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Influence of pH change on drug release from rectal suppositories

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Drugs absorbed from the anal region enter blood circulation bypassing the liver. Thus, their bioavailability can be increased by avoiding the "first-pass-effect" [1, 2]. Therefore the need for a formulation of diuretic rectral suppositories has been expressed [3].

The aim of our research was, on the one hand, to formulate rectal suppositories containing ethacrynic acid in order to improve diuretic therapy. On the other hand, we wanted to study the effect of pH changes of the acceptor phase as the proper pH is essential for simulating physiological conditions. Examinations were performed both in destilled water and in phosphate buffer (pH 7.5) with five suppository bases: Massa Estarinum BC, Suppocire AML, Witepsol S 58, Suppocire AP as lipophilic bases and Macrogolum 1540 as a hydrophilic base. Drug release was determined. Release values obtained with the hydrophilic Macrogolum 1540 base in aqueous medium were manifold higher than those determined with lipophilic bases or powder. This is due to the fact that pourly water-soluble drugs are better released from hydrophilic suppositories. It, however, the results obtained in aqueous medium and buffer medium are compared, it can be seen that drug release from the lipophilic bases was increased about tenfold in the acceptor phase of pH = 7.5. The lipophilic base Suppocire AML proved to be the best in both acceptor phases. On the other hand, the change of the acceptor phase did not have a significant infcluence on drug release from the hydrophilic base Macrogolum 1540 (Fig.).

It is obvious that the kinetics of release from lipophilic and hydrophilic bases differ, as drug diffusion from the hydrophilic base showed a considerable increase only after the first hour. This finding is related to the longer disintegration time of hydrophilic bases, which is in fact not disintegration because hydrophilic bases have to be dissolved in the rectal fluid.

It can be concluded that Suppocire AML was the best lipophilic base both in aqueous and buffer phases, and the hydrophilic Macrogolum 1540 was also found to be suitable for the formulation of ethacrynic acid suppositories.

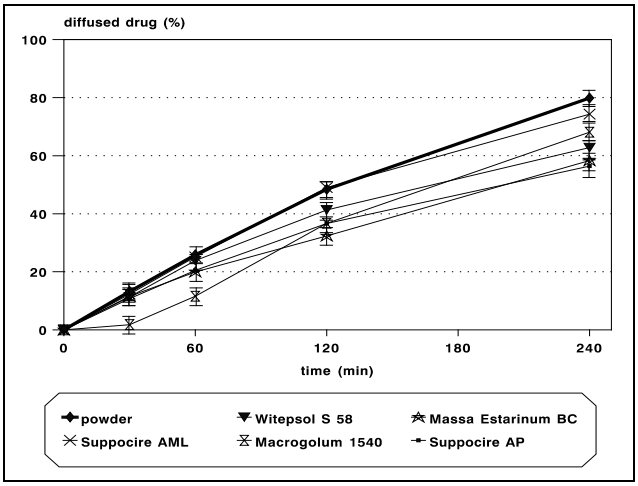

Fig.: Ethacrynic acid release from suppositories (acceptor phase: pH = 7.5 phosphate buffer)

Experimental

1. Materials

Ethacrynic acid was from EGIS (Hungary). Suppocire AML, AP were from Gattefossé (France); Witepsol S58, Massa Estarinum BC were from Condea Chemie GmbH (previously Hüls AG.) (Germany); Macrogolum 1540 is official in the Hungarian Pharmacopoeia Ed. VII.

2. Formulation method

Suppositories were formulated by moulding. Their drug content was 2.5 w/w%, which corresponded to the therapeutic dose: a 2 g adult suppository contains about 50 mg ethacrynic acid. The poorly water-soluble ethacrynic acid was incorporated in various suppository excipients.

3. In vitro release study

Experiments were performed using the method of dynamic membrane diffusion which is a useful method for following the rate of drug release and membrane diffusion from the powder without excipient and from the different suppository compositions as well. The acceptor phases were distilled water and phosphate buffer at a pH 7.5. The suppositories were individually packed in a kidney dialysing membrane (Visking®) and placed into distilled water or buffer of body temperature (37 ± 0.5 °C). The samples were exposed to slight shaking and the acceptor phase was replaced after 30, 60, 120, 240 min. The quantity of ethacrynic acid in these samples was measured with a spectrophotometer at $\lambda = 278$ nm. The mean values were calculated from 5 parallel measurements each time.

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