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Studies on gynecological hydrophilic lactic acid preparations

Part 2: Effects of Eudragit® E-100 on properties of methylcellulose gels

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Methylcellulose gels containing lactic acid have pH values from 2.00 to 2.60, i.e. out of the physiological value range (3.8 to 4.4). Application of Eudragit E enabled expansion of the pH value range of the gels to 2.14–4.61. Depending on gel composition and amount of lactic acid, the gels show viscosities from 52 mPa · s to 320 mPa · s with raising flow limits.

1. Introduction

Disruption of the biological/chemical balance of biocenosis in the vagina results in pH increases out of the physiological range. Physiological bacteria disappear, therefore the reaction of vaginal secretion becomes more basic and microbial, fungal or protozoa based inflammation may occur.

Lipophilic basic drugs are incompatible with the hydrophilic environment of the vagina and must of applied in the recumbent posture. Therefore, the possibility for application of hydrophilic gels, being simulants of the natural vaginal secretion and easily maintained on the mucosa, has been examined [1]. The pH of methylcellulose gels containing lactic acid differ from the physiologic value. Attention has been paid to the polymers containing amino groups, being substances which maintain the pH value due to reaction with lactic acid. Particularly, Eudragit E containing amino groups which react with lactic acid [2–4] is widely used in pharmacy.

In this study, we were interested in determining the influence of Eudragit E on the physical properties such as pH, viscosity and flow limit of lactic acid containing methylcellulose gels.

2. Investigations and results

In the course of consecutive additions of lactic acid solutions, the pH value of the Eudragit E suspension remained within the range of 5.5–6. after addition of an equivalent amount of lactic acid, the pH value of the neutralization point amounted to 3.5–4, irrespective of its concentration.

The measurements proved that at the stoichiometric neutralization point, 1 g of Eudragit E neutralizes 0.329 g pure lactic acid. The molar ratio of lactic acid Eudragit E® was assumed as 1 : 1.

The pH values of stoichiometric gels specified in Table 1 amount to 4.61 at 24 °C and 5.06 at 37 °C. The higher the

Table 1: Effect of Eudragit E-100, lactic acid and hydrophilizing agents on pH of methylcellulose gels

1	2	3	4	pH		4′	pH		4″	pH	
MC	EE	LA	G	24 °C	37 °C	PG	24 °C	37 °C	PEG-200	24 °C	37 °C
4.00	1.50	0.50		5.06	4.61						
4.00	1.50	1.00		3.62	3.26						
4.00	1.50	2.00		2.86	2.60						
4.00	1.50	4.00		2.35	2.14						
4.00	1.50	0.50	5.00	4.38	4.05	5.00	4.38	4.09	5.00	4.30	4.09
4.00	1.50	1.00	5.00	3.60	3.34	5.00	4.10	3.99	5.00	4.32	3.18
4.00	1.50	2.00	5.00	2.94	2.70	5.00	3.72	3.42	5.00	3.08	2.87
4.00	1.50	4.00	5.00	2.60	2.35	5.00	3.11	2.87	5.00	2.75	2.46
4.00	1.50	0.50	10.00	3.89	3.64	10.00	4.22	3.97	10.00	4.52	4.31
4.00	1.50	1.00	10.00	3.40	3.16	10.00	3.59	3.40	10.00	3.49	3.28
4.00	1.50	2.00	10.00	2.98	2.73	10.00	3.08	2.80	10.00	2.92	2.68
4.00	1.50	4.00	10.00	2.76	2.50	10.00	2.58	2.36	10.00	2.48	2.21
4.00	1.50	0.50	15.00	4.39	4.15	15.00	5.10	4.89	15.00	4.09	3.87
4.00	1.50	1.00	15.00	3.59	3.34	15.00	3.82	3.58	15.00	3.54	3.33
4.00	1.50	2.00	15.00	2.97	2.70	15.00	3.29	3.02	15.00	3.15	3.86
4.00	1.50	4.00	15.00	2.65	2.40	15.00	2.95	2.75	15.00	2.79	2.49
4.00	1.50	0.50	20.00	4.50	4.22	20.00	4.62	4.30	20.00	4.29	3.97
4.00	1.50	1.00	20.00	3.92	3.71	20.00	3.59	3.38	20.00	3.70	3.51
4.00	1.50	2.00	20.00	3.30	3.02	20.00	2.99	2.78	20.00	3.15	2.95
4.00	1.50	4.00	20.00	2.96	2.66	20.00	2.60	2.40	20.00	2.94	2.60
4.00	1.50	0.50	25.00	4.46	4.19	25.00	4.84	4.52	25.00	4.80	4.37
4.00	1.50	1.00	25.00	3.65	3.38	25.00	3.68	3.45	25.00	3.86	3.56
4.00	1.50	2.00	25.00	3.09	2.89	25.00	3.23	2.95	25.00	3.54	3.21
4.00	1.50	4.00	25.00	2.67	2.46	25.00	2.93	2.65	25.00	2.99	2.68

MC: methylcellulose; EE: Eudragit E®; LA: lactic acid; G: glycerol; PG: 1,2-propylene glycol

lactic acid Eudragit E molar ratio the lower the pH value of the resulting gels, at 24 °C, reduction of the ratio from 2 : 1 to 8 : 1 resulted in reduction of the pH from 3.62 to 2.35, whereas at 37 °C the pH values were 3.26 and 2.14, respectively.

Addition of hydrophilizing agents resulted in a slight reduction in the pH values of the gels, from 0.52 to 0.76 of the unit.

As it can be seen from Table 2 increases in the lactic acid Eudragit® ratio resulted in higher viscosity values for the maximum shearing rates (4860) of methylcellulose gels.

Table 2: Effect of Eudragit E-100®, lactic acid an hydrophilizing agents on viscosity of methylcellulose gels

1 MC	2 EE	3 LA	4 G	η (mPa · s)	4′ PG	η (mPa · s)	4″ PEG-200	η (mPa · s)
4.00	1.50	0.50		286				
4.00	1.50	1.00		320				
4.00	1.50	2.00		236				
4.00	1.50	4.00		303				
4.00	1.50	0.50	5.00	320	5.00	286	5.00	286
4.00	1.50	1.00	5.00	320	5.00	185	5.00	303
4.00	1.50	2.00	5.00	202	5.00	236	5.00	253
4.00	1.50	4.00	5.00	286	5.00	253	5.00	185
4.00	1.50	0.50	10.00	286	10.00	253	10.00	270
4.00	1.50	1.00	10.00	303	10.00	236	10.00	253
4.00	1.50	2.00	10.00	219	10.00	270	10.00	270
4.00	1.50	4.00	10.00	286	10.00	202	10.00	303
4.00	1.50	0.50	15.00	166	15.00	236	15.00	219
4.00	1.50	1.00	15.00	146	15.00	253	15.00	270
4.00	1.50	2.00	15.00	78	15.00	151	15.00	270
4.00	1.50	4.00	15.00	236	15.00	253	15.00	253
4.00	1.50	0.50	20.00	29	20.00	354	20.00	196
4.00	1.50	1.00	20.00	148	20.00	421	20.00	106
4.00	1.50	2.00	20.00	270	20.00	236	20.00	113
4.00	1.50	4.00	20.00	236	20.00	438	20.00	253
4.00	1.50	0.50	25.00	52	25.00	303	25.00	151
4.00	1.50	1.00	25.00	115	25.00	320	25.00	166
4.00	1.50	2.00	25.00	139	25.00	253	25.00	185
4.00	1.50	4.00	25.00	131	25.00	263	25.00	108

Table 3: Effect of Eudragit E-100®, lactic acid and hydrophilizing agents on spreading rate of methylcellulose gels

1 MC	2 EE	3 LA	4′ PG	spread (cm)	t (min)
4.00	1.50	0.50	5.00	0.5	15.00
4.00	1.50	1.00	5.00	0.5	15.00
4.00	1.50	2.00	5.00	0.5	15.00
4.00	1.50	4.00	5.00	0.5	15.00
4.00	1.50	0.50	10.00	1.5	15.00
4.00	1.50	1.00	10.00	1.5	15.00
4.00	1.50	2.00	10.00	1.5	15.00
4.00	1.50	4.00	10.00	1.5	15.00
4.00	1.50	0.50	25.00	0.5	15.00
4.00	1.50	1.00	25.00	0.5	15.00
4.00	1.50	2.00	25.00	0.5	15.00
4.00	1.50	4.00	25.00	0.5	15.00

1 MC	2 EE	3 LA	4′ PEG-200	spread (cm)	t (min)
4.00	1.50	0.50	25.00	2.00	15.00
4.00	1.50	1.00	25.00	2.00	15.00
4.00	1.50	2.00	25.00	2.00	15.00
4.00	1.50	4.00	25.00	2.00	15.00

t: time
Note: emaining gels do not spread

Viscosity of the gel composed of a 1 : 1 ratio amounted to 286 mPa · s. Viscosity of the gel composed of a 2 : 1 ratio amounted to 320 mPa · s. For the ratio of 4 : 1 the viscosity was 236 mPa · s whereas for the 8 : 1 ratio the viscosity value was equal to 303 mPa · s. Addition to hydrophylizing agents had an insignificantly effect on the viscosity of the gels. Viscosity of the gels containing glycerol was lower. At 5–25% glycerol concentration the viscosity of gel dropped from 320 mPa · s down to 52 mPa · s. Respective values for 1,2-propylene glycol amounted to 286–303 mPa · s. For PEG-200 additives, the viscosity range was equal to 286–151 mPa · s.

Table 3 shows that methylcellulose based gels characterized by 1 : 1 to 8 : 1 lactic axid. Eudragit E ratios do not spread under the conditions of the applied biopharmaceutical model [1]. Additions of 5–25% of 1,2-propylene glycol and PEG-200 result in an insignificant rise in spreading ability. In dependence upon composition, spots of the gels move by 0.5 to 2 cm from their original position. Gels composed of 5–25% glycerol do not spread at all.

3. Discussion

By selection of a suitable lactic acid Eudragit E ratio, preparations characterized by physiological pH values have been obtained. Gels containing higher ratios have lower pH values, due to some excess of acid required for neutralization of base secretion present during inflammations of the vagina.

The gels are characterized by various viscosity values, correlated with the flow limit. The higher the viscosity the higher the flow limit.

The rheological data do not present the full picture of behaviour of the gels *in vivo*. The biopharmaceutical model approximates physiological conditions and enables differentiation of preparations characterized by various adhesion and spreading characteristics. Examinations of the gels proved that many preparations do not spread, i.e. have suitable adhesion. It is assumed, that the non-spreading gels will be well maintained in their application place. However, this has to be verified *in vivo*.

4. Experimental

4.1. Materials

Aqua purificata: acc. to FPV. Lactic acid: P.Z.F. Cefarm, Wroclaw, Poland. Methylcellulose: Aldrich Chemical Company Ltd. Gillingham, Dorest SP84 S1, England. 1,2-Propylene glycol: P.O.Ch., Gliwice, Poland. Polyoxyethylene glycol 200: LOBA-Chemie Wien-Fischamend, Austria. Glycerol p.a.: P.O.Ch., Gliwice, Poland. Eudragit E-100®: Röhm Pharma GmbH, Weiterstadt, Germany.

4.2. Methods

4.2.1. Measurements of pH, viscosity and spreading

Measurements of pH, viscosity and spreading coefficients have been carried out in a biopharmaceutical model described in a former paper [1].

4.2.2. Determination of the Eudragit E neutralization point with lactic acid

Eudragit E-100 was powdered in a mortar. The powder 1 g was put into 9 g of water in an Erlenmeyer conical flask. Then lactic acid was added to the suspension by 0.5 ml portions of 5% solution or by equivalent volumes of 10%, 15% or 20% solutions. After each portion the mixture was heated to 40 °C, cooled down to room temperature, made up with water to replace the evaporated amount, the pH value was measured.

4.2.3. Gel preparation technique

Eudragit E was dissolved at 40 °C in a water solution of lactic acid, comprising a half of the prescribed water amount. After cooling to room temperature, hydrophilizing agents and the remaining amount of water were

added. Then methylcellulose was added to the mixture. Gels composed of 4% methylcellulose, 1.5% Eudragit E, 0.5–4% lactic acid or 5–25% hydrophiling agents were obtained. The amounts of particular components are specified in Table 1.

4.2.4. Measurement of adhesion

The apparatus consisted of a 500 cm^3 round-bottomed flask with a grounded joint, the neck of which was kept in horizontal position. The flask was half-immersed in a water bath at 37 °C and rotated at 20 r.p.m.

By means of a syringe and a slightly bent glass tube, gel was applied into the lowest part of the horizontally positioned flask. The diameter of the preparation spot was measured. After starting the rotation, the time required for ultimate spreading of the preparation over the circumference of the flask was measured.

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