AN INVESTIGATION OF SOME METHODS OF CONTROLLING THE RATE OF DRUG RELEASE FROM A BIOADHESIVE MATRIX

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In a previous study it was found that prolonged mucosa-adhesion of Carbopol 934P containing granules could be achieved by the incorporation of hydrophobic or insoluble components into the formulation (Smart & Kellaway 1989). Mucosa-adhesive macromolecules become adhesive on hydration, but may overhydrate to form a slippery mucilage. Restricted hydration of a drug/mucosa-adhesive matrix may prolong both adhesion and drug release. In this study, the release of a water soluble drug from discs of Carbopol 934P (Cb934P) and Carbopol 1342 (Cb1342), a hydrophobically modified Carbopol, was evaluated, and strategies for extending the release from Cb934P investigated.

In an initial study granules were prepared containing Cb934P and an agent to reduce swelling. These were placed into contact with a 0.9% NaCl solution and those that demonstrated stability, limited hydration, and adhesive properties for prolonged periods were selected. Hydrophobic materials e.g. stearic acid (SA), insoluble macromolecules e.g. ethylcellulose (EC), sparingly soluble macromolecules e.g. hydroxypropylmethylcellulose (HPMC), and divalent cations e.g. $CaCl_2$ successfully achieved this. 13mm diameter, 500mg compacts were prepared using a 5 tonne force for 5s. Each compact contained either 150mg saccharin sodium or, in the case of the $CaCl_2$ containing formulations, 20mg tartrazine as the model drug. 3 compacts of each formulation were tested in the dissolution apparatus II of the BP 1988 using a McIlvaine's buffer pH 6.8 as the dissolution media, and paddles rotated at 75rpm. The % drug release was calculated from the absorbance of the dissolution media. For each formulation graphs of the mean % release versus time were plotted, and from these The times for 50%($T_{50\%}$) and 90%($T_{90\%}$) release found (Table 1). Using the method described by Law et al(1985), n values were calculated from the gradient of a graph of log % drug release against log time. When n = 1, zero order release kinetics are indicated and n = 0.5 corresponds to diffusion controlled, Higuchi type release kinetics.

Table 1.

Formulation - per compact	n value	$T_{50\%}$ (min)	$T_{90\%}$ (min)
350mg Cb934P	0.63	144	368
175mg Cb934P, 175mg SA	0.58	101	278
175mg Cb934P, 175mg HPMC	0.57	287	799
175mg Cb934P, 175mg EC	0.81	638	1316
390mg Cb934P, 90mg $CaCl_2$	0.69	158	372
350mg Cb1342	0.57	188	529

The Cb934P formulation demonstrated sustained release and the inclusion of an insoluble or sparingly soluble macromolecule was a successful method of extending this. The EC containing formulation appeared to be the most successful (having a T_{90} time of almost a day) and was the nearest to ideal zero order kinetics. The HPMC containing formulation and Cb1342 formulation both showed prolonged, near Higuchi like release. Other strategies, the inclusion of a hydrophobic material or a divalent cation, although observed to reduce the rate of hydration and swelling, had a limited effect on drug release. It may be concluded that prolonged drug delivery from a mucosa-adhesive matrix is achievable, and this may provide the way forward in the development of new bioadhesive controlled drug delivery systems.

Law, T.K., et al(1985) J. Pharm. Pharmacol. 37: 6P
Smart, J.D., Kellaway, I.W.(1989) ibid. 41: 134P