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Rheology-based substantiation of a gel-former choice for vaginal gel

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Abstract.
Aim: The purpose of this work is to select a gel former in the vaginal gel.
Methods: The structural-mechanical properties were determined using the Rheolab QC rheometer by Anton Paar produced in Austria, which meets the requirements of ISO 3219 standard.
Results: The rheological parameters of gel samples with different gel formers have been studied. It has been established that the sample based on Aristoflex AVC has the highest index of the destroyed structure viscosity and the relaxation period, unlike other samples, which allows it to be selected as a gel forming component in the vaginal gel.
Conclusions: Aristoflex AVC was selected as a gel forming component in the vaginal gel.
Keywords: gel, vaginal gel, hyaluronic acid, resveratrol, rheology

INTRODUCTION

Gel is an effective semisolid dosage form for local application, which is a single, two- or multiphase system with a liquid dispersion medium whose rheological properties are due to the presence of gel formers at relatively low concentrations. The formation of gels is associated with the emergence and strengthening of bonds between the macromolecules of polymers with the formation of a spatial grid, which holds up to 99% of the total volume of the solvent in the intervals [1]. Gels possess certain rheological and structural-mechanical properties, which include viscosity, plasticity, elasticity and resilience. The strength of the internal structure depends on the nature and ratio of the components of the gel base and is estimated by the yield shear stress and thixotropy, which characterize the state of the system in static conditions, as well as the plastic viscosity, which characterizes the state of the system in dynamic conditions. Rheological parameters also affect such quality indicators of the drug as resistance to destruction, the convenience and ease of application to the surface of the skin, the bioavailability of the active substance, in addition, optimization of the production process can be carried out using data from rheological studies .The study of rheological parameters is important for choosing the mixing speed, temperature regime and determining the critical stages in the industrial production of drugs in the form of gel [2-5].In the course of rheological research it is necessary to determine such indicators as viscosity, deformation, shear stress. Shear stress is a measure of the intensity of the resistance of the internal forces of elasticity. The yield stress characterizes the ability of the bases and gels to perform some resistance to smearing, the ability to squeeze out of tubes and dispensers of industrial equipment [6,7]. Therefore, the definition of these indicators is a necessary step in the development of a semisolid dosage form of proper quality.

MATERIALS AND METHODS

The objects of the study were gel samples consisting of gel former, purified water, propylene glycol, lactic acid. Based on literature data and pharmacological studies resveratrol and hyaluronic acid were chosen as active substances. The pH of the manufactured gels was 4.5, which corresponds to the physiological value of the acidity of the vaginal mucous membrane [8].

For the study, we have selected 6 gel formers: Aristoflex AVC by Clariant (neutralized linked copolymer of acrylamidopropylpropane sulfonic acid and vinyl pyrrolidone), Sepimax Zen by Seppic (neutralized associative polymer with excellent resistance to electrolytes), Sepinov EMT 10 by Seppic (a powder polymer with excellent stabilizing properties), Hydroxyethylcellulose (HEC) produced by Ashland Aqualon Functional Ingredients (cellulose derivative, nonionic water soluble polymer), Carbopol Ultrez 21 , manufactured by Lubrizol (high molecular weight polymer of acrylic acid) and Methocel by Dow Pharmaceutical Solutions (water-soluble ether of cellulose - methylcellulose and hydroxypropyl methylcellulose) at a concentration of 1.5%. All samples were selected based on literature data on indicators of viscosity, pH, electrolyte resistance, degree of mucoadhesiveness. The samples were made in laboratory conditions at a temperature of 25 ° C., and the mixing speed was 100 rpm.

The structural-mechanical properties were determined using the Rheolab QC rheometer by Anton Paar produced in Austria, which meets the requirements of ISO 3219 standard. During the study, the systems of coaxial cylinders C-CC27 / SS were used. The ambient temperature was 25 C. The process of measuring the rheological curve included a linear rise and linear decline of shear rate with 105 measurement points (from 0.1 s^{-1} to 350 $s^{-1)}$ and point measurement length 1 s [9]. The results of the study were processed using the software.

Determination of the degree of the structure deformation was carried out using the Rebinder method by formula (1):

$$\alpha = \frac{\eta_0 - \eta_{e\phi}}{\eta_0 - \eta_n}, \qquad (1)$$

where: η_0 - the greatest viscosity;

$\eta_{e\phi}$ - effective viscosity;

η_n - the viscosity of the extremely destroyed structure.

The values of mechanical stability were calculated by the formula (2):

$$MC = \frac{\tau_1}{\tau_2}, \qquad (2)$$

where: τ_1 - the limit of the structure flow before destruction;

τ_2 - the limit of structure flow after destruction.

RESULTS AND DISCUSSION

At the first stage of the research an organoleptic analysis of the prepared samples was carried out. Results of organoleptic analysis are given in Table 1.

The results given in the table show that all samples are homogeneous in consistency, have the same color and specific odor. Samples with the addition of Carbopol Ultrez 21, Methocel, HEC, Aristoflex AVC are sticky to the touch, which may contribute to gel adhesion with mucous membranes, but the density of samples No. 4 and No. 6 is much lower than others. Samples No. 2, No. 3 are adhesive, capable of stretching, lengthening without breaking.

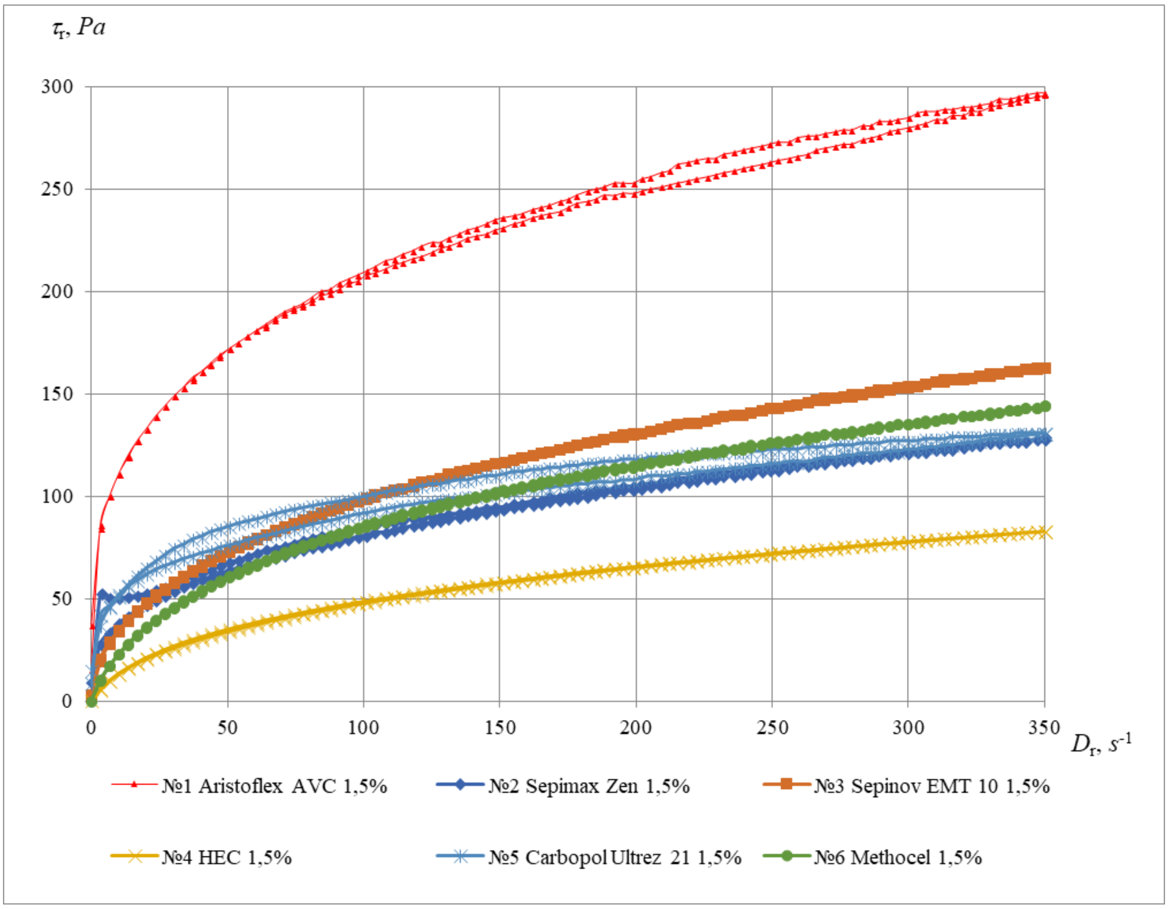

Figure 1 - Rheograms of the flow of gels samples № 1-6

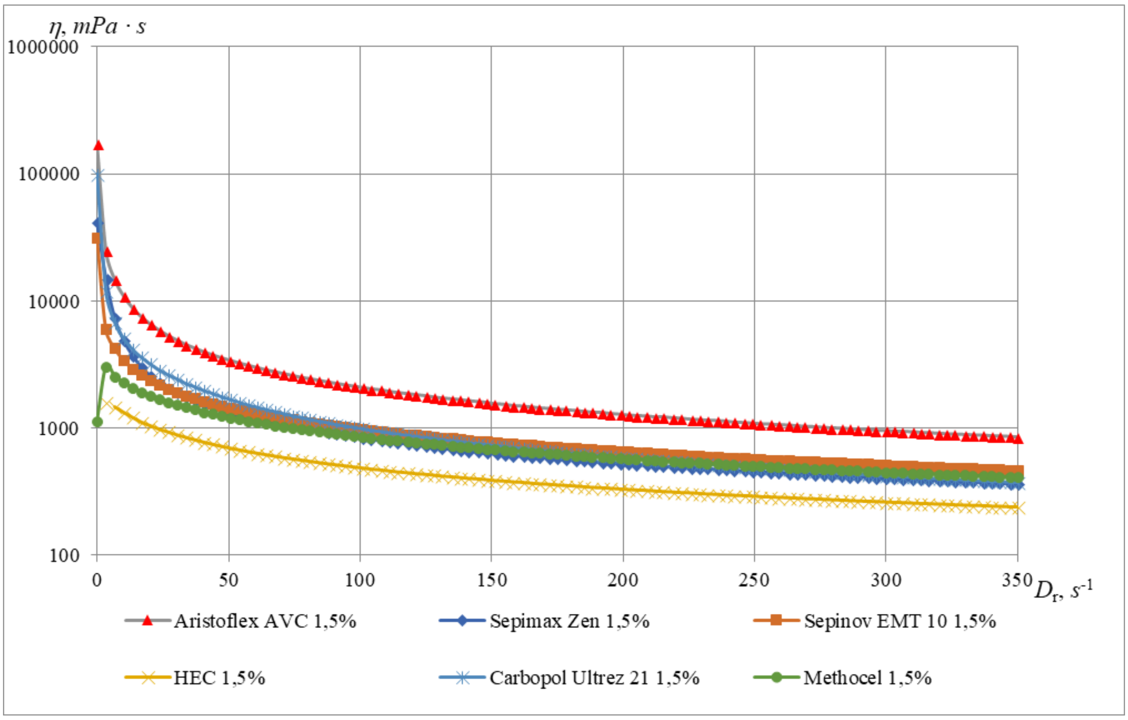

Figure 2 - The viscosity change curves of the samples under investigation, depending on the shear rate

Table 1: Organoleptic characteristics of the samples.

№	Gel-former	Organoleptic characteristics
1	Aristoflex AVC	Gel with a small amount of air bubbles, with a slight specific odor, of homogeneous consistency, light brown color, sticky, not viscid.
2	Sepimax Zen	Gel with a slight specific odor, with a large amount of air bubbles, light brown color, homogeneous consistency, sticky, low-viscid.
3	Sepinov EMT 10	Gel of homogeneous consistency, light brown color, with a slight specific odor, without air bubbles, non-sticky, slightly viscid.
4	HEC	Gel, light brown color, with a slight specific odor, homogeneous after mixing, loose, liquid consistency, slightly sticky, viscid.
5	Carbopol Ultrez 21	Gel of homogeneous consistency with a slight specific odor, with a large amount of air bubbles, light brown color, sticky, non-viscid
6	Methocel	Gel without air bubbles, loose, with a slight specific odor, light brown color, homogeneous after mixing, sticky, viscid.

Table 2: Specimen strength indicators.

Sample	No. 1 Aristoflex AVC	No. 2 Sepimax Zen	No. 3 Sepinov	No.4 HEC	No. 5 Carbopol Ultrez 21	No. 6 Methocel
The degree of the structure deformation	7,23	2,86	5,64	0,13	8,53	0,26
Mechanical stability	1,2	0,73	0,88	0,2	1,3	0,3

To mix gel systems, it is necessary to spend a certain amount of energy to overcome the forces of internal friction or viscosity, which for non-Newtonian systems depends on the shear stress. To do this, it is necessary to determine the structural and mechanical properties of samples of gels with selected gel formers. Therefore, at the next stage, we have conducted rheological studies of selected gel systems. According to the results of the study, flow rheograms were constructed (Fig. 1).

The obtained results indicate that all samples, at constant external conditions and at different shear rates, change their indicators, which suggests that they relate to the non-Newtonian type of flow. Unlike Newtonian structured systems, these systems are characterized by not dynamic but effective viscosity. The fluidity of the structured system occurs at a moment when the stress of the shear forces exceeds the stress, which is called the limit of fluidity [10-13].

As can be seen from Figure 1, for selected systems, a gradual decrease in viscosity is observed as the shear rate increases. Increasing the shear stress to the values of the yield line leads to a jump-like change in viscosity. With increasing loading, the viscosity of the samples decreases, but after removing the influence of external forces, the intensity is restored, which indicates the pseudoplastic flow type and the thixotropy of the structure. Since all the test specimens have the property of completely recovering after destruction, this suggests the presence of interaction between particles and molecules through the layers of the dispersion medium at the expense of the Van der Waals coupling forces, which allows them to be attributed to the coagulation structures [14-15].

According to the calculated hysteresis loop area, it was found that it varies in the row Carbopol Ultrez 21, Aristoflex AVC, Sepimax Zen, Methocel, HEC, Sepinov EMT 10, starting from 2406.54 Pa / s to 109.49 Pa / s. Unlike the hysteresis loop area values, the area under the hysteresis loop changes its values from 79990.44 Pa / s to 20125.41 Pa / s in the row Aristoflex AVC, Sepinov EMT 10, Sepimax Zen, Carbopol Ultrez 21, Methocel, HEC. All samples are very different for initial viscosity, samples of HEC and Methocel are of minimal value, which does not exceed 2.5 Pa · s. Samples based on Sepimax Zen and Sepinov EMT 10 have approximately the same values in the range of 31.6-42.04 Pa · s, but the largest values have samples based on the Carbopol Ultrez 21 (99.5 Pa · s) and Aristoflex AVC 174, 05 Pa · s The least stable systems that begin to destroy with minimum external forces are samples based on HEC, Methocel and Sepinov EMT 10, the viscosity of the beginning of the system destruction does not exceed 6 Pa · s. Samples based on Carbopol Ultrez 21 and Sepimax Zen require more external forces, the viscosity of initial structure destruction is 12-15 Pa · s. A more robust structure is a sample based on Aristoflex AVC - 24.84 Pa · s. The sample based on Aristoflex AVC has the largest relaxation period in terms of the highest viscosity of a non-destructed structure and of the maximally destroyed structure as opposed to other samples with significantly lower performance. All samples except No. 1 and No. 5 have a small area of the hysteresis loop, which suggests an insignificant destruction of the structure under the influence of external forces. The obtained data confirm the calculations of the structure deformation degree by the method of Rebinder.

The obtained data indicate that according to the index of the degree of structural destruction, samples based on Aristoflex AVC, Carbopol Ultrez 21 and Sepinov EMT 10 are the most stable ones. Samples based on HEC and Methocel have a figure significantly lower then 1.0, indicating their instability under the influence of external forces and the possibility of stratification and sedimentation of active substances. Also, the closest to 1 are samples number 1 and number 5. The data obtained can be explained by the presence of spatial grid in the studied sample, expressed the stronger the greater is the difference between η_o and η_p and increase in flow limit, which characterizes the strength of the structure. Figure 2 shows curves of viscosity variation depending on the shear rate.

As can be seen from Fig. 2. all samples are plastic systems in which the yield point is clearly expressed and its excess causes a sharp decrease in the value of effective viscosity. The results of the study of the viscosity dependence on the shear rate gradient indicate that the structural viscosity of the samples 1-6 decreases rapidly in the range 0.1 - 20 s^{-1} and then decreases gradually. For samples 1 and 5, the yield stress is in the range of 0.1-10 $s^{-1,}$ in contrast to 10-20 s^{-1} for samples 2,3,4,6, which allows concluding that they have a stronger structure. In the area of small values, the curves of samples 1, 5 have straight-line regions with a small inclination to the abscissa, indicating a rather low rate of deformation. Thus, as a result of the research, it has been found that, according to the complex of structural and mechanical properties, further studies on the development of the composition and technology of gel are reasonable to carry out with the sample No. 1 based on Aristoflex AVC, which is the most stable structure with optimal viscosity parameters for vaginal gels , .The use of the Carbopol Ultrez 21-based sample can lead to difficulties in the extrusion and packaging process, while samples based on Sepimax Zen, Sepinov EMT 10, Methocel and HEC do not have the proper consumer characteristics.

CONCLUSIONS

- according to organoleptic parameters, it was found that samples with the addition of Carbopol Ultrez 21, Methocel, HEC, Aristoflex AVC are sticky to the touch, which may contribute to gel adhesion with mucous membranes of the genitals;

- all samples obtained relate to the non-Newtonian type of fluidity, have a pseudoplastic flow type and a thixotropy of the structure, which allows them to be attributed to the coagulation structures. According to the indicators of the degree of destruction of the structure, mechanical stability, hysteresis area, the most stable are samples based on Carbopol Ultrez 21 and Aristoflex AVC;

- the rheological parameters of gel samples with different gel formers have been studied; it has been established that samples with the addition of HEC, Methocel, are inappropriate to use in the technology of semisolid formulations for vaginal application, since the initial viscosity of the samples does not exceed 2.5 mPa, which is insufficient for long fixation in place of application;

- It has been established that the sample based on Aristoflex AVC has the highest index of the destroyed structure viscosity and the relaxation period, unlike other samples, which allows it to be selected as a gel forming component in the vaginal gel.

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