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Studies on gynaecological hydrophilic lactic acid preparations

Part 6: Use of Eudragit® E-100 as lactic acid carrier in intravaginal tablets

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Hydrophilic intravaginal tablets based on methylcellulose and containing lactic acid component with Eudragit® E-100 undergo swelling in standard conditions. A high flow-limit of the gel that originates from the tablets as well as its dynamic viscosity should allow for the durable dosage form in the vagina. By choosing a 1 : 1 ratio of lactic acid to Eudragit® E-100, it is possible to obtain tablets disintegrating into a gelform at physiological range of 3.8–4.4. An increase in the amount of lactic acid in the complex in relation to the polymer up to 2 : 1 and 3 : 1 ratios results in gels with a lower pH. These gels possess an acid reserve that might be able to neutralise the excess of alkali present in severe vaginal infections.

1. Introduction

Symptomatic treatment of inflammatory conditions within the vagina results in frequent recurrences due to elevated pH-levels that deviate from the physiological values. The efficacy of anti-inflammatory drugs and agents that normalise the physiological environment of the vagina is largely dependent on the duration of drug contact with vaginal mucosa. Many drugs fulfil these requirements only with the patient in a lying position [1, 2]; however, in the case of gynaecological treatment it is essential to ensure the action of the drug throughout daily activities of the patient [3]. Gels with a hydrophilic polymer excipient containing lactic acid, are able to meet these requirements due to their adhesive properties [4–7].

The aim of the study was to investigate hydrophilic vaginal tablets containing lactic acid complexed with Eudragit® E-100 that undergo gelation at the site of application enabling gradual release of lactic acid.

2. Investigations and results

Twenty-seven series of tablets with a methylcellulose excipient containing lactic acid complexed with Eudragit® E-100 in molar proportions of 1 : 1, 2 : 1, 3 : 1 and 5 and 10% content of glycerol, 5, 10, 15, 20% of sorbitol or 5% of glycerol and 5, 10, 15% of sorbitol were prepared.

The investigations indicate different patterns of swelling within each of the series in relation to the content of hydrophilising substance and the ratio of lactic acid to Eudragit® E-100. The increase of hydrophilising substance content is accompanied by the increase of the degree of swelling expressed in millimeters of gel column formed in a calibrated cylinder as well as by the rate of swelling expressed by the height of the rising column of gel in mm/min. The analysis of the investigated series reveales that the rate of swelling as well as the height of rising gel column in the calibrated cylinder increase with the increase of glycerol content from 5% to 10%.

A similar relation between the increase of gel column and swelling rate is observed as the effect of 1 : 1, 2 : 1, 3 : 1 lactic acid to Eudragit® E-100 ratio at a constant level of hydrophilising agent.

On the other hand, the content of sorbitol exerts an inversely proportional effect on the above mentioned parameters.

In conclusion, tablets containing glycerol as a hydrophilising agent reveal the most favourable swelling parameters in respect to increases in the volume of gel as well as swelling rate.

Data presented the Table indicate that gels arising from tablets containing lactic acid complexed with Eudragit® E-100 in 1 : 1, 2 : 1 and 3 : 1 ratios and 5% glycerol content have pH-values of 4.28 to 2.90. On increasing the glycerol content to 10%, the pH values range from 4.20 to 2.88. The addition of 5, 10, 15% of sorbitol to tablets containing 5% of glycerol results in pH values ranging from 4.18 to 2.82. The pH values of gels arising from tablets containing sorbitol alone in concentrations 5, 10, 15, and 20% range from 4.29 to 2.91. Gels containing lactic acid complex with Eudragit® E-100 in 1 : 1, 2 : 1, 3 : 1 ratio as well as 5% glycerol reveal dynamic viscosities between 108.4 and 148.7 mPas at the maximum curdling rate. Similar results have been obtained for the remaining gels. Increasing the glycerol content to 10% results in values ranging from 96.2 to 136.4 mPa · s. The 5, 10, 15% addition of sorbitol to tablets containing 5% of glycerol results in a decrease in dynamic viscosity to 54.2 to 86.6 mPa · s. The viscosity of gels arising from tablets containing only sorbitol in concentrations of 5, 10, 15, and 20% ranges from 45.5 to 106.7 mPa · s (Fig.).

Table: Influence of the composition of the tablet on pH, dynamic viscosity and swelling properties of intravaginal tablets

BN	MC (g)	GL (g)	SR (g)	LA (g)	E (g)	LA : E	pH	V (mPas)	HG (mm)
I a	87.35	5.0	0.0	2.24	5.41	1 : 1	4.28	148.7	25.0
I b	85.11	5.0	0.0	4.48	5.41	2 : 1	3.30	130.3	22.5
I c	82.87	5.0	0.0	6.72	5.41	3 : 1	2.90	108.4	25.0
II a	82.35	5.0	5.0	2.24	5.41	1 : 1	4.09	86.6	18.5
II b	80.11	5.0	5.0	4.48	5.41	2 : 1	3.11	78.7	20.5
II c	77.87	5.0	5.0	6.72	5.41	3 : 1	2.82	72.6	21.0
III a	77.35	5.0	10.0	2.24	5.41	1 : 1	4.15	71.7	19.5
III b	75.11	5.0	10.0	4.48	5.41	2 : 1	3.13	64.7	21.0
III c	72.87	5.0	10.0	6.72	5.41	3 : 1	2.90	54.2	18.0
IV a	72.35	5.0	15.0	2.24	5.41	1 : 1	4.18	71.7	19.0
IV b	70.11	5.0	15.0	4.48	5.41	2 : 1	3.15	64.7	20.0
IV c	67.87	5.0	15.0	6.72	5.41	3 : 1	2.97	54.2	19.0
V a	82.35	10.0	0.0	2.24	5.41	1 : 1	4.20	136.4	21.0
V b	80.11	10.0	0.0	4.48	5.41	2 : 1	3.14	121.6	21.5
V c	77.87	10.0	0.0	6.72	5.41	3 : 1	2.88	96.2	24.5
VI a	87.35	0.0	5.0	2.24	5.41	1 : 1	4.16	106.7	20.0
VI b	85.11	0.0	5.0	4.48	5.41	2 : 1	3.12	101.4	18.0
VI c	82.87	0.0	5.0	6.72	5.41	3 : 1	2.91	96.2	13.5
VII a	82.35	0.0	10.0	2.24	5.41	1 : 1	4.21	90.9	16.5
VII b	80.11	0.0	10.0	4.48	5.41	2 : 1	3.20	87.4	17.5
VII c	77.87	0.0	10.0	6.72	5.41	3 : 1	2.94	83.9	17.0
VIII a	77.35	0.0	15.0	2.24	5.41	1 : 1	4.27	84.0	17.0
VIII b	75.11	0.0	15.0	4.48	5.41	2 : 1	3.26	70.0	15.0
VIII c	72.87	0.0	15.0	6.72	5.41	3 : 1	2.98	59.5	14.0
IX a	72.35	0.0	20.0	2.24	5.41	1 : 1	4.29	68.2	15.0
IX b	70.11	0.0	20.0	4.48	5.41	2 : 1	3.29	53.3	14.0
IX c	67.87	0.0	20.0	6.72	5.41	3 : 1	2.93	45.5	11.0

BN – Batch Number, MC – Methylcellulose, GL – Glycerol, SR – Sorbitol, LA – Lactic acid, E – Eudragit® E-100, LA : E – Lactic acid to Eudragit ratio, V – Dynamic viscosity, HG – Height of gel column after 10 min of measurement

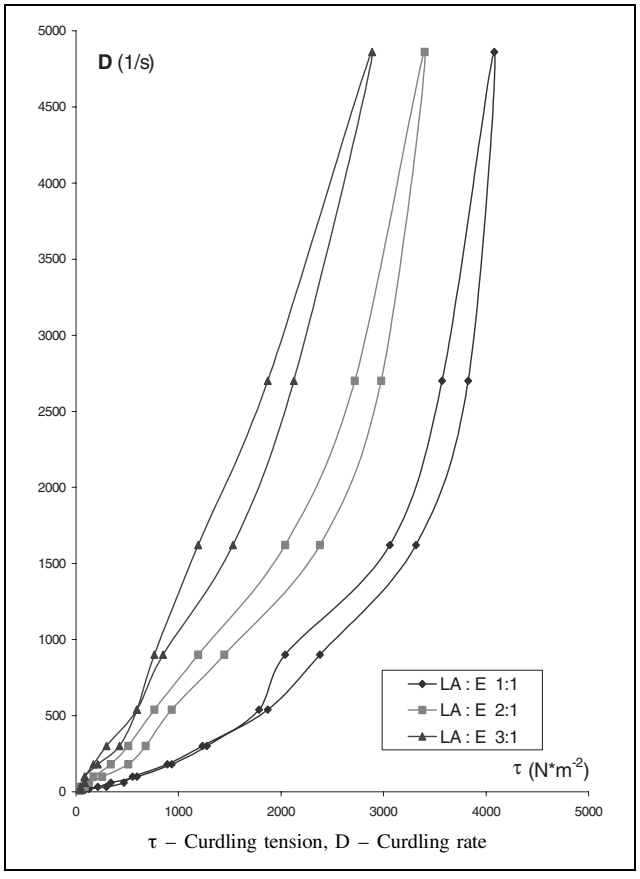

Fig.: Flow of gel from tablets (batch number VIIIa, b, c)

3. Discussion

Under the assumed conditions of the biopharmaceutical model, all investigated series of tablets undergo swelling producing a gel with a specific viscosity. The analysis of rheological graphs shows that these gels are characterised by a high flow-limit. The high flow-limit should prevent them from being displaced on the vaginal mucosa, providing a long-term release of lactic acid into the vaginal environment. Tablets containing glycerol swell most readily. They become completely swollen within 10 min of measurement, forming a 25 mm gel column. These properties indicate that the tablets are most suitable for gynaecological purposes. The pH of the investigated gels containing lactic acid complexed with Eudragit® E-100 in 1 : 1 ratio correspond to natural physiological acidity of the vagina, which ranges from pH 3.8 to 4.4. Tablets containing 2 : 1 and 3 : 1 ratios of lactic acid to polymer possess an acid reserve that might neutralise the excess of alkali present in advanced inflammatory conditions within the vagina.
The above conclusions still require verification *in vivo*.

4. Experimental

4.1. Materials

Aqua purificata, acc. To FP V. Lactic acid, PZF Cefarm, Wrocław. Methylcellulose, Aldrich Chemical Company Ltd. Gillingham – Dorest SP 84 SL – England. Propylene-1,2-glycol, Polskie Odczynniki Chemiczne, Gliwice. Polyoxyethylene glycol 200, LOBA-Chemie, Wien – Fishamend. Glycerol pro analysis, Polskie Odczynniki Chemiczne, Gliwice. Eudragit E-100, Röhm GmbH, Chemische Fabrik, Germany. D-sorbitol, Polskie Odczynniki Chemiczne, Gliwice.

4.2. Methods

4.2.1. Measurements of pH and viscosity

(see [4])

4.2.2. Production of hydrophilic intravaginal tablets

The manufacturing process of tablets containing lactic acid complexed with Eudragit® E-100 consisted of the following stages:
1. Solvation of methylocellulose,
2. Obtaining lactic acid – Eudragit® E-100 complex,
3. Implementing the complex into methylcellulose,
4. Addition of solid hydrophilising agent,
5. Tableting.

Stage 1. Solvation of methylcellulose with glycerol requires an anhydrous environment in order to prevent swelling of the polymer. Glycerol was dissolved in 96% ethanol, 50 ml of ethanol being used for 100 g methylcellulose. An homogenous mixture of methylcellulose wetted with this solution was dried at 40 °C. The dry mass was standardized by sieving through a 0.5 mm sieve. In the case of tablets not containing glycerol, this stage was omitted.

Stage 2. Eudragit® E-100 combines with organic acids through tertiary amine groups. This property was used in the complexing procedure. The required amount of powdered Eudragit® E-100 was poured over a weighed amount of lactic acid. The mass was stirred to obtain an homogenous suspension. The mixture was left for about 24 h until a clear thick liquid has formed, which could be combined with methylcellulose [5].

Stage 3. The formed complex was combined with solvated and non-solvated methylcellulose. The obtained mixture was mixed to obtain an homogenous mass and dried at 40 °C in order to evaporate water present in the lactic acid solution. The dry mass was powdered.

Stage 4. In the case of sorbitol, owing to its strong hydroscopic potential, it was added to the methylcellulose mixture with adsorbed lactic acid – Eudragit® E-100 complex. The completed mass was standardised by mixing.

Stage 5. Tablets were obtained by means of direct tableting. In the case of tablets intended for quick and complete swelling, the optimum form consisted of a large diameter and low height cylinder. Taking into account the technical potentials of available tableting machine EKO manufactured by ERWEKA (Germany), flat tablets with the diameter of 10 mm, 3 mm thich and weighing 333 mg were manufactured.

4.2.3. Investigation of obtained tablets

Preliminary investigations have confirmed that pharmacopeal parameters such as hardness and grindability of the investigated tablets are within the norms set in FP V.

The purpose of the tablets was to produce a gel after insertion into vagina, thus the main emphasis was laid on the measurement of the conversion rate of the tablet into gel as well as on detailed investigation of gel in relation to its usefulness in gynaecology.

For measurement of swelling, a calibrated cylinder with the diameter of 11 mm was used. The cylinder containing 5 ml of distilled water was heated in a thermostated water bath at 37 °C. The tablet was placed on the bottom of the vessel and the height of formed gel column was measured at regular intervals.

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