# DETERMINATION OF VAGINAL GEL COMPOSITION ON THE BASIS OF BIOPHARMACEUTICAL AND RHEOLOGICAL RESEARCHES

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## Introduction

The period of hormonal instability in women is accompanied by such unpleasant manifestations of the genitourinary system as: itching, dryness, inflammation of the mucous membranes [1]. To treat urogenital symptoms, it is advisable to use vaginal gels that provide maximum therapeutic activity. As active substances, we have selected hyaluronic acid and resveratrol. Hyaluronic acid has a moisturizing and regenerating effect, resveratrol has antioxidant, estrogen-like, anti-inflammatory properties. The introduction of hydrophilic non-aqueous solvents (HNS) into the gel will provide a higher intensity of resveratrol release from the dosage form. In the previous studies, propylene glycol (PG) was selected as the HNS, which contributes to the uniform distribution of hyaluronic acid and is a resveratrol solvent in the gel [2,3]. It is non-toxic, exhibits penetrating properties, has a liquid consistency, which allows its use as a part of the gel without additional production costs. As a gelling agent, the aristoflex AVC was used, the choice of which was justified by previous rheological studies [4].

**The aim of the work**. The aim of the work is to determine the content of gelling agent in the composition of the vaginal gel for the treatment of urogenital symptoms during the period of women's hormonal instability and to determine the concentration of a non-aqueous solvent propylene glycol in the gel to provide release of the active ingredient, resveratrol.

## Materials & methods

To determine the rational content of PG in vaginal gel, samples were prepared with resveratrol and hyaluronic acid, the composition of which is given in Table.1.

**Table 1. Model samples of gels**

| Sample number | Propylene glycol content, % | Aristoflex AVC content, % |
|---|---|---|
| 1 | 10 | 1.5 |
| 2 | 15 | 1.5 |

Biopharmaceutical studies of resveratrol release by equilibrium dialysis through a semipermeable membrane for 6 hours were performed [5]. The optical density of the samples obtained was determined using Evolution 60-S spectrophotometer at a wavelength of 270 nm in a cuvette with layer thickness of 1 cm. The samples were placed in a volumetric flask and diluted with phosphate buffer solution of pH 4.5 to obtain a solution with an optimal optical density value, which is within the limits of the Beer-Lambert law. A phosphate buffer solution of pH 4.5 was used as the control solution , which corresponds to the physiological parameters of the genital mucous membranes.

The concentration of the samples obtained (g / ml) was calculated by the formula (1), using the optical densities of the standard solutions obtained during the construction of the graph:

$$C = \frac{A \cdot C_{cm} \cdot b}{A_{cm}}, \quad (1)$$

where: *A* - optical density of the investigated solution;
*A st* - optical density of the standard solution;
*C st* - concentration of standard solution g / ml;
*b* - dilution

The concentration of the gelling agent was determined by rheological performance using the Rheolab QC rheometer, by Anton Paar, Austria, which meets the requirements of ISO 3219. The composition of the prototype samples is given in Table 2.

**Table 2. Composition of the prototype samples**

| Sample number | Aristoflex AVC content, % | Propylene glycol content, % |
|---|---|---|
| 2a | 1 | 15 |
| 2b | 1.5 | 15 |
| 2c | 2 | 15 |

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 increase and a linear decrease in the shear rate with 105 measuring points (0.1 $s^{-1}$ to 350 $s^{-1}$) and a measurement time point of 1 s. The results of the study were processed using the software RheoCompass ™ [6,7].

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

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

where: $\tau_1$ - the yield stress before destruction;

$\tau_2$ - the yield stress of the structure after the destruction.

Statistical processing was carried out using Microsoft Excel software.

## Results & discussion

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Graphical comparison of the total amount of resveratrol, which has passed into solution g / ml 10 $^{-5}$ is shown in Figure 1.

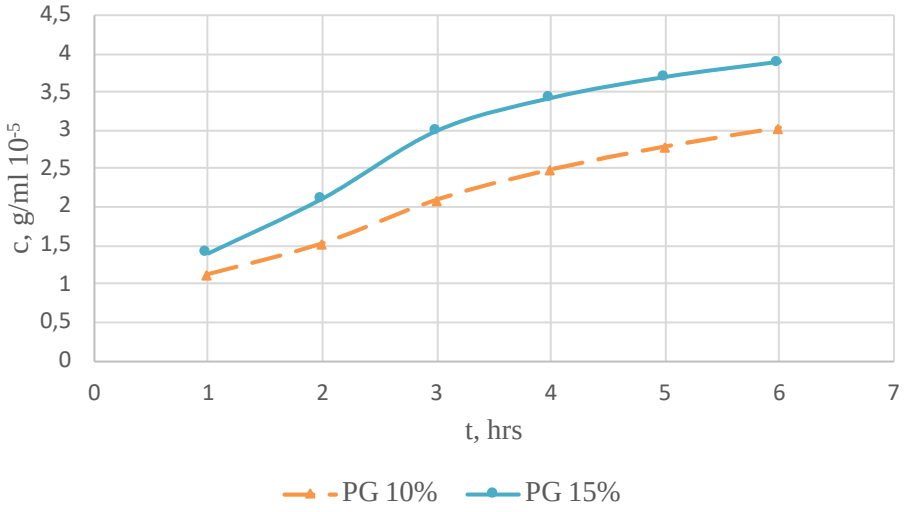


**Fig.1 The total amount of resveratrol passed into the solution, g / ml 10 $^{-5}$.**

The results shown in Fig. 1 indicate that increase in the concentration of propylene glycol to 15% contributes to an increase in the velocity and completeness of the active ingredient release from the gel samples. During 6 hours of the experiment from the sample number 2 to the solution 1,3 times greater amount of resveratrol had passed in comparison with the sample number 1. Thus, it was found that 15% PG content in the gel is rational. An increase in the content of PG in the composition of the gel is inappropriate according the literature and will lead to a significant dilution of the dosage form [8, 9].

The next stage of the research was the choice of gelling agent concentration in the gel composition. Samples with concentration of aristoflex 1%, 1.5% and 2% were used for the study (Table.2). The results of the study are shown in Figure 2.

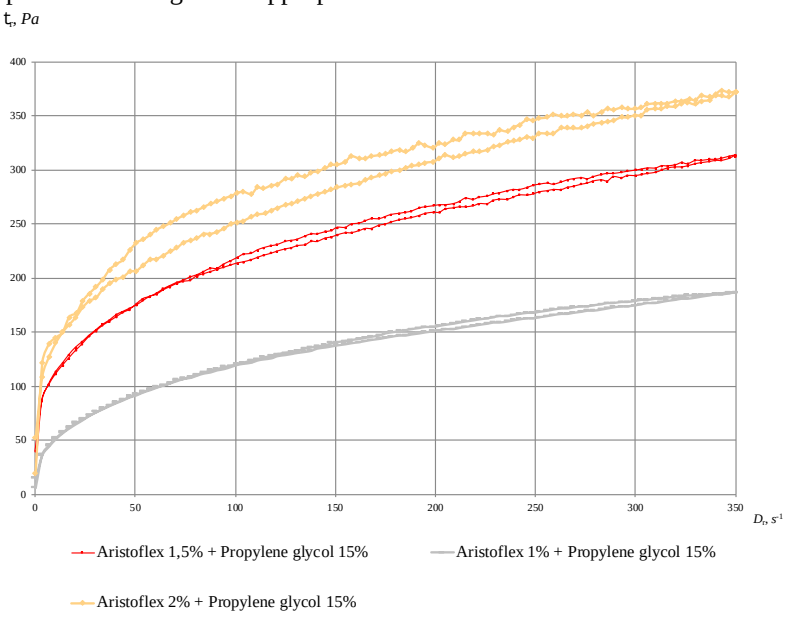


**Fig.2 Rheograms of gel samples with different concentration of gel former.**

As can be seen from Figure 2, all systems are coagulating with a pseudoplastic flow type and a certain

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degree of thixotropy. A sample of Aristoflex of concentration 1% is a liquefied system that has practically no structure, as evidenced by the minimum area of the hysteresis loop 951.12. The difference between the initial and final viscosity is 77,000 mPa * s, which may indicate instability of the sample at a minimum effect of external forces. An increase in the concentration of the gel former results in the strengthening of the structure. Specimens with aristoflex concentration of 1.5% and 2% require an increase in shear strength by 2 times for the dilution of the structure compared to a sample with a gel concentration of 1%. However, in a sample with a concentration of 1.5%, the area of the hysteresis loop (1375.62) is smaller than the area in the sample with a concentration of 2% (5350.26), which indicates a greater ability to evenly distribute in the place of application and the best consumer properties of sample 2b [ 10,11]. The dependence of the viscosity of the experimental samples on the shear rate is shown in Fig. 3

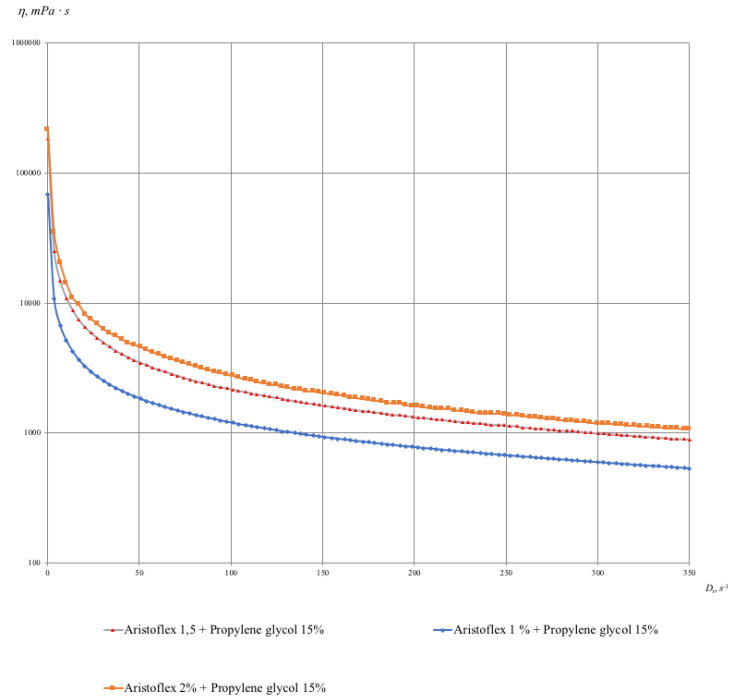


**Fig. 3. Viscosity change curves of the samples under investigation, depending on the shear rate.**

As can be seen from Fig. 3 with an increase in the shear rate, the specimen with aristoflex concentration 1% is the least strong. With an increase in the shear rate in this sample there is a sharp initial loss of viscosity parameters compared with others. The effect of shear rate in specimens with aristoflex concentration of 1.5% and 2% occurs more gradually. An increase in the content of the gel former leads to the formation of a more dense structure as confirmed by the yield strength indicators given in Table 3.

**Table 3. Indicators of samples' strength**

| **Sample** | **Aristoflex AVC 1%** | **Aristoflex AVC 1.5%** | **Aristoflex AVC 2%** |
|---|---|---|---|
| Yield strength | 0.91 | 1.12 | 1.41 |

According to the results presented in Table. 3 it was established that the index of yield strength of the sample with aristoflex concentration of 1.5% is maximally close to 1, unlike other samples. Aristoflex sample of concentration 1% is an unstable system as indicated by yield strength of less than 1. The results of the study of the yield strength of the specimen containing 2% of aristoflex indicate a dense structure, which may lead to its uneven distribution at the site of application and deterioration of the active substance release from the drug. The obtained data indicate the possibility of a sample with the gel former concentration of 1.5% to withstand mechanical effects in the process of homogenization and to have a necessary consistency when applied [12].

To confirm the appropriateness of choosing a concentration of 1.5%, a comparison of structural and mechanical parameters with the drug "Ginodek" in the form of vaginal gel, which is widely used in the treatment of gynecological diseases has been performed.

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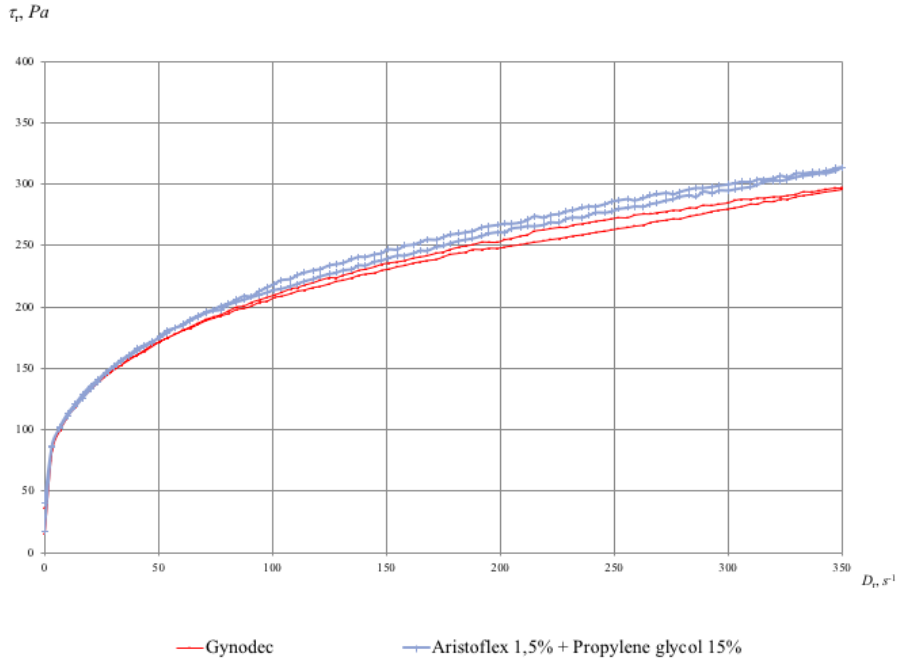


**Fig. 4. Rheograms of investigated samples**.

As can be seen from Figure 4, the samples do not differ significantly from each other in rheological indexes, which can testify of qualitative consumer characteristics of gel with aristoflex concentration 1.5% .

To determine the influence of PG on rheological parameters of the gel, a comparative analysis of the structural and mechanical parameters of samples, containing PG in the amount of 15% and without PG was carried out, the results of which are given in Table 3.

**Table 3. Structural-mechanical parameters of gel samples**

| **Indicator** | **Aristotleflex 1.5% + PG 15%** | **Aristoflex 1.5%** |
|---|---|---|
| Initial viscosity [Pa * s] | 174 ± 0.87 | 183 ± 0.81 |
| Finishing viscosity [Pa * s] | 0.848 ± 0.73 | 0.897 ± 0.77 |
| Viscosity of the restored structure [Pa * s] | 370 ± 0.91 | 398 ± 0.57 |
| Viscosity of the beginning of the flow [Pa * s] | 24, 84 ± 0.65 | 25.1 ± 0.43 |
| The area of the hysteresis loop | 1397.02 ± 0.71 | 1375.62 ± 0.54 |
| Area under the hysteresis loop | 79990.44 ± 0.72 | 83555.43 ± 0.62 |

The data of the structural and mechanical parameters of the two samples, given in the table, differ from each other on average by no more than 3,4%, which indicates their almost identical structure and properties. Based on the results of the study, it can be concluded that addition of propylene glycol to the gel does not significantly affect the rheological properties.

**Conclusion**

1) Biopharmaceutical studies using equilibrium dialysis through a semipermeable membrane have been conducted to determine the concentration of propylene glycol in the composition of vaginal gel. Quantitative resveratrol content was determined spectrophotometrically by the standard method. It has been established that the optimal concentration of PG, which contributes to the maximum release of the active substance, is 15% of the total mass of the sample.

2) According to the results of the determination of rheological indicators, the optimal concentration of aristoflex has been set as 1.5%. This content of the gelling agent provides a stable coagulation structure with a pseudoplastic type of flow, which determines the consumer and biopharmaceutical properties of the drug.

3) The results obtained should be used in further studies on the development of vaginal dosage forms with plant components.

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**Aim**. The aim of the work is to determine the content of gelling agent in the composition of the vaginal gel for the treatment of urogenital symptoms during the period of women's hormonal instability and to determine the concentration of a non-aqueous solvent propylene glycol in the gel to provide release of the active ingredient, resveratrol. **Materials and methods.** As objects of the study samples of gels with resveratrol and hyaluronic acid with varying concentrations of gelling agent aristoflex AVC and non-aqueous solvent propylene glycol have been taken. Biopharmaceutical studies by equilibrium dialysis through a semipermeable membrane for 6 hours were performed to select propylene glycol concentration. The optical density of the samples obtained was determined using Evolution 60-S spectrophotometer. The concentration of the gelling agent was determined by rheological performance using the Rheolab QC rheometer, by Anton Paar, Austria. **Results**. In the course of the study, a comparison was made between resveratrol release from samples with propylene glycol concentration of 10% and 15%. At 6th hour of the experiment, a larger amount of resveratrol, which has passed to the solution, was observed in a sample with propylene glycol concentration 15%. It has been established that an increase in the concentration of propylene glycol contributes to an increase in the rate of the active ingredient release from gel samples. Thus, for further studies on the development of vaginal gel composition, the concentration of non-aqueous solvent was chosen to be 15%. At the next stage, the choice of gel-former concentration in the gel was made. In the course of the study, rheological properties of samples with gel-former concentration of 1%, 1.5% and 2% have been compared. The obtained rheograms of gel samples indicate that all systems are coagulating with a pseudoplastic flow type and a certain degree of thixotropy. A sample with the concentration of 1% is a liquefied system that has practically no structure, as evidenced by the large difference between initial and final viscosity. An increase in the concentration of gelling agent to 2% leads to a strengthening of the structure. The sample with Aristoflex concentration 1,5% has optimal rheological parameters that can provide high biological availability of active substances. **Conclusions**. It has been established that the optimal concentration of PG, which contributes to maximal release of the active substance, is 15% of the total mass of the sample. According to the results of rheological research, the rational content of the gel-former in the gel is 1,5%.

**Keywords**. Vaginal gel, rheology, dialysis, resveratrol.

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