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Studies on gynaecological hydrophilic lactic acid preparations

Part 4: Effects of polyvinyl pyrrolidone K-90 on properties of methylcellulose gels

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In continuing the investigation of the binding of lactic acid with basic polymers polyvinyl pyrrolidone K-90 (PVP) was used. Use of PVP in mixtures with lactic acid in experimentally determined and calculated proportions allowed the preparation of gels with pH 3.8–4.4, i.e. maintaining the physiological conditions in the vagina. The viscosity of the methylcellulose gels increases proportionally to the amount of the PVP – lactic acid complex added. Examination of the gels in the biopharmaceutical model, which simulated the physiological conditions of the vagina, allowed determination of the mobility of the preparations in patients.

1. Introduction

Previous publications presented the results of the study of gynaecological preparations of complexes of Eudragit® E-100, comprising the III-order amino groups [1], lactic acid and chitosan [2], i.e. a I-order amine. The complexes formed gels maintaining physiological conditions, specific to the environment of the vagina. Attention was then paid to polyvinyl pyrrolidone K-90, which comprises III-order amino groups in heterocyclic rings. The polymer may be used in medicinal preparations as a carrier for lactic acid, reproducing the physiological environment of the vagina.

Polyvinyl pyrrolidone K-90 may form complexes with substances of an acid nature like: sulphathiazole, sodium salicylate or phenobarbital, as well as with acids – mandelic acid, p- and m-hydroxybenzoic acids, p-aminobenzoic acid, salicylic acid [3, 4], and also with phenol, resorcin, catechol, hydroquinone, 1-naphthol, tannin and pyrogallol [5].

Szajdak and Uchman [6] showed the occurrence of weak bonds in the complex of mefacit and PVP.

Pellerat et al. [7] demonstrated that penicillin, insulin, and prostygmin have prolonged therapeutic activity when administered to a patient together with polyvinyl pyrrolidone. Similar effects were observed by Durel [8] who administrated PVP with sulfonamides.

Siguier et al. [9] showed that PVP prolongs the analgetic effects of morphine, white Higuchi and Kuramoto [3, 4] proved that PVP forms weak bonds with some therapeutic agents. The formation of these complex compounds provides a mechanism for such modification of pharmacological action [10].

Under certain conditions of pH molecules of PVP may have a basic nature [11], so that complex compounds with lactic acid may be formed.

2. Investigations and results

Solutions of PVP K-90 were mixed with solutions of lactic acid in concentrations of 0.005%, 0.01%, 0.05% and 0.1%. The pH decreased in proportion to the volume and concentration of lactic acid used. The basicity of the mixtures remained within the range of physiological conditions in the vagina.

Calculations proved that 1 g of PVP K-90 may bind 0.003 g of pure lactic acid. Based on this proportion complexes were prepared comprising 5%, 10%, 20% and 30% of PVP K-90. All the preparations in form of gels comprising 3% methylcellulose, have physiological basicity. pH of the gels comprising from 0.013 to 0.075% of lactic acid in complexes with PVP K-90 remained within the range of 3.96–4.17 (see Table 1).

Addition of hydrophilizing agents results in a very small change of basicity, within the limits of error of measurements. As can be seen from Table 2, the absolute viscosity of the gels measured at 4860 rpm was 354; 506; 886 and 1687 mPa · s, respectively.

Addition of hydrophilizing agents does not changes the values in any significant degree.

The absolute viscosity of 3% methylcellulose gels comprising 5–30% PVP K-90 and 5–25% of glycerol remains within the range of 135–1687 mPa · s. Addition of 1,2-propylene glycol results in viscosity values remaining in the range of 219–1552 mPa · s. Gels cotaining PEG-200 have absolute viscosity in the range 118–1687 mPa · s.

Results of rheological measurements permit prediction of the behavior of the preparations on the vaginal mucosa. To gain more information, the gels were tested in a biopharmaceutical model.

Gels comprising 0.075% of lactic acid, 30% PVP K-90 and hydrophilizing agent additives remained in place and showed no tendencies to flow down. Other gels moved, flowing down with a velocity of 0.8–6.5 cm per 5 min of measurement.

3. Discussion

By selection of an appropriate proportion of lactic acid to PVP K-90 the basicity (pH) of the preparations may be adjusted, to match the physiological environment of the vagina. Increased amounts of lactic acid result in lower pH values of the gels, whereas excess acid neutralizes excess bases, characteristic of inflammatory conditions of the vagina.

The gels have different viscosities. However, rheological parameters alone are not sufficient to predict their behavior in patients. The physiological conditions may be simulated by a biopharmaceutical model [12], providing more information on adhesion and mobility of the preparations in conditions close to a physiological state. The biopharmaceutical tests proved that many of the preparations have no tendency to flow, and that their adhesion is excellent. It may be expected that preparations having low mobility will remain at in the application sites for long periods. The assumption will be verified *in vivo*.

Table 1: Effect of the amounts of PVP K-90, lactic acid and hydrophilizing agents on pH of methylcellulose gels

1 MC (g)	2 PVP (g)	3 LA (g)	4 G (g)	PH	4′ PG (g)	PH	4″ PEG-200 (g)	pH
3.00	5.00	0.013		3.96				
3.00	10.00	0.028		4.05				
3.00	20.00	0.050		4.10				
3.00	30.00	0.075		4.17				
3.00	5.00	0.013	5.00	4.38	5.00	4.22	5.00	3.47
3.00	10.00	0.028	5.00	4.04	5.00	4.06	5.00	3.62
3.00	20.00	0.050	5.00	4.09	5.00	4.56	5.00	3.85
3.00	30.00	0.075	5.00	3.82	5.00	4.17	5.00	3.77
3.00	5.00	0.013	10.00	4.29	10.00	4.38	10.00	3.30
3.00	10.00	0.028	10.00	4.08	10.00	4.12	10.00	3.39
3.00	20.00	0.050	10.00	4.03	10.00	4.14	10.00	3.69
3.00	30.00	0.075	10.00	3.93	10.00	4.21	10.00	3.66
3.00	5.00	0.013	15.00	4.26	15.00	4.31	15.00	3.21
3.00	10.00	0.028	15.00	4.09	15.00	4.20	15.00	3.36
3.00	20.00	0.050	15.00	4.02	15.00	4.16	15.00	3.65
3.00	30.00	0.075	15.00	3.88	15.00	4.19	15.00	3.60
3.00	5.00	0.013	20.00	4.21	20.00	4.35	20.00	3.17
3.00	10.00	0.028	20.00	4.02	20.00	4.21	20.00	3.42
3.00	20.00	0.050	20.00	4.09	20.00	4.22	20.00	3.62
3.00	30.00	0.075	20.00	3.97	20.00	4.30	20.00	3.59
3.00	5.00	0.013	25.00	4.27	25.00	4.38	25.00	3.16
3.00	10.00	0.028	25.00	4.06	25.00	4.29	25.00	3.46
3.00	20.00	0.050	25.00	4.06	25.00	4.29	25.00	3.65
3.00	30.00	0.075	25.00	3.95	25.00	4.30	25.00	3.60

MC: methylcellulose; PVP: Polyvinyl pyrrolidone; LA: lactic acid; G: glycerol; PG: 1,2-propylene glycol

Table 2: Effect of the amounts of PVP K-90, lactic acid and hydrophilizing agents on viscosity of methylcellulose gels

1 MC (g)	2 PVP (g)	3 LA (g)	4 G (g)	η (mPa · s)	4′ PG (g)	η (mPa · s)	4″ PEG-200 (g)	η (mPa · s)
3.00	5.00	0.013		354				
3.00	10.00	0.028		506				
3.00	20.00	0.050		886				
3.00	30.00	0.075		1687				
3.00	5.00	0.013	5.00	286	5.00	303	5.00	329
3.00	10.00	0.028	5.00	405	5.00	371	5.00	447
3.00	20.00	0.050	5.00	708	5.00	675	5.00	691
3.00	30.00	0.075	5.00	1670	5.00	1130	5.00	1468
3.00	5.00	0.013	10.00	286	10.00	270	10.00	261
3.00	10.00	0.028	10.00	320	10.00	329	10.00	286
3.00	20.00	0.050	10.00	708	10.00	843	10.00	843
3.00	30.00	0.075	10.00	1215	10.00	1350	10.00	1333
3.00	5.00	0.013	15.00	219	15.00	261	15.00	236
3.00	10.00	0.028	15.00	320	15.00	337	15.00	219
3.00	20.00	0.050	15.00	691	15.00	793	15.00	759
3.00	30.00	0.075	15.00	1383	15.00	1181	15.00	1603
3.00	5.00	0.013	20.00	168	20.00	303	20.00	168
3.00	10.00	0.028	20.00	320	20.00	270	20.00	295
3.00	20.00	0.050	20.00	691	20.00	725	20.00	658
3.00	30.00	0.075	20.00	1485	20.00	1468	20.00	1687
3.00	5.00	0.013	25.00	135	25.00	219	25.00	118
3.00	10.00	0.028	25.00	270	25.00	354	25.00	253
3.00	20.00	0.050	25.00	691	25.00	759	25.00	742
3.00	30.00	0.075	25.00	1687	25.00	1552	25.00	1350

4. Experimental

4.1. Materials

Aqua purificata, as specified by FP V. Lactic acid, PZF Cefarm, Wrocław. Methylcellulose, Aldrich Chemical Company Ltd. Gillingham – Dorset SP8 4SL – England. 1,2-Propylene glycol, Polskie Odczynniki Chemiczne, Gliwice. Polyoxyethylene glycol 200, LOBA – Chemie, Wien – Fishamend. Glycerol AR grade, Polskie Odczynniki Chemiczne, Gliwice. Polyvinyl pyrrolidone K-90, Fluka AG Busch SG.

4.2. Methods

4.2.1. Measurements of pH and viscosity

pH and viscosity were measured as described earlier [12].

4.2.2. Determination of the lactic acid to PVP K-90 ratios

1.0 g PVP K-90 was put into a conical flask containing 9.0 g water. Next, the contents were titrated with 0.5 ml portions of 0.005% lactic acid solution. The procedure was repeated with 0.01%, 0.05% and 0.1% solutions of lactic acid. After introduction of each portion of acid the pH value of the solution was measured.

4.2.3. Gel preparation technique

Polyvinyl pyrrolidone K-90 was dissolved in a solution of lactic acid in water, prepared using half the prescribed amount of water. After cooling, hydrophilizing agent was added and the remaining amount of water was poured in. Methylcellulose was added to the mixture. The gels obtained comprised 3% of methylcellulose, 5–30% PVP K-90; H 0.013–0.075% lactic acid and 5–25% of particular hydrophilizing agents.
For specification of the gels see Table 1.

4.2.4. Measurement of adhesion

The biopharmaceutical model consists of a round – bottomed flask, used for measuring the gel flow rate in simulated *in vivo* conditions [12].

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