ASSESSMENT OF PHARMACEUTICAL PROPERTIES OF THERMOSENSITIVE GYNECOLOGICAL POWDERS CONTAINING LACTIC ACID COMPLEXED WITH CHITOSAN

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Abstract

*pH of gels ranged from 3.92 to 4.44 for gels 1:1 and from 2.36 to 2.84 for 8:1 ratio. The addition of 20%, 23% or 25% poloxamer 407 increases the pH ranged from 4.00 to 4.91 for gels with 1:1 ratio and from 2.56 to 3.42 for 8:1 ratio. Rheological studies demonstrated that the investigated gels obtained from powders have the dynamic viscosity ranged from 53 mPa*s to 398 mPa*s for the 1:1 stoichiometric ratio in the complex and from 19 mPa*s to 242 mPa*s for 8:1 ratio. The addition of calcium alginate with polyoxyethylene glycol-200 reduces the pH and maintains high dynamic viscosity. The thermosensitive gels obtained from thermosensitive powders shows high adhesion and are difficult to separate from the probe.*

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

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1. Introduction

The continuous action of a vaginal drugs during daily activity time of a patient is a vital question in gynecological treatment. The use of hydrophilic gels with high adhesion properties and ability to spread over the vaginal mucosa enable prolonged action of the drug. The preparations, remaining at the site of application, produce adequate pH in the environment thanks to the content of lactic acid complexed with chitosan [1 - 12]. The tested thermosensitive powders pass in the gel under natural conditions covering the vaginal mucosa.

The aim of this study was to investigate the effect of selected hydrophilizing substances and calcium alginate on the physic-chemical properties of powders containing poloxamer 407 for gynecological purposes. The influence of the hydrophilizing substances such as polyoxyethylene glycol-200, polyoxyethylene glycol-400 and calcium alginate on the pharmaceutical properties of powders on the pH of the gel was tested. Formulations were prepared with varying pH and rheological properties. Powders passes in gels were examined for their properties. In the texturometer for this purpose, the adhesion test the thermosensitive gel were performed.

2. Materials and Methods

2.1. Materials

The following chemicals of analytical grade were used in experiments: lactic acid (P.Z.F. Cefarm (Wrocław, Poland), chitosan with deacetylation degree of 93.5% (Sea Fisheries Institute, Gdynia, Poland), methylcellulose (Aldrich Chemical Company Ltd. Gillingham – Dorest SP 84 SL, England), poloxamer 407 (Sigma – Aldrich Chemie GmbH, Germany), calcium alginate (Aldrich Chemical Company Ltd. Gillingham – Dorest SP 84 SL, England) polyoxyethylene glycol 200 (Aldrich Chemical Company Ltd. Gillingham – Dorest SP 84 SL, England), polyoxyethylene glycol 400 (Aldrich Chemical Company Ltd. Gillingham – Dorest SP 84 SL, England), aqua purificata, acc. to FP X.

2.2. Methods

2.2.1. Preparation of hydrophilic intravaginal powder

The preparation of powder containing lactic acid complexed with chitosan consisted of the following stages:

1. Preparation of the lactic acid - chitosan complex.

The required amount of powdered chitosan was added to a known amount of lactic acid and was mixed. The mixture was left for 24h until a clear, thick fluid was formed that could be joined with methylcellulose [4].

2. *Preparation of powder from methylcellulose and poloxamer 407.*

The poloxamer 407 was mixed with a known amount of methylcellulose. Next the mixture was added to the lactic acid complexes with chitosan and polyoxyethylene glycol-200 or polyoxyethylene glycol-400. The resulting powder was thoroughly pulverized. Homogenous powder was obtained sieved through a sieve having a mesh size of 0,16 mm.

3. Preparation of the tested gel.

A gel was obtained by mixing the powder with, known amount of distilled water and was cooled to 5 - 10 °C to enhance the process of gelation. The homogenous gel was weighed and additional amount of distilled water was added to obtain the initial mass.

2.2.2. Analytical methods

2.2.2.1. Dynamic viscosity measurement

Rheological investigations were performed using a rotational viscosimeter Rheotest 2 Medingen Dresden. The determinations were performed in I a and II a range on a K-1 cone with the diameter of 36 mm and 0.917 fissure at 37°C. The shear angle was measured using

12 shear rates in ascending direction and 11 rates in the descending direction. The values of the shear stress and viscosity were calculated from measurements at the temperature of 37°C.

2.2.2.2. Measurement of adhesion

TPA test of texture profile analysis was performed with Exponent Stable Micro Systems texture analyzer TA-XT 2 plus.

The measuremets were conducted in order to illustrate the influence of the type of methylcellulose on the adhesion strength of prepared gels

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

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

The measurement was started by placing the gel in a cylindrical vessel with a transparent plexiglass texturometer. Then, the probe was lowered just above the surface of the gel so that there was direct contact between them (remained in this position for 10 seconds). After selecting the appropriate parameters of the program, the measurement started. The probe began to rise at a speed of 10 mm /s at a height of 40 mm above the surface of the gel after contact with the surface of the gel. All gels were tested three times and the results reported as the average of three measurements at the temperature of 37°C.

3. Results and Discussion

Gels obtained from powders, containing lactic acid complexed with chitosan in a stoichiometric ratio 1:1, 2;1, 3:1, 4:1 and 8:1. Their pH ranged from 3.92 to 4.44 for gels 1:1 and from 2.36 to 2.84 for 8:1 ratio. The addition of 20%, 23% or 25% poloxamer 407 increases the pH ranged from 4.00 to 4.91 for gels with 1:1 ratio and from 2.56 to 3.42 for 8:1 ratio. Further addition of the 25% poloxamer 407 and 5% polyoxyethylene glycol-200 and 1% calcium alginate change the pH ranged from 4.46 to 4.90 for gels 1:1 and from 2.45 to 3.34 for 8:1 ratio (Table 1).

Table 1. Influence of viscosity of gels containing 4% methylcellulose and 5% polyoxyethylene glycol-200, 1% calcium alginate and 25% poloxamer 407 on pH

Stoichiometric ratio lactic acid to chitosan	pH gels with methyl-cellulose 4000 mPa*s	pH gels with methyl-cellulose 1500 mPa*s	pH gels with methyl-cellulose 400 mPa*s	pH gels with methyl-cellulose 25 mPa*s	pH gels with methyl-cellulose 15 mPa*s
1:1	4.46	4.51	4.65	4.73	4.90
2:1	3.90	4.28	4.59	4.69	4.68
3:1	3.52	3.79	4.00	4.15	4.56
4:1	3.12	3.23	3.51	3.62	3.83
8:1	2.45	3.06	3.09	3.20	3.34

The enrichment of the composition of the tested powders containing 25% poloxamer 407 and 5% polyoxyethylene glycol-400 resulted in increased pH ranged of the formulation to between 4.58 to 4.92 for gels 1:1 and from 2.64 to 3.53 for 8:1 ratio (Table 2).

Table 2. Influence of viscosity of 4% methylcellulose and 5% polyoxyethylene glycol-400 with 1% calcium alginate and 25% poloxamer 407 on pH

Stoichiometric ratio lactic acid to chitosan	pH gels with methyl-cellulose 4000 mPa*s	pH gels with methyl-cellulose 1500 mPa*s	pH gels with methyl-cellulose 400 mPa*s	pH gels with methyl-cellulose 25 mPa*s	pH gels with methyl-cellulose 15 mPa*s
1:1	4.58	4.64	4.72	4.87	4.92
2:1	4.05	4.38	4.61	4.75	4.85
3:1	3.68	3.89	4.15	4.23	4.70
4:1	3.26	3.32	3.59	3.72	3.96
8:1	2.64	3.21	3.24	3.37	3.53

Rheological studies demonstrated that the investigated gels obtained from powders have the dynamic viscosity ranged from 53 mPa*s to 398 mPa*s for the 1:1 stoichiometric ratio in the complex and from 19 mPa*s to 242 mPa*s for 8:1 ratio.

A modification of the composition of the tested powders with 25% poloxamer 407, 1% calcium alginate and 5% polyoxyethylene glycol-200 has increased the range of the dynamic viscosity of formulations from 620 mPa*s to 750 mPa*s for gels 1:1 and from 595 mPa*s to 680 mPa*s for 8:1 ratio. Further addition of the 25% poloxamer 407, 1% calcium alginate and 5% polyoxyethylene glycol-400 resulted in a further increase in dynamic viscosity of the formulations from 780 mPa*s to 845 mPa*s for gels 1:1 and from 650 mPa*s to 765 mPa*s for 8:1 ratio.

The gels obtained from powders possess the work of adhesion - the energy needed to separate the gel the probe 48.90 g/s for gels contained 25% poloxamer 407, 1% calcium alginate and 5% polyoxyethylene glycol-200, and 51.81 g/s for gels contained 25% poloxamer 407, 1% calcium alginate and 5% polyoxyethylene glycol-400.

The presented studies have shown that it is possible to obtain gels with high adhesion to vaginal mucous membrane. The use of methylcellulose with different values of the viscosity and poloxamer 407 allows to obtain various formulations with a wide range of pH. Rheological investigations revealed an increase in the dynamic viscosity of preparations containing lactic acid complexed with chitosan in a stoichiometric ratio 1:1 in comparison to the gels with ratio 8:1. The thermosensitive gels obtained from thermosensitive powders show good adhesion.

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 investigations demonstrated that the methylcellulose with different viscosity and addition of the poloxamer 407 significantly affect the adhesive properties of hydrophilic gels obtained from powders, but at the same a wide range of pH.
2. The thermosensitive gels obtained from thermosensitive powders gives good adhesion to the vaginal mucosa.

5. References

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