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Effect of acceptor phosphate buffer pH value on indomethacin release

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This contribution investigated *in vitro* release of the antirheumatic drug indomethacin in relation to phosphate buffer pH in the acceptor part of the permeation apparatus. Drug release was studied from a hydrogel containing 3% of hydroxyethyl cellulose and from a cream. UV-spectroscopic evaluations were done after the preparation of the study drugs. Indomethacin release depends on the pH of the acceptor phosphate buffer, the higher pH value the better release.

Indomethacin, a poorly water-soluble non-steroidal anti-inflammatory drug (Nokhodchi 2005), inhibits the production of inflammatory agents (prostaglandins) by inhibiting cyclooxygenase (Brooks 1998). To increase the solubility of poorly water-soluble drugs, excipients such as ethanol, glycerol, and propylene glycol are often used (Kawakami et al. 2006). In this study ethanol and propylene glycol were used.
Curry and Brown in their study examined indomethacin stability. They found that the drug was not stable in alkaline solutions; solutions at pH 7.4 showed no changes up to 24 h, but decomposition of the drug was rapid in alkaline solutions (Curry and Brown 1982). Also the release profile of indomethacin from liquisolid compacts showed that the amount of drug release and the solubility were higher at higher pH values (Nokhodchi 2005).
Based on these results, it could be concluded that the stability and solubility of indomethacin depend on pH value. It might be assumed that release of indomethacin also depends on pH value. As Fig. 1 and 2 show, drug release

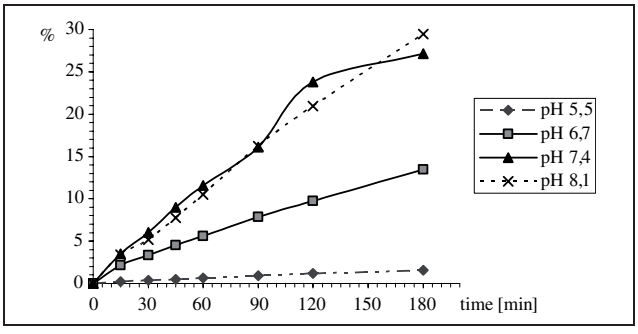

Fig. 1: Time dependence of indomethacin release from hydrogel in relation to pH of buffered aqueous medium (pH 5.5, 6.7, 7.4, 8.1)

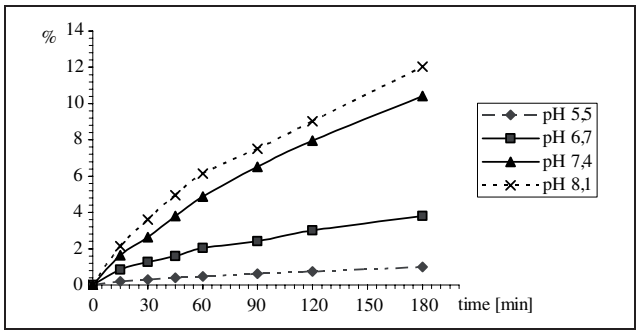

Fig. 2: Time dependence of indomethacin release from cream in relation to pH of buffered aqueous medium (pH 5.5, 6.7, 7.4, 8.1)

from the hydrogel and cream increased significantly with increasing pH. Indomethacin was released better with an acceptor phosphate buffer at pH 7.4 and 8.1, which relates to its distribution factor (pKa = 4.5), while the phosphate buffer become yellowish after 90 min of release. The range of pH values from 5.5 to 8.1 was chosen because of the pH of skin and body fluids.

Experimental

1. Material

Indomethacin-1-(4-chlorbenzoyl)-5-methoxy-2-methyl-1-*H*-indole-3-acetic acid, hydroxyethyl cellulose, propylene glycol, ethanol, glycerol, Cremophor A6, Cremophor A25, cetylstearyl alcohol, liquid paraffin, isopropyl palmitate, Sepicide HB, Sepicide CI, NaOH, KH_2PO_4, cellophane.

2. Instruments

Spectrophotometer – Philips Pye Unicam Ltd., Cambridge (United Kingdom); permeation apparatus – R&D Workshop of the Department of Galenic Pharmacy, Faculty of Pharmacy, Comenius University in Bratislava.

3. Preparation of the hydrogel

Hydroxyethyl cellulose is readily soluable in cold water. Gels were prepared by mixing hydroxyethyl cellulose into cold water, and after 15 min of bulking, the dispersion was heated to 80 °C. Propylene glycol (10%), ethanol (10%) and indomethacin (1%) were added to the cooled gel and the mixture was homogenized. The sample was finally made-up with water to the required volume and was left to stand for 24 h.

4. Preparation of the cream

Cremophor A6 (2.5%), Cremophor A25 (2.5%), cetylstearyl alcohol (5%), isopropyl palmitate (10%) and liquid paraffin (10%) were melted together, then water with Sepicide HB (0.3%) and Sepicide CI (0.2%) was warmed to 5 °C above then oil phase. The aqueous phase was slowly mixed into the oil phase and at the end glycerol (5%) with indomethacin (1%) was mixed into the cream base.

5. Evaluation of indomethacin release

A series of six permeation chambers was used, 3.0 g of the study formulation was placed in the donor chamber, and 20 ml of phosphate buffer (pH 5.5, 6.7, 7.4 or 8.1) was placed in the acceptor part. The acceptor phase was mixed with a magnetic stirrer. Indomethacin was left to permeate at 37 °C through a hydrophilic membrane into the phosphate buffer. The amounts of drug released were determined spectroscopically at 318 nm after 15, 30, 45, 60, 90, 120 and 180 min. The drug release was evaluated after the preparation of the study drugs.

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