

INFLUENCE OF HYDROPHILIC POLYMERS ON THE PROPERTIES OF GYNECOLOGICAL POWDERS CONTAINING LACTIC ACID COMPLEXED WITH CHITOSAN

Katarzyna Małolepsza-Jarmołowska

*Faculty of Pharmacy
The “Silesian Piasts” memorial Medical University of Wrocław,
ul. Borowiecka 211A, 50-556 Wrocław, Poland.
e-mail: katarzynamj@poczta.onet.pl*

Abstract

Tested impact of polyvinyl alcohol, dextrane and calcium alginate for the properties of the powders containing poloxamer 407 and lactic acid complexed with chitosan. For researches was prepared formulations with different pH and rheological properties. The thermosensitive gels obtained from thermosensitive powders possess the work of adhesion with different values. The researches revealed that the dynamic viscosity of the gels obtained from powders is high. A wide range of pH of the thermosensitive gels allows the selection of the optimum formulation. The gels obtained from the powders containing polyvinyl alcohol or dextrane or calcium alginate were characterized by the specific dynamic viscosity. The researches demonstrated that the methylcellulose with different values of the viscosity with poloxamer 407 significantly affect the adhesive properties of thermosensitive hydrophilic gels obtained from powders.

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

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1. Introduction

Successful treatment of the condition is handicapped by frequent recurrences after termination of routine therapy. Anatomical and physiological conditions in the vagina do not facilitate easy application of the drug neither its maintenance on the site of application. The hydrophilic gynecological 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]. These powders for gynecological becomes under natural conditions in the thermosensitive gel covering the vaginal mucosa.

Aim of this study was to investigate the influence of selected hydrophilic polymers on the physico-chemical properties of powders for gynecological purposes. The impact of polyvinyl alcohol and dextrane in the properties of the powders containing poloxamer 407 and lactic acid complexed with chitosan was tested. The formulations with different pH and rheological properties were prepared. Gels obtained from powders were examined for their properties. The adhesion test of the thermosensitive gel were performed in the texturometer. The thermosensitive gels obtained from thermosensitive powders possess the work of adhesion with different values. The researches revealed that the dynamic viscosity of the gels obtained from powders is high. A wide range of pH of the thermosensitive gels allows the 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 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), polyvinyl alcohol (Aldrich Chemical Company Ltd. Gillingham – Dorest SP 84 SL, England), dextrane (Aldrich Chemical Company Ltd. Gillingham – Dorest SP 84 SL, England), calcium alginate (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 IX.

2.2. Methods

2.2.1. 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 24h 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, calcium alginate and poloxamer 407, by adding a known amount of this compound to the lactic acid complexes with chitosan, polyoxyethylene glycol-400 and polyvinyl alcohol or dextrane. The resulting powder was thoroughly pulverized. Homogenous powder was obtained sieved through a sieve having 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 distilled water. In order to enhance the process of gelation, the mixture was cooled to 5 - 10 °C. The homogenous gel was weighed and supplemented with distilled water to the initial weight.

2.2.2. Measurements of physical properties

2.2.2.1. Rheological investigations (dynamic viscosity)

Rheological investigations were performed using a rotational viscosimeter Rheotest-2 Medingen Dresden. The determinations of viscosity 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. Viscosity and torque were calculated from appropriate formulas. The obtained results were used to plot the flow curves of the investigated gels.

2.2.2.2. Measurement of texture

The measurements was performed using a probe (P/1S) in the shape of a ball, built in stainless steel, with a diameter of 1 inch.

Main measurement parameters were as follows: speed of downward movement of the probe during the test, and was 0.5 mm / s, 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 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 is no direct contact between them. After selecting the appropriate parameters in the program, started to study. The probe after contact with the surface of the gel (remains in this position for 10 seconds) 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.

3. Results and Discussion

Gels obtained from powders, containing lactic acid complexed with chitosan reveal 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 [12]. 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 1:1 and from 2.56 to 3.42 for 8:1 ratio [12]. Further addition of the 25% poloxamer 407 and 5% polyvinyl alcohol increases the pH ranged from 4.28 to 4.89 for gels 1:1 and from 2.81 to 3.46 for 8:1 ratio (Table 1).

Table 1. Influence of the composition of powders containing 4% methylcellulose, 25% poloxamer 407 on pH gels obtained from investigated powders with poloxamer407 and 0.5% polyvinyl alcohol

Stoichiometric ratio lactic acid to chitosan	pH gels with addition methyl-cellulose 4000 mPa*s	pH gels with addition methyl-cellulose 1500 mPa*s	pH gels with addition methyl-cellulose 400 mPa*s	pH gels with addition methyl-cellulose 25 mPa*s	pH gels with addition methyl-cellulose 15 mPa*s
1:1	4.28	4.38	4.56	4.70	4.89
2:1	3.90	4.31	4.51	4.62	4.78
3:1	3.59	3.78	4.00	4.26	4.59
4:1	3.24	3.39	3.59	3.75	4.27
8:1	2.81	2.98	3.34	3.42	3.46

The enrichment 1% dextrane of the composition of the tested powders containing 25% poloxamer 407 resulted in increased pH ranged of the formulation to between 4.49 to 4.96 for gels 1:1 and from 2.85 to 3.52 for 8:1 ratio (Table 2).

Rheological studies demonstrated that the researches gels obtained from powders possess the dynamic viscosity 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 0.5% polyvinyl alcohol of the composition of the tested powders containing 25% poloxamer 407 has increased the range of the dynamic viscosity of formulations from 680 mPa*s to 735 mPa*s for gels 1:1 and from 566 mPa*s to 598 mPa*s for 8:1 ratio (Table 3).

Table 2. Influence of the composition of powders containing 4% methylcellulose, 25% poloxamer 407 on pH gels obtained from investigated powders with poloxamer407 and 1% dextrane

Stoichiometric ratio lactic acid to chitosan	pH gels with addition methyl-cellulose 4000 mPa*s	pH gels with addition methyl-cellulose 1500 mPa*s	pH gels with addition methyl-cellulose 400 mPa*s	pH gels with addition methyl-cellulose 25 mPa*s	pH gels with addition methyl-cellulose 15 mPa*s
1:1	4.49	4.58	4.69	4.78	4.96
2:1	4.23	4.46	4.60	4.70	4.81
3:1	3.65	3.82	4.27	4.35	4.62
4:1	3.31	3.45	3.65	3.80	4.34
8:1	2.85	3.20	3.41	3.49	3.52

Table 3. Influence of the composition of powders containing 4% methylcellulose, 25% poloxamer 407 on rheological properties (dynamic viscosity η [mPa*s]) gels obtained from investigated powders with poloxamer407 and 0.5% polyvinyl alcohol

Stoichiometric ratio lactic acid to chitosan	η[mPa*s] gels with addition methyl-cellulose 4000 mPa*s	η[mPa*s] gels with addition methyl-cellulose 1500 mPa*s	η[mPa*s] gels with addition methyl-cellulose 400 mPa*s	η[mPa*s] gels with addition methyl-cellulose 25 mPa*s	η[mPa*s] gels with addition methyl-cellulose 15 mPa*s
1:1	735	728	705	698	680
2:1	729	723	698	688	672
3:1	696	683	680	673	660
4:1	678	671	672	665	652
8:1	598	587	584	577	566

Further addition 1% dextrane of the 25% poloxamer 407 resulted in a further increase in dynamic viscosity of the formulations from 699 mPa*s to 768 mPa*s for gels 1:1 and from 630 mPa*s to 673 mPa*s for 8:1 ratio (Table 4).

Table 4. Influence of the composition of powders containing 4% methylcellulose, 25% poloxamer 407 on rheological properties (dynamic viscosity η [mPa*s]) gels obtained from investigated powders with poloxamer407 and 1% dextrane

Stoichiometric ratio lactic acid to chitosan	η [mPa*s] gels with addition methyl-cellulose 4000 mPa*s	η [mPa*s] gels with addition methyl-cellulose 1500 mPa*s	η [mPa*s] gels with addition methyl-cellulose 400 mPa*s	η [mPa*s] gels with addition methyl-cellulose 25 mPa*s	η [mPa*s] gels with addition methyl-cellulose 15 mPa*s
1:1	768	762	750	719	699
2:1	759	753	741	700	681
3:1	740	729	715	692	679
4:1	692	686	680	675	668
8:1	673	662	658	649	630

A modification 1% calcium alginate and 5% polyoxyethylene glycol-400 of the composition of the tested powders containing of the 25% poloxamer 407, 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 17.34 g/s for gels containing 25% poloxamer 407 and 0.5% polyvinyl alcohol, 19.41 g/s for gels containing 25% poloxamer 407 and 1% dextrane (Fig. 1), 51.81 g/s for gels containing 25% poloxamer 407, 1% calcium alginate and 5% polyoxyethylene glycol-400 (Fig. 2).

Laboratory tests have shown that it is possible to obtain gels with high adhesion properties to vaginal mucous membrane. The use of methylcellulose with different values of the viscosity and poloxamer 407 allows to obtain different formulations with a wide range of pH. Rheological investigations revealed an increase in the dynamic viscosity of preparations containing lactic acid complexed with chitosan reveal a stoichiometric ratio 1:1 in comparison to the gels with ratio 8:1. The modification of the composition of the tested powders containing 0.5% polyvinyl alcohol or 1% dextrane has increased the range of the dynamic viscosity of formulations. The enrichment of the composition of the tested powders containing of the 1% calcium alginate and 5% polyoxyethylene glycol-400 resulted in a further increase in dynamic viscosity of the formulations. The thermosensitive gels obtained from thermosensitive powders possess the work of adhesion with different values. Results obtained in the experimental studies proved that it is possible to produce a thermosensitive preparation with optimal pharmaceutical and application properties.

Influence of hydrophilic polymers on the properties of gynecological powders containing lactic acid complexed with chitosan

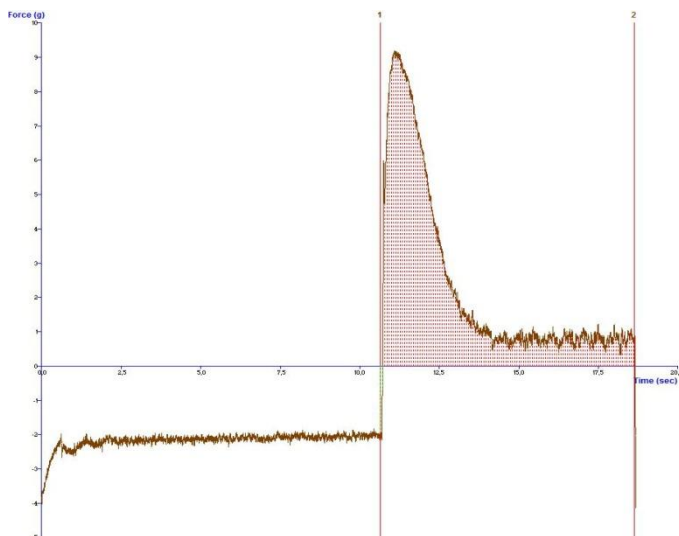


Figure 1. Measurement of texture gels with 25% poloxamer 407 and 1% dextrane with addition methylcellulose 4000 mPa*s and stoichiometric ratio lactic acid to chitosan 1:1

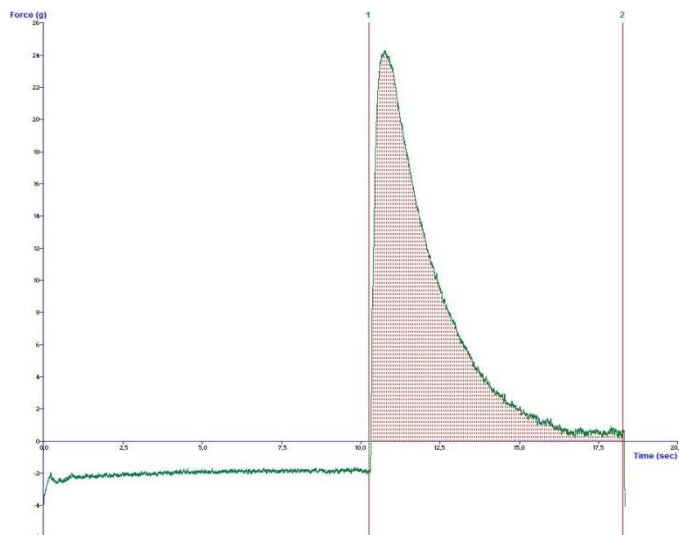


Figure 2. Measurement of texture gels with 25% poloxamer 407, 1% calcium alginate and 5% polyoxethylene glycol-400 with addition methylcellulose 4000 mPa*s and stoichiometric ratio lactic acid to chitosan 1:1

4. Conclusions

1. The researches demonstrated that the methylcellulose with different values of the viscosity with poloxamer 407 significantly affect the adhesive properties of thermosensitive hydrophilic gels obtained from powders.
2. The gels obtained from the powders containing polyvinyl alcohol or dextrane or calcium alginate were characterized by the high dynamic viscosity and the wide range of pH.
3. The thermosensitive gels obtained from thermosensitive powders possess the work of adhesion with different values.

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