# THE EFFECT OF A HYDROPHILIZING SUBSTANCE ON THE PROPERTIES OF THERMOSENSITIVE HYDROPHILIC GELS CONTAINING LACTIC ACID COMPLEXED WITH CHITOSAN

**Katarzyna Małolepsza-Jarmołowska**

*Department of Pharmaceutical Technology,*
*Faculty of Pharmacy*
*The "Silesian Piasts" memorial Medical University of Wroclaw,*
*ul. Szewska 38, 50-139 Wrocław, Poland.*
*e-mail: katarzynamj@poczta.onet.pl*

**Abstract**
*Commonly applied drug forms tend to leave the vagina when the patient assumes an upright position. Permanent contact of the drug form with the vaginal mucosa during daily activities of the patient is an indispensable condition for 24-hour therapy. This condition may be fulfilled by drug forms with high ability to adhere to vaginal mucosa. The investigations demonstrated that the thermosensitive polymer - poloxamer 407 increases significantly the adhesive properties of hydrophilic gels, but at the same time it increases their pH. The use of pectin resulted in a decrease of the pH. The addition of glycerol or 1,2-propylene glycol caused further decrease of the pH. Rheological investigations demonstrated positive pharmaceutical properties of the investigated preparations. The obtained parameters gels should provide positive application effects. The investigations revealed that it is possible to obtain gels with high adhesion properties to vaginal mucous membrane.*

**Key words:** *lactic acid complexed with chitosan, pectin, thermosensitive polymer-poloxamer 407, hydrophilic gels, vaginal infections, anti-inflammatory drugs.*

## 1. Introduction

Recurrent vaginitis is a clinical problem that still lacks successful solution. Commonly applied drug forms tend to leave the vagina when the patient assumes an upright position.

Permanent contact of the drug form with the vaginal mucosa during daily activities of the patient is an indispensable condition for 24-hour therapy.

This condition may be fulfilled by drug forms with high ability to adhere to vaginal mucosa. Available literature does not offer any significant progress in the efficacy of vaginitis therapy [1 - 3].

The use of hydrophilic gels with high adhesion properties and ability to spread over the vaginal mucosa enable prolonged action of the drug [4 - 11]. The preparations, remaining at the site of application, produce adequate pH in the environment thanks to the content of lactic acid complexed with chitosan. The use of a thermosensitive polymer affects further adhesion of the investigated preparations [12].

The aim of the study was to investigate optimization of pharmaceutical properties of hydrophilic gels containing lactic acid complexed with chitosan.

## 2. Materials and methods

### 2.1. Materials

Lactic acid – P.Z.F. Cefarm (Wrocław, Poland). Chitosan - deacetylation degree of 93.5% – Sea Fisheries Institute (Gdynia, Poland). Polyoxyethylene glycol 200 (PEG 200) - LOBA – Chemie, Wien – Fishamend (Austria). Methylcellulose, Aldrich Chemical Company Ltd. Gillingham – Dorest SP 84 SL – (England). Glycerol, Sigma – Aldrich Chemie GmbH, Germany. 1,2-Propylene glycol, Sigma – Aldrich Chemie GmbH, Germany. Lemon-apple pectin, SIGMA – Aldrich Chemical Company Ltd. (Gillingham, England). Poloxamer 407, Sigma – Aldrich Chemie GmbH, Germany. Aqua purificata, acc. To FP VI.

### 2.2. Methods

#### *2.2.1. Measurements of pH and viscosity*

(see [11])

*2.2.1.1. Determination of pH*

For pH measurement of the investigated gels, the potentiometric method was used, in which a combined electrode integrated into a multifunctional computer meter, ELECTRON CX-742 was immersed into the investigated gel. Prior to the measurement the computer meter was calibrated by two buffer solutions with pH 7.00 and pH 4.00.

*2.2.1.2. Rheological investigations*

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 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. Technology of manufacture of hydrophilic intravaginal gel***

The production of gel 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 gel from methylcellulose with poloxamer 407, pectin and glycerol or 1,2-propylene glycol*

A gel was obtained from methylcellulose with poloxamer 407 and pectin by adding a known amount of this compound to the solution of glycerol or 1,2-propylene glycol in 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.

Lactic acid complexes with chitosan was added to methylcellulose with poloxamer 407 and pectin gel and stirred until an homogenous gel was obtained. Distilled water was added to obtain the initial mass.

## 3. Results and discussion

Gels containing lactic acid complexed with chitosan at a stoichiometric ratio 1:1 and 2:1 and 5 - 25% content of polyoxyethylene glycol 200 reveal pH from 2.5 to 4.6. The addition of 20 - 25% poloxamer 407 increases the pH to 4.55 to 5.30 for 1:1 gels and 4.00 to 4.85 for 2:1 gels (***Table 1***).

The addition of 1.0; 2.0; 3.0% pectin decreases the pH of the investigated gels to 4.53 to 4.86; 4.26 to 4.80; 4.15 to 4.48 for 1:1 gels and 3.78 to 4.20; 3.89 to 4.36; 3.60 to 3.90 for 2:1 gels.

The addition of 5 - 25% glycerol or 1,2-propylene glycol decreases the pH of investigated gels with pectin to 4.00 to 4.80 (1:1) and 3.60 to 4.10 (2:1); 4.10 to 4.82 (1:1) and 3.55 to 4.30 for 2:1 gel (***Table 2***).

Rheological studies demonstrated that the reference gels possess the dynamic viscosity from 159.16 to 354.41 for the 1:1 stoichiometric ratio in the complex and from 236.27 to 388.16 for 2:1 ratio. The addition of poloxamer 407 at concentrations of 20 to

***Table 1.*** *Influence glycerol and pectin on pH investigated gels containing 4.0% methylcellulose and 25% poloxamer 407.*

| Stoichiometric ratio lactic acid to chitosan | Concentration glycerol, % | pH gels with addition glycerol | pH gels with glycerol and addition: | | |
|---|---|---|---|---|---|
| | | | 1.0% pectin | 2.0% pectin | 3.0% pectin |
| 1:1 | 5 | 4.44 | 4.40 | 4.19 | 4.00 |
| | 10 | 4.48 | 4.42 | 4.30 | 4.20 |
| | 15 | 4.58 | 4.52 | 4.45 | 4.22 |
| | 20 | 4.88 | 4.68 | 4.55 | 4.38 |
| | 25 | 4.98 | 4.80 | 4.73 | 4.42 |
| 2:1 | 5 | 3.90 | 3.66 | 3.64 | 3.60 |
| | 10 | 4.10 | 3.80 | 3.70 | 3.62 |
| | 15 | 4.20 | 3.86 | 4.20 | 3.75 |
| | 20 | 4.35 | 3.95 | 3.90 | 3.76 |
| | 25 | 4.45 | 4.10 | 4.28 | 3.78 |

***Table 2.*** *Influence 1,2-propylene glycol and pectin on pH investigated gels containing 4.0% methylcellulose and 25% poloxamer 407.*

| Stoichiometric ratio lactic acid to chitosan | Concentration 1,2-propylene glycol, % | pH gels with addition 1,2-propylene glycol | pH gels with 1,2-propylene glycol and addition: | | |
|---|---|---|---|---|---|
| | | | 1.0% pectin | 2.0% pectin | 3.0% pectin |
| 1:1 | 5 | 4.52 | 4.48 | 4.20 | 4.10 |
| | 10 | 4.60 | 4.56 | 4.35 | 4.21 |
| | 15 | 4.61 | 4.58 | 4.50 | 4.25 |
| | 20 | 4.90 | 4.70 | 4.57 | 4.40 |
| | 25 | 5.10 | 4.82 | 4.75 | 4.45 |
| 2:1 | 5 | 4.00 | 3.68 | 3.66 | 3.55 |
| | 10 | 4.20 | 3.70 | 3.74 | 3.60 |
| | 15 | 4.31 | 3.72 | 4.15 | 3.65 |
| | 20 | 4.40 | 4.00 | 4.25 | 3.72 |
| | 25 | 4.55 | 4.10 | 4.30 | 3.82 |

25% increases the dynamic viscosity from 506.14 to 641.20 for 1:1 and 540.35 to 692.55 for 2:1 ratios (***Table 3***).

The addition of 1.0; 2.0; 3.0% pectin increases the dynamic viscosity from 590.22 to 799.35 mPa*s for 1:1 and 620.32 to 768.11 mPa*s for 2:1 ratios.

The addition of 5 - 25% glycerol or 1,2-propylene glycol increases the dynamic viscosity gels with pectin from 589.12 to 815.25 for 1:1 and 644.43 to 770.11 for 2:1; 598.31 to 820.23 for 1:1 and 650.33 to 782.14 for 2:1 ratios (***Table 4***).

All the investigations were performed at 37 °C.

The investigations demonstrated that the thermosensitive polymer - poloxamer 407 increases significantly the adhesive properties of hydrophilic gels, but at the same time it increases their pH.

***Table 3.*** *Influence glycerol and pectin on rheological properties investigated gels containing 4.0% methylcellulose and 25% poloxamer 407.*

| Stoichiometric ratio lactic acid to chitosan | Concentration glycerol, % | Dynamic viscosity gels in mPa*s with glycerol and addition pectin: | | | |
|---|---|---|---|---|---|
| | | 0% | 1.0% | 2.0% | 3.0% |
| 1:1 | 5 | 680.30 | 699.11 | 750.31 | 815.25 |
| | 10 | 600.11 | 620.43 | 700.44 | 798.44 |
| | 15 | 599.43 | 655.25 | 660.21 | 790.35 |
| | 20 | 555.12 | 589.12 | 600.35 | 750.28 |
| | 25 | 590.22 | 610.33 | 599.22 | 765.51 |
| 2:1 | 5 | 698.35 | 720.44 | 730.44 | 770.11 |
| | 10 | 610.45 | 696.32 | 699.23 | 760.49 |
| | 15 | 579.14 | 666.42 | 750.11 | 756.36 |
| | 20 | 587.26 | 654.11 | 680.24 | 740.22 |
| | 25 | 598.31 | 644.43 | 670.33 | 730.55 |

***Table 4.*** *Influence 1,2- propylene glycol and pectin on rheological properties investigated gels containing 4.0% methylcellulose and 25% poloxamer 407.*

| Stoichiometric ratio lactic acid to chitosan | Concentration glycerol, % | Dynamic viscosity gels in mPa*s with 1,2-propylene glycol and addition pectin: | | | |
|---|---|---|---|---|---|
| | | 0% | 1.0% | 2.0% | 3.0% |
| 1:1 | 5 | 690.28 | 700.35 | 756.42 | 820.23 |
| | 10 | 650.33 | 667.48 | 720.31 | 779.44 |
| | 15 | 600.44 | 676.26 | 658.22 | 786.58 |
| | 20 | 580.21 | 598.31 | 620.44 | 780.11 |
| | 25 | 599.58 | 600.56 | 599.15 | 760.49 |
| 2:1 | 5 | 700.34 | 734.11 | 778.23 | 782.14 |
| | 10 | 630.11 | 699.44 | 698.16 | 780.22 |
| | 15 | 582.28 | 668.55 | 690.23 | 760.33 |
| | 20 | 590.42 | 650.33 | 664.16 | 758.24 |
| | 25 | 600.54 | 651.12 | 660.44 | 750.35 |

The use of pectin resulted in a decrease of the pH. The addition of glycerol or 1,2-propylene glycol caused further decrease of the pH.

Rheological investigations demonstrated positive pharmaceutical properties of the investigated preparations.

The obtained parameters gels should provide positive application effects.

## 4. Conclusions

1. The use of the thermosensitive polymer - poloxamer 407 in the technology of investigated gynaecological gels results in a significant increase in their pH.
2. The use of pectin resulted in a decrease of the pH.
3. The addition of glycerol or 1,2-propylene glycol caused further decrease of the pH.

4. The rheological investigations demonstrated that the poloxamer 407 increases significantly the adhesive properties of hydrophilic gels.
5. The investigations revealed that it is possible to obtain gels with high adhesion properties to vaginal mucous membrane and physiological pH.

## 5. References


1. *Denney JM, Culhane JF; (2009) Bacterial vaginosis: A problematic infection from both a perinatal and neonatal perspective. Sem. Fet. & Neonat. Med. Vol. 14, pp. 200-203.*
2. *Brandt M., Abels C., May T., Lohmann K., Schmidts – Winkler I., Hoyme U. B.; (2008) Intravaginally applied metronidazole is as effective as orally applied in the treatment of bacterial vaginosis, but exhibits significantly less side effects. Eur. J. Obstet. Gynecol. Reprod. Biol. Vol. 141, pp. 158-162.*
3. *Donders G. G. G., Larson P. G., Platz-Christensen J. J., Hallen A., Meijden W., Wölner-Hanssen P.; (2009) Variability in diagnosis of clue cells, lactobacillary grading and white blood cells in vaginal wet smears with conventional bright light and phase contrast microscopy. Eur. J. Obstet. Gynecol. Reprod. Biol. Vol. 145, pp. 109-112.*
4. *Kubis A. A., Małolepsza-Jarmołowska K.; (1996) Studies on gynecological hydrophiling preparations comprising lactic acid. Part 1: Effects of lactic acid and hydrophiling agents on physical and chemical properties of methylcellulose gels. Pharmazie Vol. 51, pp. 989-990.*
5. *Małolepsza-Jarmołowska K,, Kubis A. A.; (1999) Studies on gynecological hydrophilic lactic acid preparations. Part 2: Effects of Eudragit® E-100 on properties of methylcellulose gels. Pharmazie Vol. 54, pp. 441-443.*
6. *Małolepsza-Jarmołowska K., Kubis A. A.; (2000) Studies on gynaecological hydrophilic lactic acid preparations. Part 3: Effects of chitosan on the properties of methylcellulose gels. Pharmazie Vol. 55, pp. 610-611.*
7. *Małolepsza-Jarmołowska K., Kubis A. A.; (2001) Studies on gynaecological hydrophilic lactic acid preparations. Part 4: Effects of polyvinyl pyrrolidone K-90 on properties of methylcellulose gels. Pharmazie Vol. 56, pp. 160-162.*
8. *Małolepsza-Jarmołowska K., Kubis A. A., Hirnle L.; (2003) Studies on gynaecological hydrophilic lactic acid preparations. Part 5: The use of Eudragit® E-100 as lactic acid carrier in intravaginal tablets. Pharmazie Vol. 58, pp. 260-262.*
9. *Małolepsza-Jarmołowska K., Kubis A. A., Hirnle L.; (2003) Studies on gynaecological hydrophilic lactic acid preparations. Part 6: Use of Eudragit® E-100 as lactic acid carrier in intravaginal tablets. Pharmazie Vol. 58, pp. 334-336.*
10. *Małolepsza-Jarmołowska K.; (2006) Studies on gynaecological hydrophilic lactic acid preparations. Part 7: Use of chitosan as lactic acid carrier in intravaginal tablets (globuli vaginales). Pharmazie Vol. 61, pp. 780 - 782.*
11. *Małolepsza-Jarmołowska K.; (2007) Studies on gynaecological hydrophilic lactic acid preparations. Part 8: Use of chitosan as lactic acid carrier in intravaginal tablets. Acta Pol. Pharm. Vol. 64, pp. 69-72.*
12. *Małolepsza-Jarmołowska K.; (2010) The effect of poloxamer 407 on the properties of hydrophilic gels containing lactic acid complexed with chitosan. Progress on Chemistry and Application of Chitin and Its Derivatives, Vol. XV pp. 143-148.*