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Studies on gynaecological hydrophilic lactic acid preparations

Part 7: Use of chitosan as lactic acid carrier in intravaginal tablets (globuli vaginales)

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Intravaginal tablets based on hydrophilic methylcellulose and containing lactic acid complexed with chitosan undergo deformation under standard conditions.The high flow – limit of the gel originating from the tablets as well as its dynamic viscosity should ensure the durability of this dosage form on the vaginal mucosa. By selecting either ratios of lactic acid to chitosan of 1 : 1 or 2 : 1 it is possible to obtain tablets that disintegrate into a gel form 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 polymer to a 4 : 1 ratio results in gels with a lower pH while giving an acid reserve that can neutralize the excess of alkali present in severe vaginal infections.

1. Introduction

The administration of lactic acid bacilli in vaginitis, when the pH is increased above physiological values, does not promote development and restoration of the physiological pH (Mauhmoud et al. 1995; Szczurowicz et al. 1993; Nyirjesy et al. 1995). The treatment of the inflammatory condition if the physiological pH has not been restored results in the recurrence of the disease. Moreover, therapeutic agents used until now can only be applied with the patient in a lying position, which considerably limits their continuity of action.

In our previous investigations (Kubis and Małolepsza-Jarmołowska 1996; Małolepsza-Jarmołowska and Kubis 1999, 2000, 2001; Małolepsza-Jarmołowska et al. 2003a, 2003b) we have used preparations containing lactic acid complexed with chitosan, which should provide gradual release of the active substance and in consequence lead to increased acidity of the vaginal discharge. The rheological properties result in continuity of the action thanks to adhesion to the mucous membranes.

The aim of the present work was to investigate hydrophilic intravaginal tablets containing lactic acid complexed with chitosan and forming a highly adhesive gel. Such a formula permits gradual release of the lactic acid after administration.

2. Investigations and results

Thirty-three series of tablets containing lactic acid complexed with chitosan in molar proportions 1 : 1, 2 : 1 and 4 : 1 were prepared. The suppository excipient consisted of 16, 20 and 25% gelatin, 15, 20 and 25% glycerol, 15% PEG-200 and 15% propylene-1,2-glycol as well as 0, 2, 4, 6% and 8% methylcellulose.

The investigations indicated that the composition of the excipient does not have a significant effect on the temperature at which the tablets undergo deformation.

All the preparations investigated were stable to deformation at 25 °C for 20 min, indicating the possibility of storing them at room temperature. At 30 °C the tablets deformed on average within 7 min.

At 35 °C the time in which deformation of the investigated tablets occured was significantly shorter compared to the time at 30 °C and ranged between 1–2 min depending on the composition. At 37 °C all the tablets investigated underwent deformation within 2 min.

As shown by the data presented in the Table, gels formed from tablets containing a lactic acid and chitosan complex in addition to 15, 20 and 25% glycerol were found to have a pH range between 4.95–5.06 for a 1 : 1 ratio of lactic acid and chitosan and 3.43–3.56 for a 4 : 1 ratio. A comparison of the pH of the gels formed from tablets containing 15% of hydrophilizing substances showed that the pH obtained using lactic acid complexed with polymer in the proportions investigated was between 5.00 and 3.67 for propylene-1,2-glycol, between 4.98 and 3.65 for PEG-200 and between 4.96 and 3.46 for glycerol.

The data presented in the Table also show that the dynamic viscosity of gels formed from tablets containing 15, 20 and 25% of glycerol and lactic acid complexed with chitosan ranged from 287–793 mPa · s for a 1 : 1-ratio of lactic acid and chitosan and from 114–810 mPa · s for a 4 : 1-ratio.

The dynamic viscosity of gels formed from tablets containing 15% of hydrophilizing substances, in addition to lactic acid complexed with polymer in the proportions investigated, ranged from 405–844 mPa · s for propylene-1,2-glycol, from 591–405 mPa · s for PEG-200, and from 523–641 mPa · s for glycerol.

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

BN	Gel. (g)	MC (g)	HS (g)	LA (g)	CH (g)	A (g)	LA : CH	pH	V (mPa · s)	Dt (g)
A1	16.0	0.0	15.0GL	1.4	2.06	65.54	1 : 1	4.95	287	70.0
A2	16.0	0.0	15.0GL	2.8	2.06	64.14	2 : 1	3.95	456	70.0
A3	16.0	0.0	15.0GL	5.6	2.06	61.34	4 : 1	3.43	114	71.0
B1	16.0	2.0	15.0GL	1.4	2.06	63.54	1 : 1	4.97	422	80.0
B2	16.0	2.0	15.0GL	2.8	2.06	62.14	2 : 1	4.02	506	80.0
B3	16.0	2.0	15.0GL	5.6	2.06	59.34	4 : 1	3.47	270	80.0
C1	16.0	4.0	15.0GL	1.4	2.06	61.54	1 : 1	4.96	540	90.0
C2	16.0	4.0	15.0GL	2.8	2.06	60.14	2 : 1	4.01	641	90.0
C3	16.0	4.0	15.0GL	5.6	2.06	57.34	4 : 1	3.46	523	91.0
D1	16.0	6.0	15.0GL	1.4	2.06	59.54	1 : 1	4.97	472	98.0
D2	16.0	6.0	15.0GL	2.8	2.06	58.14	2 : 1	4.00	692	98.0
D3	16.0	6.0	15.0GL	5.6	2.06	55.34	4 : 1	3.48	658	99.0
E1	16.0	8.0	15.0GL	1.4	2.06	57.54	1 : 1	5.00	793	119.0
E2	16.0	8.0	15.0GL	2.8	2.06	56.14	2 : 1	4.03	877	120.0
E3	16.0	8.0	15.0GL	5.6	2.06	53.34	4 : 1	3.50	810	120.0
F1	16.0	4.0	20.0GL	1.4	2.06	56.54	1 : 1	5.05	540	120.0
F2	16.0	4.0	20.0GL	2.8	2.06	55.14	2 : 1	4.10	624	120.0
F3	16.0	4.0	20.0GL	5.6	2.06	52.34	4 : 1	3.54	321	120.0
G1	16.0	4.0	25.0GL	1.4	2.06	51.54	1 : 1	5.06	742	89.0
G2	16.0	4.0	25.0GL	2.8	2.06	50.14	2 : 1	4.10	591	89.0
G3	16.0	4.0	25.0GL	5.6	2.06	47.34	4 : 1	3.56	759	90.0
H1	20.0	4.0	15.0GL	1.4	2.06	57.54	1 : 1	5.00	472	89.0
H2	20.0	4.0	15.0GL	2.8	2.06	56.14	2 : 1	4.08	641	90.0
H3	20.0	4.0	15.0GL	5.6	2.06	53.34	4 : 1	3.62	591	90.0
I1	25.0	4.0	15.0GL	1.4	2.06	52.54	1 : 1	5.05	709	90.0
I2	25.0	4.0	15.0GL	2.8	2.06	51.14	2 : 1	4.23	675	90.0
I3	25.0	4.0	15.0GL	5.6	2.06	48.34	4 : 1	3.68	624	91.0
J1	16.0	4.0	15.0PE	1.4	2.06	61.54	1 : 1	4.98	591	120.0
J2	16.0	4.0	15.0PE	2.8	2.06	60.14	2 : 1	4.06	574	120.0
J3	16.0	4.0	15.0PE	5.6	2.06	57.34	4 : 1	3.65	405	120.0
K1	16.0	4.0	15.0GP	1.4	2.06	61.54	1 : 1	5.00	624	89.0
K2	16.0	4.0	15.0GP	2.8	2.06	60.14	2 : 1	4.12	405	90.0
K3	16.0	4.0	15.0GP	5.6	2.06	57.34	4 : 1	3.67	844	91.0

BN – batch number, gel. – gelatin, MC – methylcellulose, HS – hydrofilizing substances, GL – glycerol, PE – polyoxyethylene glycol 200, GP – propylene-1,2-glycol, LA – lactic acid, CH – chitosan, A – aqua purificata, V – dynamic viscosity, Dt – deformation time

3. Discussion

As indicated by the data presented in Table, under the experimental conditions of the biopharmaceutical model, all the series of tablets investigated underwent deformation at 37 °C within 2 min, forming gels with a specific viscosity.
The analysis of the rheological graphs (Fig.) as well as data from the Table indicates that such gels are characterized by a high flow-limit. A high flow-limit should prevent them from being displaced on the vaginal mucosa, and allow long-term release of lactic acid into the vagina.
Tablets with 15 and 25% glycerol underwent deformation most rapidly.

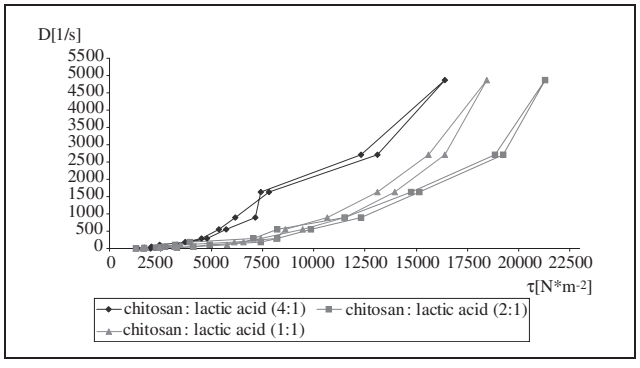

Fig. 1: Flow of suppository excipient curve (batch number A). τ – tangential stress D – shearing rate

The pH of the resulting gels containing lactic acid complexed with chitosan in ratios of 1 : 1 and 2 : 1 ranged from 3.8–4.4, which is within the limits of the physiological pH of the vagina.
Tablets containing a 4 : 1 ratio of lactic acid-polymer have enough reserve acid to neutralize the excess of alkali accompanying inflammatory conditions in the vagina.
These properties are highly useful for gynaecological purposes.

4. Experimental

4.1. Materials

Aqua purificata, acc. To FP V. Lactic acid, PZF Cefarm, Wrocław. Methylcellulose, Aldrich Chemical Company Ltd. Gillingham – Dorset SP8 4SL – England. Propylene-1,2-glycol, Polskie Odczynniki Chemiczne, Gliwice. Polyoxyethylene glycol 200, LOBA-Chemie, Wien-Fishamend. Glycerol pro analysis, Polskie Odczynniki Chemiczne, Gliwice. Chitosan, MIR, Gdynia. Gelatin, LOBA-Chemie, Wien-Fishamend.

4.2. Methods

4.2.1. Measurements of pH and viscosity

(see Małolepsza-Jarmołowska et al. 2003a)

4.2.2. Production of hydrophilic intravaginal tablets

The production of tablets containing lactic acid complexed with chitosan consisted of the following stages:
1. Preparing the lactic acid – chitosan complex.
Chitosan combines with organic acids by means of first-order amine groups. This property was used in the preparation of the complex. The required amount of powdered chitosan was poured into 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 combined with methylcellulose (Małolepsza-Jarmołowska and Kubis 1999).
2. Preparing the excipient:
a) Preparation of gel from methylcellulose
A gel was obtained from methylcellulose by adding a known amount of this compound to a solution of hydrophilizing substance in water. In order to enhance the gelation process, 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 to stand with water until swelling was complete and then dissolved by heating. Lactic acid complexed with chitosan was added to the liquid gelatin gel and heated until a homogenous gel was obtained. Distilled water was added to obtain the initial mass.
c) Preparation of the excipient and pouring into the mould
The gels prepared from methylcellulose and gelatin were combined into a homogenous excipient and supplemented with distilled water. The excipient was poured into a mould that had been previously covered with a thin layer of polyoxyethylene glycol 200.

4.2.3. Investigation of tablets obtained

Measurement of temperature at which the tablets are deformed.
This measurement was carried out according to FP.V using Krówczyński's apparatus (Małolepsza-Jarmołowska et al. 2003a).

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