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STUDIES ON GYNECOLOGICAL HYDROPHILIC LACTIC ACID PREPARATIONS
PART 8: USE OF CHITOSAN AS LACTIC ACID CARRIER IN INTRAVAGINAL TABLETS

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Abstract: Hydrophilic intravaginal tablets based on methylcellulose and containing lactic acid component with chitosan undergo swelling under 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 the 1:1 ratio of lactic acid to chitosan, it is possible to obtain tablets disintegrating into a gelform at physiological pH 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 act to neutralize the excess of alkali present in severe vaginal infections.

Keywords: hydrophilic intravaginal tablets, lactic acid complexed with chitosan, physiological pH, vaginal infections, anti-inflammatory drugs.

Vaginitis, which is characterized by increased pH, does not promote the development of Döderlein rods which are administered by means of therapeutic preparations. Non-physiological pH favors the development of the pathological flora which is associated with long-lasting therapy and frequent recurrences of the inflammatory condition (1-3).

In our investigations (4-10) we have undertaken the task of restoring the physiological pH of the vaginal discharge. For this reason, lactic acid was complexed with an alkaline polymer, chitosan.
Lactic acid, which is released from the complex by means of hydrolysis, should restore the pathological pH to the norm.

Investigated preparations should remain in the vagina throughout daily activities of the patient thanks to their favorable rheological properties.

The aim of the work was to investigate hydrophilic vaginal tablets containing lactic acid complexed with chitosan and forming highly adhesive gel. Such a formula enables a gradual release of the active substance following application.

EXPERIMENTAL

Materials

Lactic acid, PZF Cefarm, Wrocław, methylcellulose, Aldrich, England, propylene glycol, POCh, Gliwice, polyoxyethylene glycol 200, LOBA Chemie, Wien, glycerol, POCh, Gliwice, chitosan – deacetylation degree 93.5% – Sea Fisheries Institute, Gdynia, D-sorbitol, POCh, Gliwice.

METHODS

Measurements of pH and viscosity

Accomplished according to (4).

Technology of production of hydrophilic intravaginal tablets containing lactic acid complexed with chitosan

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 of methylcellulose. The homogenous mixture of methylcellulose wetted with this solution was dried at 40^{o}C. The dry mass was standardized by sieving through 0.5 mm sieve. In the case of tablets without glycerol, this stage was omitted.

Chitosan combines with organic acids through primary amine groups. This property was used in the complexing procedure. The required amount of powdered chitosan was poured over a weighed amount of lactic acid. The mass was stirred to obtain homogenous suspension. The mixture was left for about 24 h until a clear thick liquid has formed, which could be combined with methylcellulose (5). The formed complex was combined with solvated

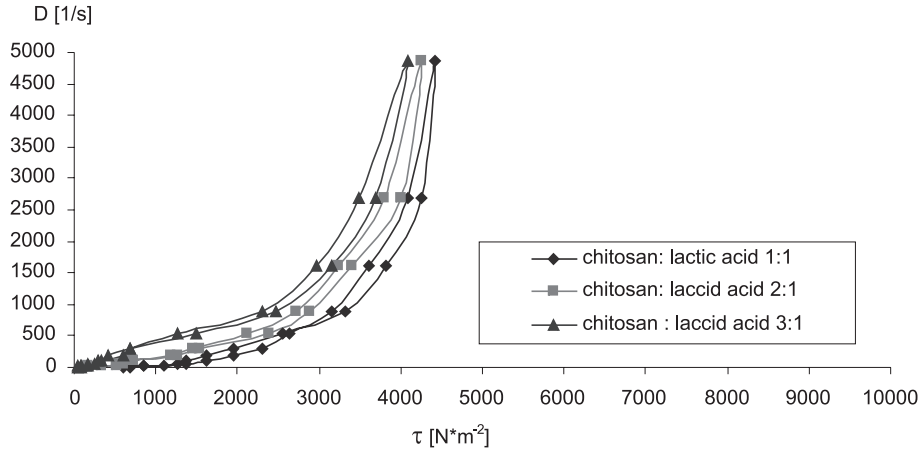

Figure 1. Curves illustrating the flow of gel from tablets (batch number III a, b, c), τ – tangential stress, D – shearing rate.

Table 1. 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]	CH [g]	LA:CH	pH	V [mPa·s]	HG [mm]
I a	89.46	5.0	0.0	2.24	3.30	1:1	4.44	174.0	22.0
I b	87.21	5.0	0.0	4.49	3.30	2:1	3.53	140.0	17.0
I c	84.97	5.0	0.0	6.73	3.30	3:1	3.29	50.7	16.0
II a	84.46	5.0	5.0	2.24	3.30	1:1	4.42	70.0	22.5
II b	82.21	5.0	5.0	4.49	3.30	2:1	3.52	38.5	20.0
II c	79.97	5.0	5.0	6.73	3.30	3:1	3.27	28.0	19.3
III a	79.46	5.0	10.0	2.24	3.30	1:1	4.40	69.1	22.0
III b	77.21	5.0	10.0	4.49	3.30	2:1	3.52	34.1	14.5
III c	74.97	5.0	10.0	6.73	3.30	3:1	3.20	21.0	18.2
IV a	74.46	5.0	15.0	2.24	3.30	1:1	4.38	35.0	22.0
IV b	72.21	5.0	15.0	4.49	3.30	2:1	3.54	28.9	11.8
IV c	69.97	5.0	15.0	6.73	3.30	3:1	3.20	19.2	13.0
V a	84.46	10.0	0.0	2.24	3.30	1:1	4.32	96.2	27.2
V b	82.21	10.0	0.0	4.49	3.30	2:1	3.57	35.8	25.0
V c	79.97	10.0	0.0	6.73	3.30	3:1	3.29	30.6	24.5
VI a	89.46	0.0	5.0	2.24	3.30	1:1	4.47	120.7	15.0
VI b	87.21	0.0	5.0	4.49	3.30	2:1	3.55	75.2	13.0
VI c	84.97	0.0	5.0	6.73	3.30	3:1	3.24	63.0	13.8
VII a	84.46	0.0	10.0	2.24	3.30	1:1	4.39	67.3	17.0
VII b	82.21	0.0	10.0	4.49	3.30	2:1	3.60	63.0	10.5
VII c	79.97	0.0	10.0	6.73	3.30	3:1	3.25	28.0	13.8
VIII a	79.46	0.0	15.0	2.24	3.30	1:1	4.39	43.7	15.0
VIII b	77.21	0.0	15.0	4.49	3.30	2:1	3.56	29.7	10.2
VIII c	74.97	0.0	15.0	6.73	3.30	3:1	3.21	23.6	11.5

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

and non-solvated methylcellulose. The obtained mixture was mixed to obtain a homogenous mass and dried at 40°C in order to evaporate water present in the lactic acid solution. The dry mass was powdered. In the case of sorbitol, owing to its strong hygroscopic potential, it was added to the methylcellulose mixture with adsorbed lactic acid – chitosan complex. The completed mass was standardized by mixing.

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 thick and weighing 330 mg were manufactured.

Investigation methods 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 Polish Pharmacopoeia VI.

The purpose of the tablets was to produce a gel after insertion into vagina, thus the main emphasis was placed 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 gynecology.

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 (see 9).

INVESTIGATIONS AND RESULTS

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

The investigations indicated different patterns of swelling within each of the series in relation to the content of hydrophilizing substance and the ratio of lactic acid to chitosan.

The increase of hydrophilizing substance content is accompanied by the increase of the degree of swelling expressed in millimeters of gel column formed in 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 revealed 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 chitosan 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 hydrophilizing agent reveal the most favorable swelling parameters in respect to increases in the volume of gel as well as swelling rate.

Data presented in Tab. 1 indicate that gels arising from tablets containing lactic acid complexed with chitosan in 1:1, 2:1 and 3:1 ratios and 5% glycerol content have pH values of 4.44 – 3.29.

On increasing the glycerol content to 10%, the pH values range from 4.32 – 3.29. The addition of 5, 10, 15% of sorbitol to tablets containing 5% of glycerol results in pH values ranging from 4.42 to 3.20.

The pH values of gels arising from tablets containing sorbitol alone in concentrations 5, 10, and 15% range from 4.47 to 3.21.

The analysis of several diagrams as well as the Table indicates that gels containing lactic acid complex with chitosan in 1:1, 2:1, 3:1 ratio as well as 5% glycerol reveal dynamic viscosities between 50.7 – 174.0 mPa·s at the maximum curdling rate. Similar curves have been obtained for the remaining gels. Increasing the glycerol content to 10% results in values ranging from 30.6 to 96.2 mPa·s. The 5, 10, 15% addition of sorbitol to tablets containing 5% of glycerol results in a decrease in the dynamic viscosity to 19.2 – 70.0 mPa·s.

The viscosity of gels arising from tablets containing only sorbitol in concentrations of 5, 10 and 15% ranges from 23.6 to 120.7 mPa·s, (Fig.1).

DISCUSSION AND CONCLUSION

Data presented in the Table indicate that 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 characterized by high flow-limit. High flow-limit should prevent them from being displaced on the vaginal mucosa, providing a long-term release of lactic acid into vaginal environment.

Tablets containing glycerol swell most readily. They become completely swollen within 10 min of measurement, forming a 27.2 mm gel column. The pH of the investigated gels containing lactic acid complexed with chitosan 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 neutralize an excess of alkali present in advanced inflammatory conditions within the vagina.

These properties indicate that the tablets are most suitable for gynecological purposes.

The above conclusions still require verification *in vivo*.

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