ASSESSMENT OF PHARMACEUTICAL PROPERTIES OF GYNAECOLOGICAL HYDROPHILIC GELS CONTAINING LACTIC ACID COMPLEXED WITH CHITOSAN

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Abstract
Gels containing lactic acid complexed with chitosan at a stoichiometric ration 1:1 and 2:1 and 5-25% content of polyoxyethylene glycol 200 are able to move from 25 to 30 cm. The addition of glycerol increases the movability gels containing lactic acid complexed with chitosan in a stoichiometric ration 1:1 from 23 cm to 26 cm and at 2:1 ratio from 25 cm to 29 cm. Gels with addition 20-25% poloxamer 407 containing lactic acid complexed with chitosan and 5-25% content of glycerol reveal pH from 4.25 to 4.98 for 1:1 and from 3.60 to 4.45 for 2:1. The investigations showed that the addition of a thermosensitive polymer increases the adhesive properties of the investigated gels, but at the same time it increases their pH. The addition of glycerol or 1,2-propylene glycol reduces the pH and maintains high adhesion. The use of hydrofilizing substances allowed to obtain physiological range pH gynaecological gels.

Key words: *lactic acid complexed with chitosan, thermosensitive polymer - poloxamer 407, glycerol, 1,2- propylene glycol, vaginal infections, anti-inflammatory drugs.*

1. Introduction

Thus ensuring a continuous action of a drug also during daily activity time of a patient is a vital question in gynaecological treatment.

Anatomical and physiological conditions in the vagina do not facilitate easy application of the drug neither its maintenance on the site of application. Insufficient duration of the drug's contact with vaginal mucosa does not provide adequate pH conditioning the physiological biocenosis of the organ.

Numerous recurrences of the condition are widely discussed by clinicians. The main problem in applied therapies is to maintain the continuity of treatment during 24 hours [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 the effect of adjuvant substances on optimization properties of the vaginal 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 - 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. Poloxamer 407, Sigma – Aldrich Chemie GmbH, Germany. Aqua purificata, acc. To FP VIII.

2.2. Methods

2.2.1. Measurements of pH

(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.

2.2.2. 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 and poloxamer 407.

A gel was obtained from methylcellulose and poloxamer 407 by adding a known amount of this compound to the solution of polyoxyethylene glycol 200 or 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 and poloxamer 407 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 ration 1:1 and 2:1 and 5-25% content of polyoxyethylene glycol 200 are able to move from 25 cm to 30 cm.

Measurements performed in a biopharmaceutical model revealed that the addition of 20% poloxamer 407 to gels containing lactic acid complexed with chitosan in a stoichiometric ration 1:1 decreases their movability 20 cm to 25 cm and at 2:1 ratio, 22 cm to 28 m. Higher concentrations of the poloxamer 407: 23% and 25% result in the movability of 20 cm to 24 cm (***Table 1***).

Table 1. *Influence PEG-200 and poloxamer 407 on able to move investigated gels.*

Stoichiometric ratio lactic acid to chitosan	Concentration in % PEG-200	Able to move gels with addition PEG-200, cm	Able to move gels with PEG-200 and addition poloxamer 407, cm		
			20%	23%	25%
1:1	5	25.0	20.0	21.5	20.0
	10	26.5	20.6	22.6	21.5
	15	27.9	23.8	22.9	22.6
	20	28.9	24.5	23.2	22.9
	25	29.4	25.0	23.9	23.8
2:1	5	26.9	22.0	21.9	20.8
	10	27.7	24.3	22.3	21.6
	15	28.6	25.8	23.2	22.4
	20	29.8	27.6	23.8	23.2
	25	30.0	28.0	24.0	23.8

Table 2. *Influence glycerol and poloxamer 407 on able to move investigated gels.*

Stoichiometric ratio lactic acid to chitosan	Concentration in % glycerol	Able to move gels with addition glycerol, cm	Able to move gels with glycerol and addition poloxamer 407, cm		
			20%	23%	25%
1:1	5	27.5	23.0	23.5	22.0
	10	27.9	23.6	23.9	22.3
	15	28.0	23.8	24.0	22.7
	20	28.4	24.5	24.6	23.5
	25	29.6	26.0	24.9	24.4
2:1	5	27.8	25.0	23.9	22.8
	10	28.4	24.3	24.3	23.4
	15	28.8	25.8	24.6	23.7
	20	29.6	27.6	24.9	24.2
	25	30.0	29.0	25.0	24.8

Table 3. *Influence 1,2- propylene glycol and poloxamer 407 on able to move investigated gels.*

Stoichiometric ratio lactic acid to chitosan	Concentration in % 1,2- propylene glycol	Able to move gels with addition 1,2- propylene glycol, cm	Able to move gels with 1,2- propylene glycol and addition poloxamer 407, cm		
			20%	23%	25%
1:1	5	28.0	25.0	24.0	23.0
	10	28.5	25.6	24.5	24.2
	15	29.2	26.0	25.8	25.3
	20	29.4	27.5	26.4	25.9
	25	29.6	28.0	27.6	26.8
2:1	5	28.5	26.0	24.8	23.8
	10	28.8	27.3	25.4	24.6
	15	29.6	28.5	26.7	25.4
	20	29.8	29.4	27.3	26.2
	25	30.0	30.0	28.0	27.8

Table 4. *Influence PEG-200 and poloxamer 407 on pH investigated gels.*

Stoichiometric ratio lactic acid to chitosan	Concentration in % PEG-200	pH gels with addition PEG-200	pH gels with PEG-200 and addition poloxamer 407		
			20%	23%	25%
1:1	5	4.43	4.55	4.62	4.84
	10	4.48	4.58	4.69	4.88
	15	4.55	4.60	4.65	4.90
	20	4.87	4.90	4.95	4.98
	25	4.95	5.05	5.26	5.30
2:1	5	3.42	4.00	4.25	4.30
	10	3.46	4.20	4.35	4.38
	15	3.51	4.40	4.48	4.50
	20	3.63	4.52	4.60	4.65
	25	3.68	4.70	4.75	4.85

Table 5. *Influence glycerol and poloxamer 407 on pH investigated gels.*

Stoichiometric ratio lactic acid to chitosan	Concentration in % glycerol	pH gels with addition glycerol	pH gels with glycerol and addition poloxamer 407		
			20%	23%	25%
1:1	5	4.43	4.25	4.40	4.44
	10	4.48	4.28	4.45	4.48
	15	4.55	4.34	4.55	4.58
	20	4.87	4.45	4.60	4.88
	25	4.95	4.50	4.64	4.98
2:1	5	3.42	3.60	3.75	3.90
	10	3.46	3.76	3.85	4.10
	15	3.51	3.89	4.16	4.20
	20	3.63	4.19	4.28	4.35
	25	3.68	4.35	4.40	4.45

Table 6. *Influence 1,2- propylene glycol and poloxamer 407 on pH investigated gels*

Stoichiometric ratio lactic acid to chitosan	Concentration in % 1,2- propylene glycol	pH gels with addition 1,2- propylene glycol	pH gels with 1,2- propylene glycol and addition poloxamer 407		
			20%	23%	25%
1:1	5	4.43	4.35	4.42	4.52
1:1	10	4.48	4.42	4.57	4.60
1:1	15	4.55	4.55	4.59	4.61
1:1	20	4.87	4.63	4.85	4.90
1:1	25	4.95	5.00	5.05	5.10
2:1	5	3.42	3.70	3.85	4.00
2:1	10	3.46	3.86	3.99	4.20
2:1	15	3.51	4.14	4.26	4.31
2:1	20	3.63	4.32	4.38	4.40
2:1	25	3.68	4.43	4.50	4.55

The addition of glycerol increases the movability gels containing lactic acid complexed with chitosan in a stoichiometric ration 1:1 from 23 cm to 26 cm and at 2:1 ratio from 25 cm to 29 cm. Higher concentrations of the poloxamer 407: 23% and 25% result in the movability of 22 cm to 25 cm (***Table 2***).

The use of a 1,2-propylene glycol affects further the movability of the gels from 25 cm to 28 cm (1:1) and from 26 cm to 30 cm (2:1) for 20% poloxamer 407. Higher concentrations of the poloxamer 407: 23% and 25% result in the movability of 23 cm to 28 cm (***Table 3***).

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 3.42 to 4.95. The addition of 20 – 25% poloxamer 407 increases the pH 4.55 to 5.30 for 1:1 gels and 4.00 to 4.85 for 2:1 gels (***Table 4***).

Gels with addition 20-25% poloxamer 407 containing lactic acid complexed with chitosan and 5-25% content of glycerol reveal pH from 4.25 to 4.98 for 1:1 and from 3.60 to 4.45 for 2:1 (***Table 5***).

Analogical gels containing addition 5-25% 1,2-propylene glycol possess pH from 4.35 to 5.10 for 1:1 and from 3.70 to 4.55 for 2:1 (***Table 6***).

All the investigations were performed at 37 °C.

The investigations showed that the addition of a thermosensitive polymer increases the adhesive properties of the investigated gels, but at the same time it increases their pH.

The addition of glycerol or 1,2-propylene glycol reduces the pH and maintains high adhesion. Investigate the effect of excipients on pharmaceutical and application properties of produced preparations was require in order to design subsequently new gynaecological drug forms with innovative properties. Own investigations revealed that there is a complex relationship between the composition of the preparations and their effect on the pH. The use of hydrofilizing substances allowed to obtain physiological range pH gynaecological gels.

4. Conclusions

1. The addition of glycerol or 1,2-propylene glycol reduces the pH and maintains high adhesion.
2. Results obtained in the experimental studies proved that it is possible to produce a preparation with optimal pharmaceutical and application properties.
3. Investigations revealed that there is a complex relationship between the composition of the preparations and their effect on the pH.

5. References

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