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Investigating Bioadhesion Indicators of Vaginal Gels Formulated with Resveratrol and Hyaluronic Acid

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Abstract

Aim. The purpose of the work is to determine the bioadhesion indices of vaginal gel with resveratrol and hyaluronic acid, as well as the choice of the type and content of mucoadhesives in the composition.

Materials and methods. As research objects samples of gels with different mucoadhesives in the composition were used. Among used mucoadhesives were: sodium alginate (FMC BioPolimer AS, Norway), methyl cellulose (Shin Etsu, Germany), Methocel – methyl cellulose with hydroxypropylmethyl cellulose (Dow Pharmaceutical Sciences, USA), OraRez® W-100L16 – vinyl methyl ether and maleic anhydride copolymer (BOAI, China). As a comparison drug, vaginal gel "Gynodec" (Yuriya-Pharm) was used. During the study, the rate of gel distribution, the degree of deformation under the influence of mechanical forces, the degree of the gel fixation on the surface of the mucosa and the adhesion ability of the samples have been determined.

Results. The study has determined that sample No. 2 with sodium alginate has the highest distribution rate, which was 1.56 cm/min. The study of the fixation of samples on the surface of the model of the mucous was performed by the method of flow. The results have showed that the sample with sodium alginate has the closest value to the reference drug. The adhesive ability of samples with different sodium alginate contents was determined. The tensimetric study has found that at a concentration of 0.5 %, the force required to separate the surface is 6158 Pa.

Conclusions. On the basis of the complex of physico-chemical studies, bioadhesion indicators of vaginal gel with resveratrol, depending on the type and concentration of mucoadhesives have been determined. According to the distribution parameters on the surface of the genital mucosa model, it has been found that the best properties compared with other types of mucoadhesives has a sample containing sodium alginate. The study by means of a strain gauge has found that the addition of sodium alginate at a concentration of 0.5 % would provide a satisfactory adhesive ability of the vaginal gel.

Keywords: vaginal gel, bioadhesion, mucoadhesives, sodium alginate, resveratrol, hyaluronic acid, membrane, hormonal disorders, climacteric, prolonged action.

1. Introduction

Among vaginal dosage forms, gels are widespread, due to the ability to provide prolonged moisturizing action, ease of use and dosage [1].

When developing the composition and technology of vaginal gels in addition to rheological characteristics it is important to evaluate the degree of bioadhesion, which determines the possibility of keeping an active pharmaceutical ingredient (API) on the surface of the affected organ by means of interphase forces for a long time [2]. If adhesive fixation occurs to the mucous membrane, this process is called mucoadhesion, which determines the time of drug retention on the surface, its uniform distribution, the absence of premature evacuation of the administered dose and the completeness of the API release [3, 4].

Properties of the mucous tissue of genital organs are due to the presence of specific glycoproteins – mucins, which are located on the apical surface of the epithelial layer or as a part of the mucus. Interaction with mucins and the possibility of long-term fixation with controlled release of active substances are provided by mucoadhesive substances, as which most often use hydrophilic polymers. They have numerous hydrophilic groups that promote adhesion and cause the swelling of polymers in the fluid and thus increase the amount of adhesive sites [5, 6].

2. Aim of research

The aim of the work is to determine the bioadhesion indices of vaginal gel with resveratrol and hyaluronic acid, as well as the choice of the type and content of mucoadhesives in the composition.

3. Objects and methods.

The subject of the study were samples of vaginal gels with different mucoadhesives at a concentration of 0.5 % [1]. The composition of the prototype samples is given in **Table 1**.

Table 1

Composition of prototype samples

The name of the substance	Sample number				
	1	2	3	4	5
Hyaluronic acid	+	+	+	+	+
Resveratrol	+	+	+	+	+
Propylene glycol	+	+	+	+	+
Aristoflex	+	+	+	+	+
Sodium alginate	–	+	–	–	–
Methylcellulose	–	–	+	–	–
Methocel	–	–	–	+	–
OraRez	–	–	–	–	+

Among used mucoadhesives were: sodium alginate (FMC BioPolimer AS, Norway), methylcellulose (Shin Etsu, Germany), Methocel – methylcellulose with hydroxypropyl methylcellulose (Dow Pharmaceutical Sciences, USA), OraRez ® W-100L16 – copolymer of vinyl methyl ether and maleic anhydride (BOAI, China).

As a reference drug, the vaginal gel “Gynodek” (Yuriya-Pharm), which contains hyaluronic acid – 2.5 % (sample number 6), was used.

Vaginal dosage forms have a short residence time at the place where the drug is applied, therefore, for its control as well as determination of fixation degree the rates of distribution and adhesion have been determined [7, 8].

The study of the gel distribution rate was carried out using a polymeric film of borosilicate fibre (manufactured in Japan) with a layer of 3.7 % solution of hydroxypropylmethylcellulose, which simulated vaginal mucus. The film was mounted at an angle of 25°, which corresponds to the physiological location of the vagina relative to the vertical axis of the vertebral column. On the film surface, the starting line was marked and applied 1.0 g of a sample. The time of the experiment was 10 minutes, which corresponds to the physiological rate of vaginal secretion. After that, measured the distance from the point of the gel application to the end point of the path and calculated the average speed of its distribution [9, 10].

Study of the deformation degree during loading was carried out according to the following procedure: a film of borosilicate fibre was mounted on the surface of the object glass; The sample of the preparation in the amount of 0.5 g was applied to the film, covered with another sample glass and measured the diameter of the resulting spot. A load (100 g) was placed on the upper slide glass and measured the diameter of the spot after 5 minutes of the experiment. The distribution coefficient was calculated according to formula 1 [11].

$$k = \frac{d^{max}}{d_0}, \quad (1)$$

where d_0 – the initial diameter of the gel spot; d_{max} – The diameter of the spot after 5 minutes of the experiment.

Determination of the degree of gel samples dilution by cervical mucus was carried out by the method of "flow" [10]. On the model membrane, the test gel samples were applied in an amount of 0.5 g and placed in a Petri dish with 25 ml of physiological saline of pH 4.0 for 1 hour. Carried out the organoleptic analysis and calculation of samples' spot areas by the formula (2).

$$S = d^2 \times \frac{\pi}{4},$$

where d^2 – diameter of the gel sample spot.

The study of adhesion ability was carried out using a tensiometer, recording of the indicators was carried out using an electronic dynamometer. The test specimen was placed in a petri dish fixed on a horizontal surface. The weight of the test sample was calculated from the ratio of 0.25 g/cm^2 of the area of the cover plate, which provides the optimum thickness of the layer to measure the separation effort of the sample-plate contact surface. A sample of gel was pressed with a plate equipped with a rod to transfer the separation effort to the dynamometer, the contact surface was previously covered with a thin layer of paraffin until it was completely wetted with a sample. To provide a uniform effort, a load (6) weighing 1 kg was placed on the plate for 60 seconds, after which the load was removed. The dynamometer with the attached contact plate was lifted upright up to the detachment of the contact plate from the surface of the sample and fixed the required separation effort according to the dynamometer readings [12].

The calculation of adhesion was carried out with the force necessary for the separation of the two surfaces after the occurrence of adhesion [13]. The force was calculated by formula (2).

$$Sm = \frac{Fm}{Ao}, \quad (2)$$

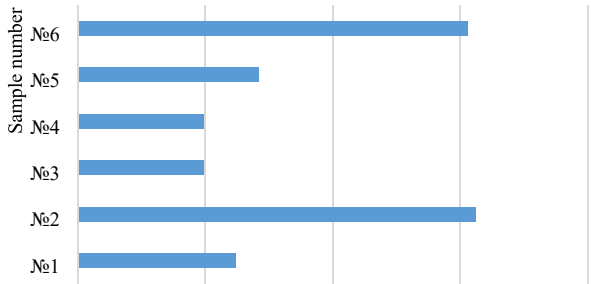
where Fm – maximum separation force; Ao – total surface area.

4. Research results

At the first stage of the study, distribution rate of the vaginal gel specimens with different gel formers was measured (**Fig. 1**).

Ability to distribute under the action of external forces is an important characteristic of semisolid dosage forms, so at the next stage, the determination of the effect of mechanical force on the distribution of experimental samples on the surface of the model mucosa has been carried out (**Fig. 2**) [14, 15].

The next step was to determine the indices of samples fixation of on the surface of the application by the "flow" method [16, 17]. The organoleptic parameters of the samples and the values of the spots area after application to the surface of the film are presented in **Table 2**.



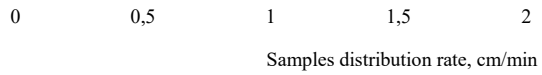


Fig. 1. Indicators of samples distribution rates

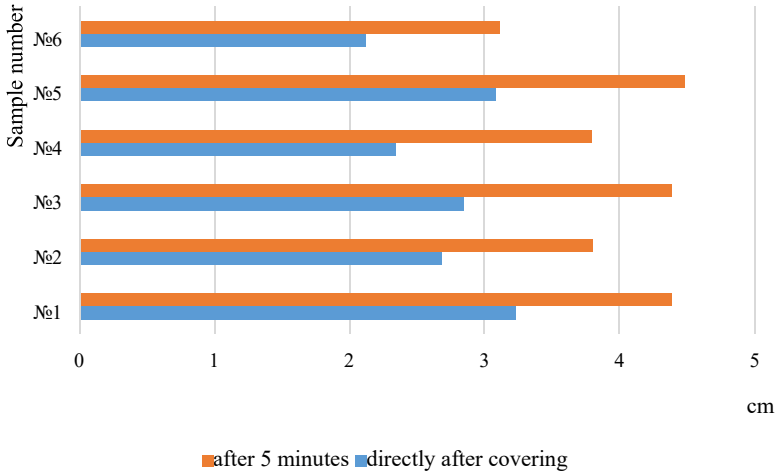


Fig. 2. Comparative characteristic of the diameter of the spots under the action of mechanical forces

Table 2
Comparative analysis of gel samples after blurring

No.	d1	d2	S	Description
1	1	1.1	0.95±0.02	There is a blur of the edges of the gel spot, the shape and relief do not change. Poor fixation on the film surface.
2	1.6	1.9	2.83±0.11	Uniform blurring of the spot edges. Full fixation on the film.
3	1.2	1.5	1.77±0.04	Changing the shape of the spot, the shape of the gel spot has changed. Partial fixation on the film.
4	1.2	1.5	1.77±0.05	Uniform blurring of edges without changing shape and relief, partial fixation on the film.
5	1.3	2.2	3.80±0.19	Uniform blurring of the edges of the spot, no fixing on the film.
6	1.5	1.7	2.27±0.04	A uniform blurring of gel spot with complete fixation on the film.

Note: d1 is the initial diameter, d2 is the final diameter, S is the gel spot area after 1 hour of experiment

To determine the final concentration of sodium alginate, the determination of the adhesive ability of the gel with different concentrations of mucoadhesives – 0.25 %, 0.5 % and 1 % was performed [18, 19]. As a comparison drug, Gynodec was used. The results of the study are shown in **Fig. 3**.

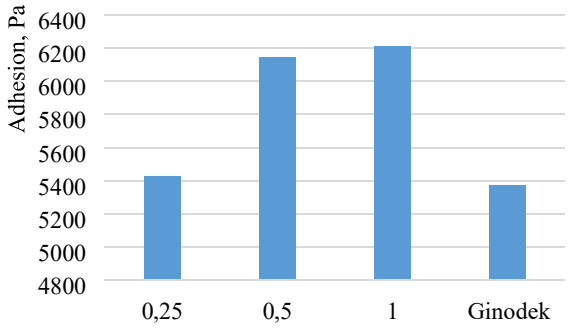


Fig. 3. The degree of samples' adhesion

5. Discussion of the research results

According to the results of the study (**Fig. 1**), it can be concluded that sample No. 2 with sodium alginate has the highest rate of distribution, which is almost identical to the comparator (1.56 and 1.53 cm/min, respectively).The samples number 3 and number 4 have the lowest values, their rate of distribution is 0.49 cm/min. Samples No. 2 and No. 6 flowed evenly over the film surface, while samples No. 1, 3, 4, and 5 stopped moving in a few minutes and formed a gel cluster in the form of a drop, indicating that the mucous membrane was covered unevenly [20].

The obtained results indicate that samples No. 2 and No. 6 have the highest internal cohesion indices, as evidenced by the area of spots and distribution coefficients, which make up 1.42 and 1.47, respectively. In other samples, there is a decrease in the adhesion to the surface, which leads to deterioration of their fixation on the surface. The distribution coefficients increase to 1.68.

The next step was to determine the indices of samples fixation of on the surface of the application by the "flow" method. As shown in **Table 2**, all samples are capable of blurring over time. The closest value of the spot area to the reference preparation has sample No. 2 with sodium alginate as an adhesive. Visual observation makes it possible to conclude that only in the samples number 2 and 6 there is complete fixation of gel spots without changing their shape. The most unstable is sample No. 5 with OraRez, which has the largest spot area (S=3.80), but during the experiment there is a blurring of the spot without fixing on the film. In other samples there is a change in shape, uneven blurring without or only with partial fixation on the surface of the film. The reduction of the area of the spots of other samples takes place in the row number 3 = number 4 > number 1, which correlates with the data of previous studies.

The results of the study indicate that the adhesive ability of the sample with the of sodium alginate concentration 0.25 % is almost identical to the preparation of comparison **(Fig. 3).** Increasing its concentration to 0.5 % contributes to a significant increase in the force required to separate the two surfaces from 5380 to 6158 Pa. A further increase in concentration to 1 % does not lead to a significant increase in adhesion degree.

Thus, based on the performed studies, it was found that a rational concentration of sodium alginate in the composition of the gel to ensure its bioadhesive properties should be considered 0.5 %.

6. Conclusions

1. On the basis of the complex of physico-chemical studies, bioadhesion indicators of vaginal gel with resveratrol, depending on the type and concentration of mucoadhesives have been determined.

2. According to the distribution parameters on the surface of the genital mucosa model, it has been found that the best properties compared with other types of mucoadhesives has a sample containing sodium alginate.

3. The study by means of a strain gauge has found that the addition of sodium alginate at a concentration of 0.5 % would provide a satisfactory adhesive ability of the vaginal gel.

4 The results of the study can be used in the further development of the composition and technology of vaginal drugs.

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