USE POLYVINYLPYRROLIDONE IN TECHNOLOGY OF GYNAECOLOGICAL POWDERS CONTAINING LACTIC ACID COMPLEXED WITH CHITOSAN

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Abstract
Gels obtained from powders containing lactic acid complexed with chitosan reveal a stoichiometric ratio of 1:1, 2:1, 3:1, 4:1 and 8:1. Their pH ranged from 3.92 to 4.44 for 1:1 gels and from 2.36 to 2.84 for the 8:1 ratio. The addition of 5% polyvinylpyrrolidone K-90 increased the pH from 4.28 to 4.52 for 1:1 and from 2.58 to 3.30 for the 8:1 ratio. The addition of 5% polyvinylpyrrolidone K-90 increased the dynamic viscosity from 84 to 510 mPa·s for 1:1 gels and from 47 to 386 mPa·s for the 8:1 ratio. The gels obtained from powders possess the work of adhesion - the energy needed to separate the gel from the probe was 15.2 g/s for gels with 5% polyvinylpyrrolidone K-15, 52.76 g/s for gels with 5% polyvinylpyrrolidone K-30, and 56.6 g/s for gels containing 5% polyvinylpyrrolidone K-90. The results proved that it is possible to produce a preparation with optimal pharmaceutical and application properties.

Key words: *lactic acid complexed with chitosan, physiological environment of vagina, hydrophilic powders passing gels, vaginal mucosa, anti-inflammatory drugs, vaginal infections.*

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1. Introduction

The use of hydrophilic gels with high adhesion properties and the ability to spread over the vaginal mucosa enables the prolonged action of the drug. The preparations, remaining at the site of application, produce an adequate pH in the environment thanks to the content of lactic acid complexed with chitosan [1 - 12].

Previously conducted studies encourage further research opportunities to optimise the pharmaceutical properties of formulations tested for gynaecological purposes. These powders for gynaecological purposes pass under natural conditions in the gel covering the vaginal mucosa.

The aim of this study was to investigate the influence of selected polymers on the physico-chemical properties of powders for gynaecological purposes.

By adopting the above-mentioned assumptions, the impact of polyvinylpyrrolidone K-15, polyvinylpyrrolidone K-30 and polyvinylpyrrolidone K-90 on the properties of the powders was tested. The study prepared formulations with different pH and rheological properties.

The device simulating the conditions in the vagina was used to study the adhesion and movement of the gel on the mucosa of the organ. Powder pass gels were examined for their properties.

In vitro studies have demonstrated that the gels obtained from the powders were maintained at the application site. Backfill after application of the apparatus simulated the natural conditions in the gel passes and covered the surface.

As a result of studies, the dynamic viscosity of the gels was obtained from powders. The test shows the thixotropical properties of gels. A wide range of pH of the gels allows selection of the optimum formulation.

2. Materials and methods

2.1. Materials

The following chemicals were used in investigations: lactic acid (P.Z.F. Cefarm (Wrocław, Poland), chitosan with a deacetylation degree of 93.5% (Sea Fisheries Institute, Gdynia, Poland), methylcellulose (Aldrich Chemical Company Ltd. Gillingham – Dorest SP 84 SL, England), polyvinylpyrrolidone K-15, K-30, K-90 (Aldrich Chemical Company Ltd. Gillingham – Dorest SP 84 SL, England), and aqua purificata, acc. to FP IX.

2.2. Methods

2.2.1. Measurements of physical properties

2.2.1.1. Rheological investigations (dynamic viscosity)

Rheological investigations were performed using a rotational viscosimeter. The determinations were performed in I a and II a range on a K-1 cone with the diameter of 36 mm

and a fissure of 0.917 at 37 °C. The shear angle was measured using 12 shear rates in the ascending direction and 11 rates in the descending direction. Viscosity and torque were calculated from appropriate formulas. The results obtained were used to plot the flow curves of the investigated gels. The results obtained in the experiment are presented in ***Table 2*** and ***Figure 1***.

2.2.1.3. Measurement of texture

To perform the measurements, a probe (P/1S) in the shape of a ball, built from stainless steel, with a diameter of 1 inch, was used.

The main measurement parameters were as follows: speed of downward movement of the probe during the test was 0.5 mm/s, the lifting speed of the probe was 10 mm/s, the maximum permissible force in the method was 100 g, the dwell time of the probe in the gel was 10 s, and the height at which the probe was raised above the surface of the gel was 40 mm.

The assay was started by placing the gel in a cylindrical vessel with a transparent plexiglass texturometer set on the table. Then, the probe was lowered just above the surface of the gel so that there was no direct contact between them. After selecting the appropriate parameters in the program, the study was started. After contact with the surface of the gel (remains in this position for 10 seconds), the probe began to rise at a speed of 10 mm/s at a height of 40 mm above the surface of the gel.

The study was conducted in order to illustrate the influence of the type of methylcellulose on the adhesion strength gels. All gels were tested three times and the results reported as the average of three measurements. The study sample gel is shown in ***Figures 2 - 4***.

2.2.2. Technology of manufacture of hydrophilic intravaginal powder

The production of powder containing lactic acid complexes with chitosan consisted of the following stages:

1. Obtaining the lactic acid-chitosan complex.

Chitosan combines with organic acids by means of I-order amine groups. This property was used in the preparation of the complex. The required amount of powdered chitosan was poured onto a weighed amount of lactic acid. The mass was stirred until a homogenous suspension was obtained. The mixture was left for 24 h until a clear, thick fluid was formed that could be joined with methylcellulose [4].

2. Obtaining the excipient-preparation of powder from methylcellulose.

A powder was obtained from methylcellulose by adding a known amount of this compound to the lactic acid complexes with chitosan and polyvinylpyrrolidone K-15, K-30, K-90. The resulting powder was thoroughly pulverised. The homogenous powder was obtained by passing through a sieve with a mesh size of 0.16 mm.

3. Obtaining the gel from powder for researches.

A gel was obtained from powder, by adding a known amount of distilled water. In order to enhance the process of gelation, the mixture was cooled to 5 - 10 °C. The homogenous gel was weighed and enough distilled water was added to obtain the initial mass.

3. Results and discussion

Gels obtained from powders, containing lactic acid complexed with chitosan, reveal stoichiometric ratios of 1:1, 2;1, 3:1, 4:1 and 8:1. Their pH ranged from 3.92 to 4.44 for 1:1 gels and from 2.36 to 2.84 for the 8:1 ratio (***Table 1***).

The addition of 5% polyvinylpyrrolidone K-15 increased the pH from 3.90 to 4.10 for 1:1 gels and from 2.40 to 2.90 for the 8:1 ratio. The enrichment of the composition of the tested powders containing 5% polyvinylpyrrolidone K-30 resulted in an increase in the pH of the formulation to between 4.20 to 4.40 for 1:1 gels and from 2.46 to 3.15 for the 8:1 ratio. Further addition of 5% polyvinylpyrrolidone K-90 resulted in a further increase in pH of the formulations from 4.28 to 4.52 for 1:1 gels and from 2.58 to 3.30 for the 8:1 ratio.

Rheological studies demonstrated that the researches gels obtained from powders possess dynamic viscosity from 53 to 398 mPa·s for the 1:1 stoichiometric ratio in the complex and from 19 to 242 mPa·s for the 8:1 ratio (***Table 2***).

The addition of 5% polyvinylpyrrolidone K-15 increased the dynamic viscosity from 68 to 420 mPa·s for 1:1 gels and from 24 to 290 mPa·s for the 8:1 ratio.

A modification of the composition of the tested powders containing 5% polyvinylpyrrolidone K-30 increased the range of the dynamic viscosity of formulations suitably from 79 to 458 mPa·s for 1:1 gels and from 35 to 340 mPa·s for the 8:1 ratio. Further addition of the 5% polyvinylpyrrolidone K-90 resulted in a further increase in dynamic viscosity of the

Table 1. *Influence of methylcellulose viscosity on pH gels obtained from investigated powders.*

Stoichiometric ratio lactic acid to chitosan	pH gels with addition methyl-cellulose				
	4000 mPa·s	1500 mPa·s	400 mPa·s	25 mPa·s	15 mPa·s
1:1	3.92	3.96	4.17	4.25	4.44
2:1	3.48	3.82	4.04	4.19	4.25
3:1	3.17	3.25	3.44	3.65	3.90
4:1	2.75	2.87	2.90	2.95	3.09
8:1	2.36	2.58	2.65	2.78	2.84

Table 2. *Influence of methylcellulose viscosity on rheological properties (dynamic viscosity η in mPa·s) of gels obtained from investigated powders.*

Stoichiometric ratio lactic acid to chitosan	η in mPa·s gels with addition methyl-cellulose				
	4000 mPa·s	1500 mPa·s	400 mPa·s	25 mPa·s	15 mPa·s
1:1	398	254	165	110	53
2:1	356	232	159	98	44
3:1	305	221	143	87	38
4:1	286	204	136	71	24
8:1	242	198	129	62	19

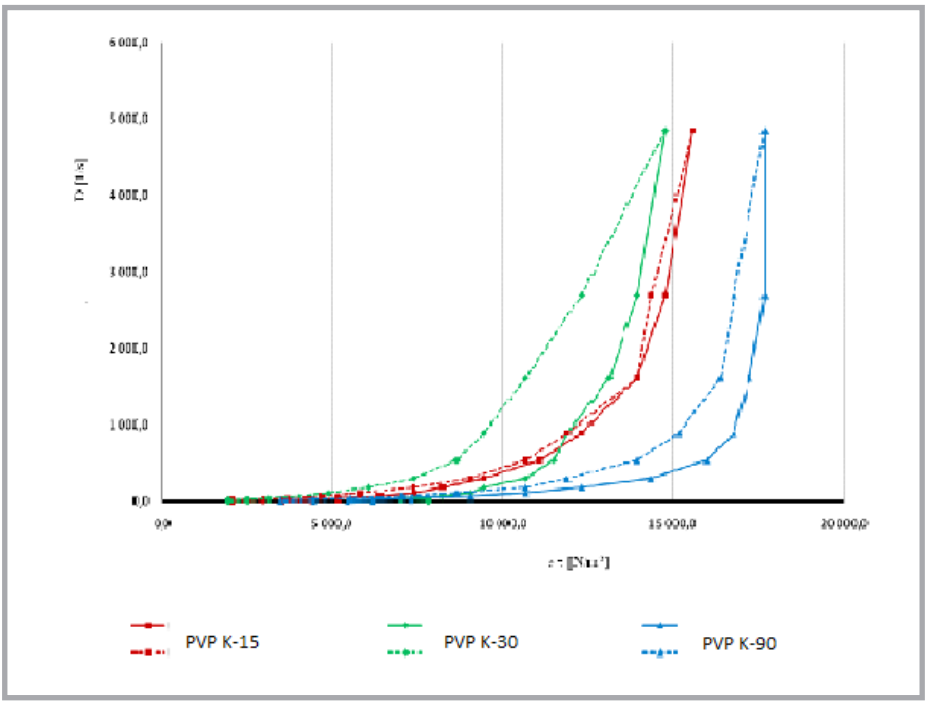

Figure 1. *Influence of the addition of 5% polyvinylpyrrolidone K-15, K-30, K-90 on dynamic viscosity of researches gels obtained from hydrophilic powders with the addition of methylcellulose 4000 mPa·s and stoichiometric ratio of lactic acid to chitosan of 1:1; PVP K-15 = MC - methylcellulose 4000 mPa·s + PVP K-15, PVP K-30 = MC - methylcellulose 4000 mPa·s + PVP K-30, PVP K-90 = MC - methylcellulose 4000 mPa·s + PVP K-90, D - shearing rate, τ - tangential stress.*

formulations, ranging from 84 to 510 mPa·s for 1:1 gels and from 47 to 386 mPa·s for the 8:1 ratio. The resulting gels exhibit thixotropic properties (***Figure 1***).

The researches of gels obtained from powders possess the work of adhesion - the energy needed to separate the gel the probe 15.2 g/s for gels containing 5% polyvinylpyrrolidone K-15 (***Figure 2***, see page 112), 52.8 g/s for gels with 5% polyvinylpyrrolidone K-30 (***Figure 3***, see page 113), and 56.6 g/s for gels with 5% polyvinylpyrrolidone K-90 (***Figure 4***, see page 114).

All of the researches were performed at 37 °C.

The studies have shown that it is possible to obtain gels with high adhesion properties to the vaginal mucous membrane. The use of methylcellulose with different values of viscosity has allowed different formulations to be obtained with a wide pH range. Rheological investigations revealed an increase in the dynamic viscosity of preparations containing lactic acid complexed with chitosan in a stoichiometric ratio of 1:1 in comparison to the gels with the ratio of 8:1. The modification of the composition of the tested powders containing 5%

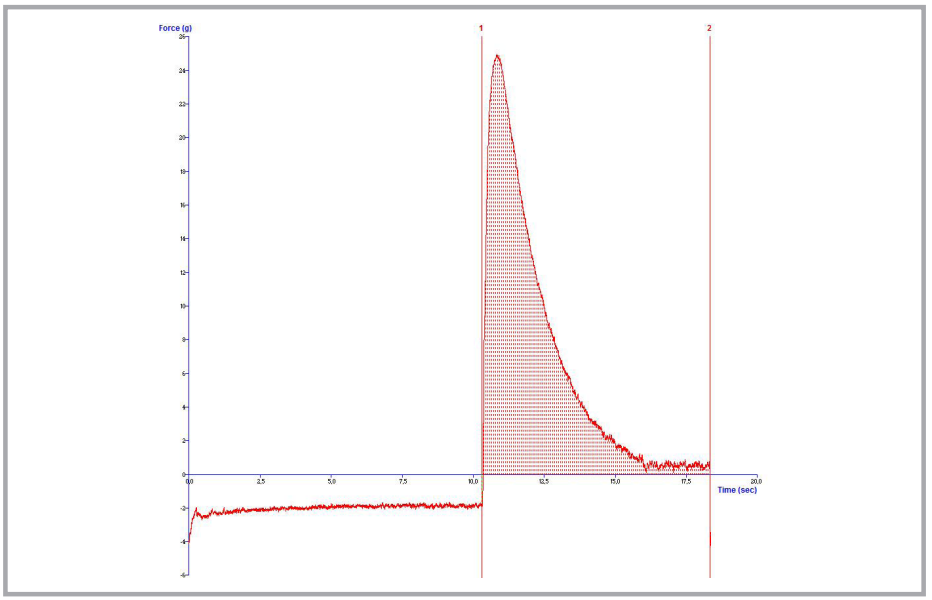

Figure 2. *Measurement of textured research gels with 5% polyvinylpyrrolidone K-15 with the addition of methylcellulose 4000 mPa·s and the stoichiometric ratio of lactic acid to chitosan of 1:1.*

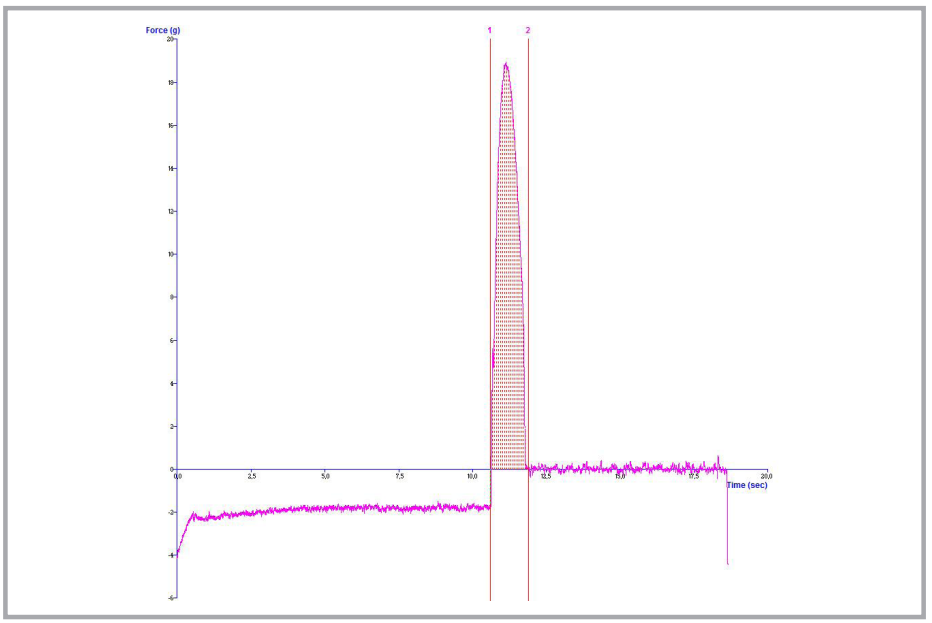

Figure 3. *Measurement of textured research gels with 5% polyvinylpyrrolidone K-30 with the addition methylcellulose 4000 mPa·s and a stoichiometric ratio of lactic acid to chitosan of 1:1.*

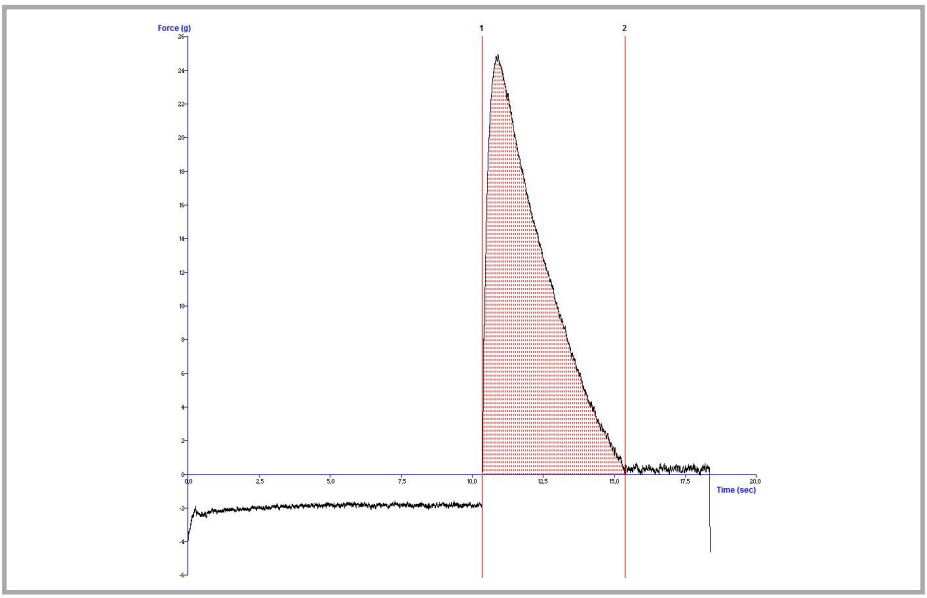

Figure 4. *Measurement of textured research gels with 5% polyvinylpyrrolidone K-90 with the addition of methylcellulose 4000 mPa·s and the stoichiometric ratio of lactic acid to chitosan of 1:1*

polyvinylpyrrolidone: K-15, K-30, K-90 has increased the range of the dynamic viscosity of formulations. The resulting gels exhibit thixotropic properties. The gels obtained from powders possess the work of adhesion - the energy needed to separate the gel from the probe with different values.

Results obtained in the experimental studies proved that it is possible to produce a preparation with optimal pharmaceutical and application properties.

4. Conclusions

1. The research demonstrated that methylcellulose with different values of viscosity significantly affected the adhesive properties of hydrophilic gels obtained from powders, but at the same a wide pH range.

2. The gels obtained from the powders were characterised by the specific dynamic viscosity and thixotropy.

3. The gels obtained from powders possess the work of adhesion.

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