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Studies on gynaecological hydrophilic lactic acid preparations

Part 5: The use of Eudragit® E-100 as lactic acid carrier in intravaginal tablets

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Intravaginal tablets based on hydrophilic methylcellulose and containing lactic acid complexed with Eudragit® E-100 undergo deformation under standard conditions. The high flow – limit of gel originating from the tablets as well as its dynamic viscosity should enable durability of this dosage form on the vaginal mucosa. By selecting either 1 : 1 or 2 : 1 ratios of lactic acid to Eudragit® E-100 it is possible to obtain tablets that disintegrate into a gelform at pH 3.8–4.4, i.e. the pH remains within the physiological range. Increasing the amount of lactic acid in the complex in relation to the polymer to a 4 : 1 ratio results in gels with a lower pH while possessing an acid reserve that can neutralize the excess of alkali present in severe vaginal infections.

1. Introduction

Current treatment modalities of vaginitis remain symptom based. However, this unidirectional pharmacological intervention is often followed by undesirable effects and recurrence of the disease.

Vaginitis is characterized by an increase in pH of the vaginal discharge [1, 2] above the physiological pH of 3.8–4.4. Administration of mature lactic acid rods does not resolve the problem because they are unable to produce the necessary acidity. Studies undertaken to date [3–7] have attempted mainly to reconstruct the physiological conditions of vaginal discharge.

The aim of the present work was to investigate the use of hydrophilic intravaginal tablets containing lactic acid/Eudragit® E-100 complex, which undergo gelation at the site of application enabling gradual release of lactic acid.

2. Investigations and results

Thirty-nine series of tablets containing lactic acid complexed with Eudragit® E-100 in molar proportions 1 : 1, 2 : 1, 4 : 1 were prepared. The suppository excipient consisted of 8, 12, 16, 20 and 25% gelatin, 10, 15, 20 and 25% glycerol, 15% PEG-200 and 15% propylene-1,2-glycol as well as 0, 2, 4 and 6% methylcellulose. The investigations indicated that the composition of the excipient does not have a significant effect on the temperature at which tablets undergo deformation.

All the investigated preparations were stable to deformation at 25 °C for 20 min, indicating the possibility of storage at room temperature. At 30 °C the tablets deformed on the average by 7 min, with the exception of preparations containing 25% glycerol as hydrolising substance, which were not completely deformed after 20 min. Moreover, tablets containing 25% gelatin did not undergo any deformation at this temperature. At 35 °C the time in which deformation of the investigated tablets occurs was significantly shorter compared to the time at 30 °C and ranged between 1–3 min depending on the composition. At 37 °C all the investigated tablets underwent deformation within 2 min.

As evidenced by data presented in the Table, gels formed from tablets containing lactic acid and Eudragit® E-100 complex as well as 10, 15, 20 and 25% glycerol, showed pH ranges from 4.42 to 4.99 for the 1 : 1 ratio of lactic acid and Eudragit® E-100 and from 3.07 to 3.46 for the ratio 4 : 1.

A comparison of the pH of the gels formed from tablets containing 15% of hydrophilizing substances revealed that the pH of the investigated proportions of lactic acid complexed with polymer was between 4.56 and 3.30 for propylene-1,2-glycol, between 4.90 and 3.51 for PEG-200, and between 4.40 and 3.02 for glycerol.

Data presented in the Table also show that the dynamic viscosity of gels formed from tablets containing 10, 15, 20 and 25% glycerol and lactic acid complexed with Eudragit® E-100 ranged from 177 to 362 mPa · s for a 1 : 1-ratio of lactic acid and Eudragit® E-100 and 108 to 329 mPas for a 4 : 1-ratio.

The dynamic viscosity of gels formed from the tablets containing 15% of the hydrophilizing substances ranged for the investigated proportions of lactic acid complexed with polymer from 151 to 303 mPa · s for propylene-1,2-glycol from 253–371 mPa · s for PEG-200, and 108–177 mPa · s for glycerol.

3. Discussion

Under the experimental conditions of a biopharmaceutical model all the investigated series of tablets underwent deformation at 37 °C within 2 min, forming gels with a spe-

Table: Influence of the excipient composition on pH, dynamic viscosity and deformation time of investigated intravaginal tablets

BN	Gel. g	MC g	HS g	LA g	E g	A g	LA : E	pH	V mPa · s	Dt s
A1	8.0	4.0	15.0GL	1.4	3.8	67.8	1 : 1	4.34	168	60.0
A2	8.0	4.0	15.0GL	2.8	3.8	66.4	2 : 1	3.45	167	61.0
A3	8.0	4.0	15.0GL	5.6	3.8	63.6	4 : 1	2.83	146	61.0
B1	12.0	4.0	15.0GL	1.4	3.8	63.8	1 : 1	4.57	185	75.0
B2	12.0	4.0	15.0GL	2.8	3.8	62.4	2 : 1	3.67	151	75.0
B3	12.0	4.0	15.0GL	5.6	3.8	59.6	4 : 1	3.15	143	77.0
C1	16.0	4.0	15.0GL	1.4	3.8	59.8	1 : 1	4.40	177	105.0
C2	16.0	4.0	15.0GL	2.8	3.8	58.4	2 : 1	3.62	167	106.0
C3	16.0	4.0	15.0GL	5.6	3.8	55.6	4 : 1	3.02	108	106.0
D1	20.0	4.0	15.0GL	1.4	3.8	55.8	1 : 1	4.42	303	80.0
D2	20.0	4.0	15.0GL	2.8	3.8	54.4	2 : 1	3.90	312	80.0
D3	20.0	4.0	15.0GL	5.6	3.8	51.6	4 : 1	3.10	236	81.0
E1	25.0	4.0	15.0GL	1.4	3.8	50.8	1 : 1	4.64	337	110.0
E2	25.0	4.0	15.0GL	2.8	3.8	49.4	2 : 1	3.95	438	112.0
E3	25.0	4.0	15.0GL	5.6	3.8	46.6	4 : 1	3.22	379	114.0
F1	16.0	4.0	10.0GL	1.4	3.8	64.8	1 : 1	4.42	362	80.0
F2	16.0	4.0	10.0GL	2.8	3.8	63.4	2 : 1	3.60	303	80.0
F3	16.0	4.0	10.0GL	5.6	3.8	60.6	4 : 1	3.07	329	82.0
G1	16.0	4.0	20.0GL	1.4	3.8	54.8	1 : 1	4.85	253	85.0
G2	16.0	4.0	20.0GL	2.8	3.8	53.4	2 : 1	4.08	270	86.0
G3	16.0	4.0	20.0GL	5.6	3.8	50.6	4 : 1	3.03	219	83.0
H1	16.0	4.0	25.0GL	1.4	3.8	49.8	1 : 1	4.99	219	100.0
H2	16.0	4.0	25.0GL	2.8	3.8	48.4	2 : 1	3.94	202	102.0
H3	16.0	4.0	25.0GL	5.6	3.8	45.6	4 : 1	3.46	236	101.0
I1	16.0	0.0	15.0GL	1.4	3.8	63.8	1 : 1	4.53	168	70.0
I2	16.0	0.0	15.0GL	2.8	3.8	62.4	2 : 1	3.66	202	70.0
I3	16.0	0.0	15.0GL	5.6	3.8	59.6	4 : 1	2.98	120	71.0
J1	16.0	2.0	15.0GL	1.4	3.8	61.8	1 : 1	4.59	185	75.0
J2	16.0	2.0	15.0GL	2.8	3.8	60.4	2 : 1	3.70	154	74.0
J3	16.0	2.0	15.0GL	5.6	3.8	57.6	4 : 1	3.17	134	73.0
K1	16.0	6.0	15.0GL	1.4	3.8	57.8	1 : 1	4.47	303	120.0
K2	16.0	6.0	15.0GL	2.8	3.8	56.4	2 : 1	3.64	303	121.0
K3	16.0	6.0	15.0GL	5.6	3.8	53.6	4 : 1	3.05	168	119.0
L1	16.0	4.0	15.0PE	1.4	3.8	59.8	1 : 1	4.90	371	80.0
L2	16.0	4.0	15.0PE	2.8	3.8	58.4	2 : 1	3.93	320	80.0
L3	16.0	4.0	15.0PE	5.6	3.8	55.6	4 : 1	3.51	253	81.0
M1	16.0	4.0	15.0GP	1.4	3.8	59.8	1 : 1	4.56	151	70.0
M2	16.0	4.0	15.0GP	2.8	3.8	58.4	2 : 1	3.76	303	72.0
M3	16.0	4.0	15.0GP	5.6	3.8	55.6	4 : 1	3.30	168	70.0

BN – Batch Number, Gel. – Gelatin, MC – Methylcellulose, HS – Hydrofilizing Substances, GL – Glycerol, PE – Polyoxyethylene glycol 200, GP – Propylene-1,2-glycol, LA – Lactic acid, E – Eudragit® E-100, A – Aqua purificata, V – Dynamic viscosity, Dt – Deformation time

cific viscosity. The analysis of rheological graphs (Fig.) as well as data from the Table indicate that such gels are characterized by a high flow-limit. An high flow-limit should prevent them from being displaced on the vaginal mucosa, and allow for a long-term release of lactic acid into the vagina. Tablets with 15% glycerol undergo deformation most rapidly, typically within 15–60 s. These properties are highly useful for gynaecological purposes. The resulting pH of the gels containing lactic acid complexed with Eudragit® E-100 in ratios of 1 : 1 and 2 : 1 range from 3.8 to 4.4 and are within the limits of physiological pH of the vagina. Tablets containing a 4 : 1 ratio of lactic acid-polymer possess enough acid reserve to neutralize the excess of alkali accompanying inflammatory conditions in the vagina.

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. Gelatin, LOBA-Chemie, Wien – Fishamend.

4.2. Methods

4.2.1. Measurements of pH and viscosity

(see [4])

4.2.2. Production of hydrophilic intravaginal tablets

The production of tablets containing lactic acid complexed with Eudragit® E-100 consisted of the following stages:

1. Obtaining the lactic acid-Eudragit® E-100 complex.
Eudragit® E-100 combined with organic acids by means of tertiary amine groups. This property was used in the preparation of the complex. The required amount of powdered Eudragit®E-100 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 [5].

2. Obtaining the excipient:
a. Preparation of gel from methylcellulose
A gel was obtained from methylcellulose by adding a known amount of this compound to the solution of hydrophilizing substance 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.

b. Preparation of gel from gelatin
Gelatin was left with water until swelling was completed and then dissolved by heating. Lactic acid complexed with Eudragit® E-100 was added to liquid gelatinous gel and heated until an homogenous gel was obtained. Distilled water was added to obtain the initial mass.

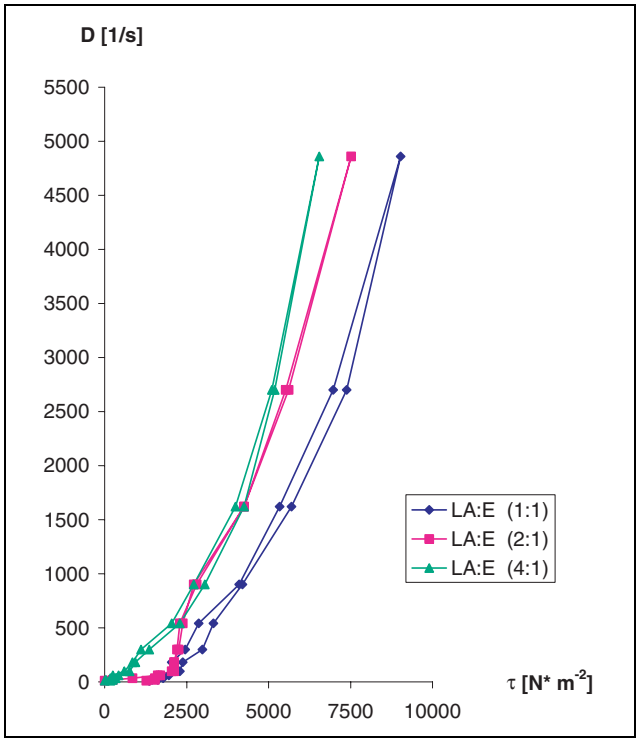

Fig.: Flow of suppository excipient curve (batch number J). τ – tangential stress, D – shearing rate

c. Preparation of the excipient and pouring into the form
Gels prepared from methylcellulose and gelatin were combined into a homogenous excipient and supplemented with distilled water. The excipient was poured into a form that had been previously covered with a thin layer of polyoxyethylene glycol 200.

4.2.3. Investigation of obtained tablets

Measurement of temperature at which the tablets are deformed.
This measurement was carried out according to FP.V in Krówczyński's apparatus [8].

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