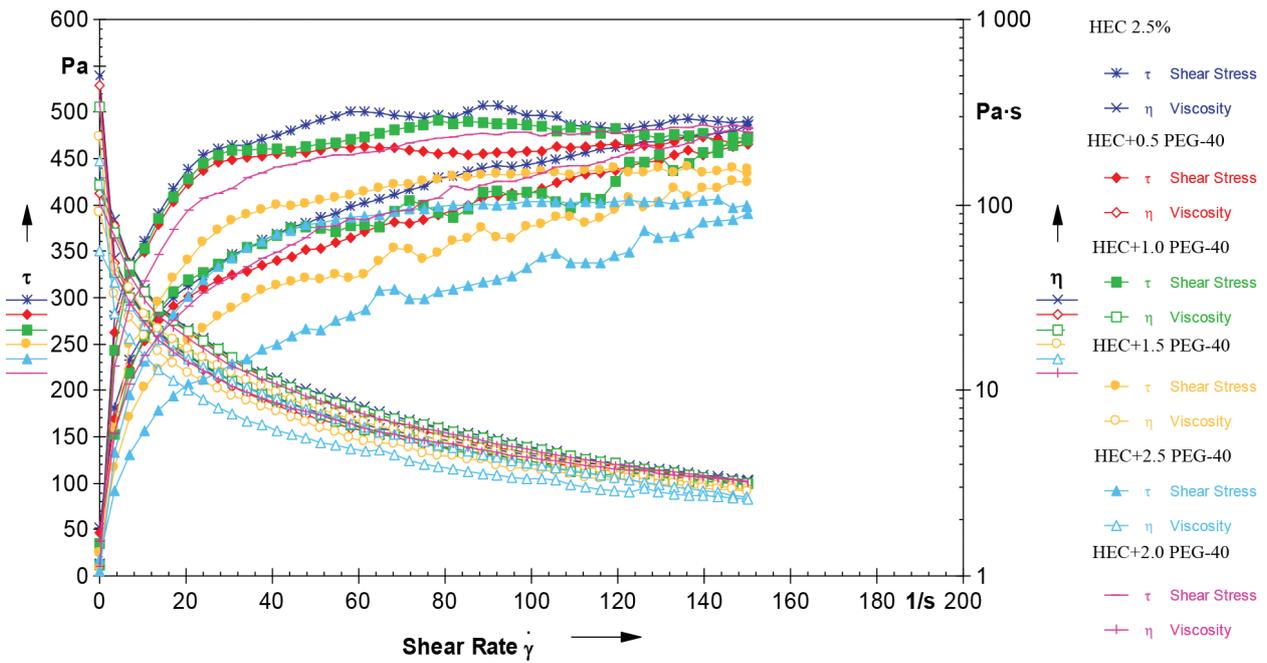


Figure 2. The dependence of the shear stress (τ , Pa) of HEC gels with the content of PEG-40 hydrogenated castor oil on the gradient of shear rate (γ , s^{-1}) and the dependence of the structural (dynamic) viscosity (η , Pa s) on the gradient of the shear rate (τ , Ra).

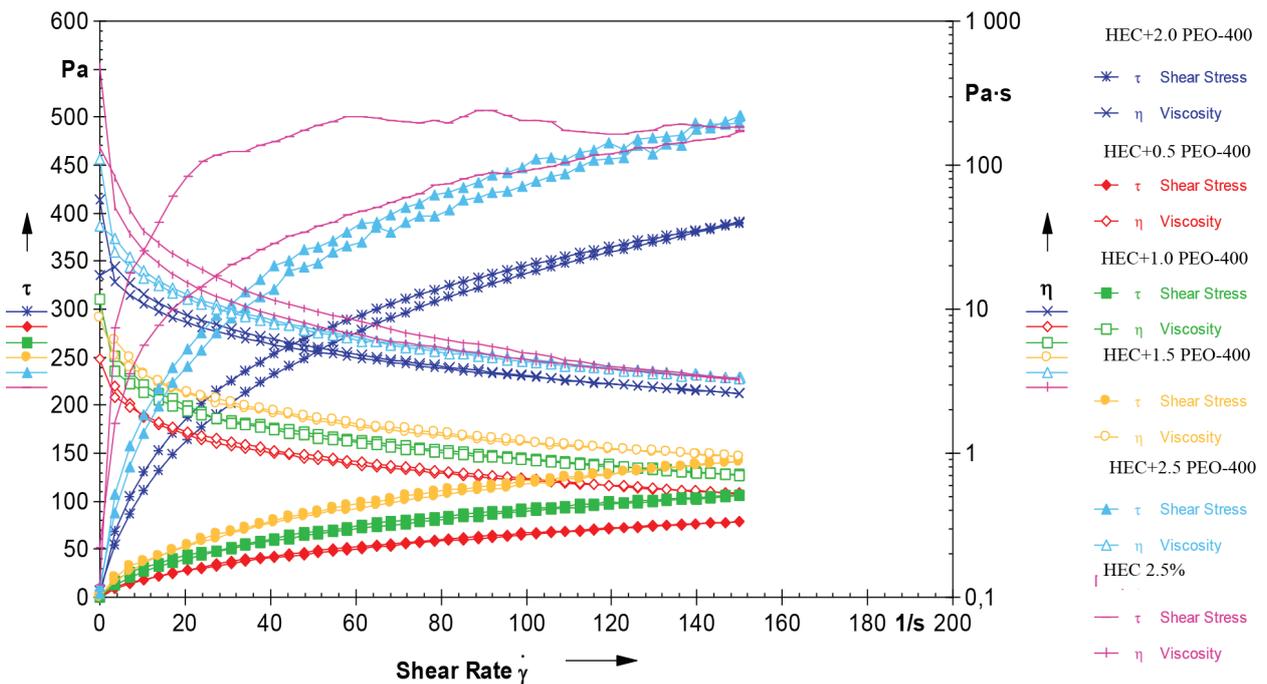


Figure 3. The dependence of the shear stress (τ , Pa) of HEC gels with PEO-400 content on the gradient of shear rate (γ , s^{-1}) and the dependence of the structural (dynamic) viscosity (η , Pa s) on the gradient of the shear rate (τ , Ra).

For this purpose, samples with the content of these substances 0.5 g, 1.0 g, 1.5 g, 2.0 g, 2.5 g were prepared. The results of their studies are given in Figs 2, 3 and 4, respectively.

It can be stated the significant change in the rheological behaviour of the HEC gels. Thus, the introduction of PEG-40 hydrogenated castor oil in the quantity up to 2.5%

of gel increases the flow limit, structural viscosity and the dynamic dilution coefficient of K_{d2} at high shear rates of 27.4 and 150 s^{-1} . System recovery is late in time, as evidenced by the significant area of the hysteresis loop.

Introduction of 2.5% of PEO-400 and PG, on the contrary, reduces the flow boundary, structural viscosity, and

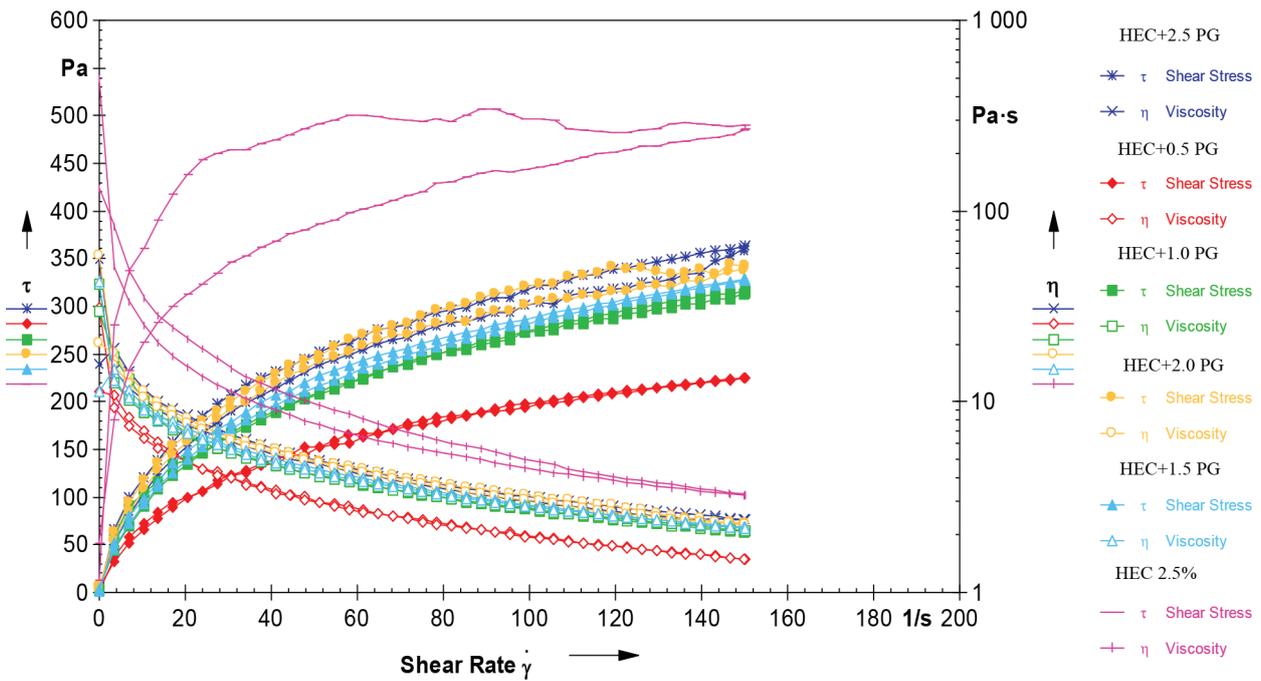


Figure 4. Dependence of the shear stress (τ , Pa) of HEC gels with the PG content from the gradient of shear rate ($\dot{\gamma}$, s^{-1}) and the dependence of the structural (dynamic) viscosity (η , $Pa \cdot s$) on the gradient of the shear rate (τ , Pa).

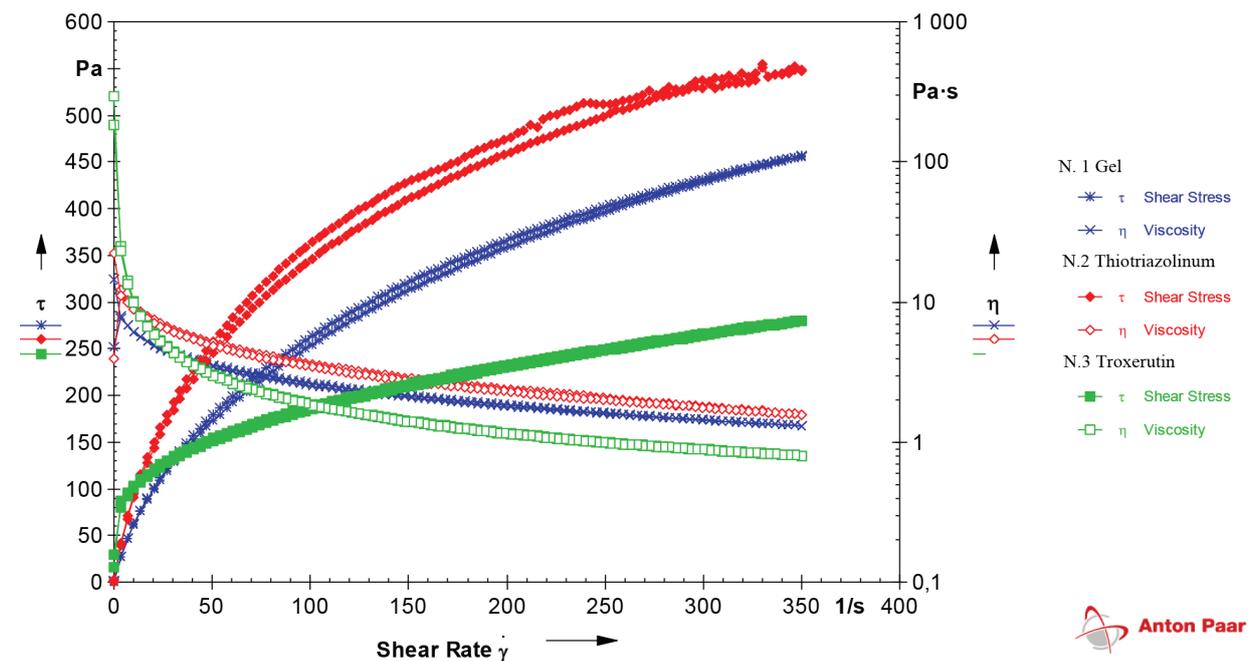


Figure 5. The dependence of the shear stress (τ , Pa) of the combined gel with test composition, Troxerutin and Thiotriazolium on the gradient of shear rate ($\dot{\gamma}$, s^{-1}) and the dependence of the structural (dynamic) viscosity (η , $Pa \cdot s$) on the gradient of the shear rate (τ , Pa).

hysteresis loop space. Judging by the values of the coefficients of dynamic rarefaction, these structured systems are mechanically stable.

Introduction of PG in the quantity from 1.0 to 2.5 g to the same extent changes the rheological properties of the gel, the obtained values are within the permissible error of the measuring instrument.

When introducing PEO-400 the linear relationship can be observed between the increase in rheological parameters and the increase in the content of this excipient.

Both for samples of gel with PG and with PEO- 400 rheopexy is maintained at low shear rates.

Taking into account the results of rheological studies and physicochemical properties of active pharmaceutical



ingredients PEG 40 hydrogenated castor oil was chosen as the most rational to support the structure of the combined gel with test composition.

The further rheological studies of the combined gel with test composition and finished medicines in the gel dosage forms, namely Troxerutin and Thiotriazolinum, were performed for comparative investigation of quality, consumer and stability indicators. The results of comparative rheological studies are represented in Fig. 5.

As can be seen from Fig. 5, the combined gel with test composition and Thiotriazolinum are dispersed systems that almost do not exhibit the flow limits (0.54 Pa and 0.36 Pa, respectively), while Troxerutin has the flow limit of 54.3 Pa. The ascending and descending curves of the stream are almost overlapping, which is typical for mud-shaped structures. This indicates high thixotropic (recoverability) properties of gel forms, with a displacement rate of 0.1 s^{-1} , the system is characterized by rheopecty properties.

The coefficients of dynamic dilution at shear rates of 3.4 and 10.3 s^{-1} are lower in gels with cellulose derivatives (No. 1 and No. 2) compared to gel with carbomers. The coefficients of dynamic dilution at displacement rates of 27.4 and 150 s^{-1} are almost at the same level.

The obtained results confirm that the developed gel corresponds to technological and consumer requirements to gels by the indicators of rheopecty and does not inferior to well-known medicines of industrial production.

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Conclusions

The obtained results of the conducted research of the rheological behavior of HEC gels of different concentrations allowed to establish the most rational concentration of HEC for the development of the combined gel with the dry extracts of white willow bark and sage leaves and methyl salicylate for the treatment of inflammatory diseases of the joints – 2.5%.

The influence of such excipients as propylene glycol, polyethylene oxide-400 and PEG-40 hydrogenated castor oil in different quantities on the rheological behaviour and rheopecty parameters of 2.5% HEC was investigated. It was determined that propylene glycol and polyethylene oxide 400 reduce rheopecty parameters, while PEG 40 hydrogenated castor oil increases these parameters. Therefore, PEG 40 hydrogenated castor oil was chosen as the most rational to support the structure of the combined gel with test composition.

The rheological properties of the developed combined gel with the dry extracts of white willow bark and sage leaves and methyl salicylate in comparison with finished medicines of domestic production in the same dosage form Troxerutin and Thiotriazolinum were investigated. The findings allow to conclude that the proposed combined gel is stable and that it has satisfactory quality and consumer characteristics, which indicates the rationality of continuing its research with a view to further implementation in industrial production.