THE INFLUENCE OF GLYCEROL ON THE RELEASE OF METRONIDAZOLE FROM GELS CONTAINING LACTIC ACID COMPLEXED WITH CHITOSAN

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1. Introduction

The effectiveness of anti-inflammatory drugs and drugs reconstructing physiological environment of vagina greatly depends on the time of contact between therapeutic substance and the mucous membrane of the organ. Many drugs conform to this requirement only when a patient is in a horizontal position. Thus ensuring a continuous action of a drug also during daily activity time of a patient is a vital question in gynaecological treatment.

The investigated preparations on methylcellulose base revealed good adhesion to the vaginal mucosa and were present on it throughout the daily activities of the patient. This property enabled the continuity of 24-hour action of the drug [1 – 7].

The addition of metronidazole to the investigated gels will enable to increase the range of application of this drug form.

The aim of the study was to measure the pharmaceutical availability of metronidazole from hydrophil gels on the base of methylcellulose containing complexes of lactic acid with chitosan.

2. Experimental methods

2.1. Materials

Lactic acid – P.Z.F. Cefarm (Wrocław, Poland).
Chitosan - deacetylation degree of 93.5% – Sea Fisheries Institute (Gdynia, Poland).
Glycerol pro analysis – POCh - (Gliwice, Poland).
Methylcellulose, Aldrich Chemical Company Ltd. Gillingham – Dorest SP 84 SL – (England).
Metronidazole, Sigma – Aldrich Chemie GmbH, Germany.
Aqua purificata, acc. to FP VI.

2.2. Apparatus

Apparatus VanKel VK 7025 with using Hanson cells apparatus for dissolution and release medical substances.

2.3. Technology of production of hydrophil preparation:

1. Weighed portion of methylcellulose was poured on the surface of water or aqueous solution of hydrophilizing substance and left to swell, next it was stirred, producing gel with 4% content of the polymer.
2. Chitosan was mixed with aqueous solution of lactic acid and left in a dark place to form complexes with acid to polymer mole ratio 1:1; 2:1; 3:1; 4:1.
3. Obtained methylcellulose gel was mixed with chitosan complexed with lactic acid calculated for 0.83 g of chitosan. Individual preparations contained 0.5; 1.0; 1.5; 2.0% of lactic acid respectively.
4. The evaporated amount of water was each time supplemented to the initial level.
5. The weighed portion of metronidazole constituting 25% of the product composition was added to gels immediately before investigations of release and mixed thoroughly
6. Ready made gel was stored in refrigerator.

3. Investigations and results

The measurements of metronidazole release from the investigated gels were carried out by means of a continuous flow acceptor compartment method . The process of release was carried out for 180 minutes, what enabled to determine the release rate constant and derivative parameters.

As shown in Table 1, during 180 minutes of the measurements, 4.50 to 5.77% of metronidazole were released from the reference preparations in respect to the increasing lactic acid

Table 1. *Kinetic parameters of reference gels.*

Lactic acid to chitosan ratio	1:1	2:1	3:1	4:1
Percentage of released metronidazole, %	4.55	5.49	5.77	4.50
Release rate constant k, h^{-1}	0.0150	0.0180	0.0210	0.0150
Half-release time $t_{0,5}$, h	46.21	38.51	33.01	46.21

Table 2. *Kinetic parameters of gels with 5%* i 25%** glycerol.*

Lactic acid to chitosan ratio	1:1	2:1	3:1	4:1
Percentage of released metronidazole, %*	3.31	3.55	5.11	2.84
Percentage of released metronidazole, %**	2.92	3.45	4.36	3.60
Release rate constant k, h^{-1} *	0.01300	0.01200	0.01110	0.00730
Release rate constant k, h^{-1} **	0.00800	0.01100	0.01340	0.00880
Half-release time $t_{0,5}$, h *	53.32	57.76	62.43	94.93
Half-release time $t_{0,5}$, h **	86.64	63.01	51.72	78.75

to chitosan mole ratio from 1:1 to 4:1. In the presence of 5% glycerol in the investigated series, from 2.84 to 5.11% were released, while in the presence of 25% of the hydrophilizing substance, from 2.92 to 4.36% of metronidazole was released. On the basis of metronidazole release rate constants presented in Table 1 and 2 half-release times of this substance were calculated for the investigated three groups of preparations. The half-release times of reference preparations with the use of this method remain in the range from 33 to 46 hrs. In case of preparations containing 5% or 25% of glycerol, they are from 53 to 95 hrs and from 52 to 87 hrs respectively.

4. Discussion and summary

On the basis of earlier measurements, the investigated reference gels reveals a good adhesion to the vaginal mucosa and remain on it for at least 6 hrs.

Prolonged half-release times of metronidazole both from reference preparations as well as from preparations modified with glycerol are differentiated and range from 33 to 95 hrs. This enables selection of a gel with optimum release time for its verification in in vivo studies.

Calculated half-release times allow a conclusion that the investigated gels, which remain for 6 hours on the vaginal mucosa, should provide constant transport of metronidazole to the inflamed mucous membrane Figures 1 and 2. These gels will be investigated *in vivo*.

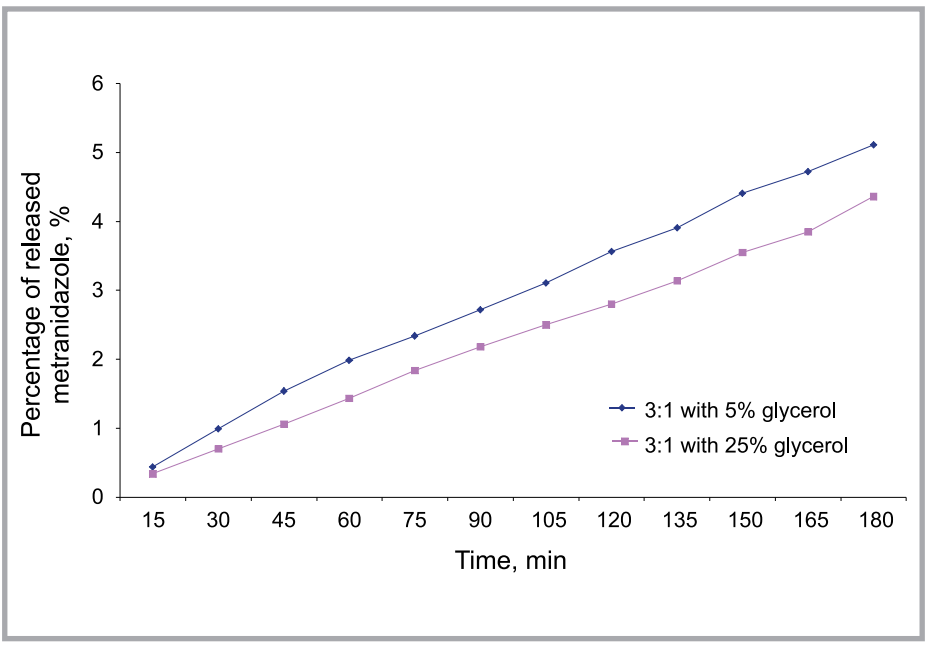

Figure 1. *Release of metronidazole from gels containing lactic acid complexed with chitosan.*

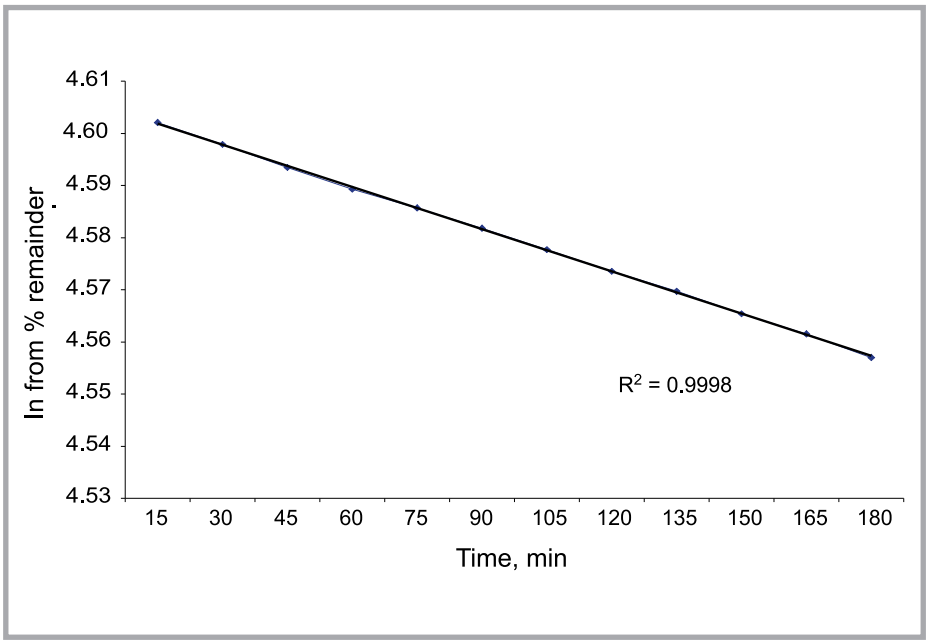

Figure 2. *Kinetic interpretation of release of metronidazole.*

5. Conclusions

1. Prolonged half-release times of metronidazole both from reference preparations as well as from preparations modified with glycerol are differentiated and range from 33 to 95 hrs.

2. Calculated half-release times allow a conclusion that the investigated gels, which remain for 6 hours on the vaginal mucosa, should provide constant transport of metronidazole to the inflamed mucous membrane

6. References

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