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SOME FORMULATION FACTORS INFLUENCING THE RATE OF DRUG RELEASE FROM BIOADHESIVE MATRICES

J.D. Smart.

The School of Pharmacy and Biomedical Sciences, Portsmouth Polytechnic, Portsmouth PO1 2DZ.

ABSTRACT

The development of monolithic matrices with controlled release and mucosa-adhesive properties was investigated. After an initial screening procedure for formulations that showed stability and minimal swelling, the rate of release of a model water soluble drug from various polyacrylic acid containing matrices was evaluated. All the formulations gave a prolonged drug release relative to a lactose containing control formulation. A formulation containing Carbopol 934P and $CaCl_2$ was found to give the slowest rate of drug release ($t_{50\%}$ of 7.77h), with release kinetics nearest to the ideal zero order. When tested in a modified tensiometer it was found that the inclusion of a relatively high loading of a model drug did not adversely affect the adhesive properties of these formulations.

INTRODUCTION

The development of adhesive dosage forms for controlled drug delivery to or via mucous membranes is of interest with regard to local drug therapy, and the

systemic administration of peptides and other drugs poorly absorbed from the gastrointestinal tract (GIT). Target sites for mucosa-adhesive drug delivery include the eye[1], GIT[2,3], cervix[4], vagina[5], oral cavity[6] and the nasal cavity[7].

Mucosa-adhesive formulations that have been developed include ointments, tablets, microparticles, solutions and bandages[8].

Mucosa-adhesive materials have been identified as being hydrophillic macromolecules containing numerous hydrogen bond forming groups, particularly carboxyl groups [9,10]. They become adhesive on hydration, and have been referred to as 'wet adhesives'. Two limitations of mucosa-adhesive materials are:-

1) They may over-hydrate to form a slippery mucilage[10].
2) The structural integrity of multilayered formulations may be disrupted by the swelling and hydration of the mucosa-adhesive component.

For the latter reason monolithic matrix formulations are of particular interest in mucosa-adhesive drug delivery. Many mucosa-adhesives (particularly the polyacrylic acids) gel in an aqueous environment. Surface gelling of a dosage form may produce a barrier that can reduce the rate of drug release. Therefore it may be possible to produce matrix formulations that are both adhesive and inherently sustained release.

In a previous in-vivo study[11] it was found that when granules containing Carbopol 934P were placed onto oral mucosa they rapidly became swollen and eroded away. Prolonged mucosa-adhesion of these granules could be achieved by the incorporation of a hydrophobic component into the formulation. Thus rapid but restricted hydration of a drug/mucosa-adhesive matrix may prolong both adhesion and drug release. Some potential strategies for controlling hydration include the introduction of hydrophobic, insoluble or sparingly soluble

components into the molecule or formulation, or increasing the degree of molecular cross linking.

MATERIALS

Carbopol (Carb) 934P, EX55 and 1342 were obtained as a gift from BF Goodrich, Middlesex, UK. Sodium carboxymethylcellulose (SCMC) high viscosity, calcium chloride, sodium chloride, sodium phosphate, stearic acid (SA) and citric acid from BDH Chemicals, Poole, UK; hydoxypropylmethylcellulose (HPMC) (Methocel K100M) from Colorcon Ltd, Orpington, UK; saccharin sodium, ethylcellulose (100cp) (EC) and tartrazine from Aldrich Chemical Co., Gillingham, UK.

METHOD

Initial investigations

In an initial 'screening' study 5.0g batches of granules containing a mucosa-adhesive material and, where appropriate, an agent to reduce swelling were prepared. 500mg of the test powder was compressed in a Specac infra-red press using a force of 5 tonnes for 5s, then broken up into granules over a 1.7mm sieve. 1 - 1.7mm diameter granules were placed in contact with a few drops of 0.9% sodium chloride solution and examined over 120min for stability and degree of swelling (increase in diameter). The most successful formulations, i.e. those that remained intact and did not show excessive swelling, were then selected for further studies.

Dissolution studies

Test discs were prepared by mixing 1.5g saccharin sodium (as the model water soluble drug) and 3.5g matrix material in a pestle and mortar, then compressing 0.5g samples into 13mm diameter discs in a Specac press using a

force of 5 tonnes for 5s. Saccharin sodium was found to form an insoluble precipitate with calcium ions, so it was replaced by 20mg tartrazine in formulations containing $CaCl_2$.

The rate of release of the model drug into a citrate phosphate buffer pH 6.8 was determined for 6 discs in a British Pharmacopoeia standard dissolution apparatus (model 6ST, Caleva Instruments Ltd, Ascot, U.K.), using paddles rotated at 75rpm. Samples were removed continuously and passed through a u/v spectrophotometer (Ultrospec II, Pharmacia LKB Biochrom Ltd, Cambridge, U.K.), and the absorbance found every 10min at 258nm for sodium saccharin and 425nm for tartrazine. Data was collected and analyzed using a PC computer program supplied by Copley Instruments Ltd (Nottingham, U.K.). For each formulation graphs of the mean % release versus time was plotted, and the times for 50% ($t_{50\%}$) and 75% ($t_{75\%}$) drug release calculated. Using the method described by Law et al.[12], n values were calculated from the gradient of a graph of log % drug release against log time. When n = 1 zero order kinetics are indicated and n = 0.5 corresponds to diffusion controlled Higuchi like release kinetics.

Adhesion studies.

Discs were prepared using the same powder mix as the dissolution study, but 50mg, 6.2mm diameter discs were produced using a 1 tonne force for 5s.

Adhesion studies were completed using the apparatus and procedure described in a previous study[13]. The test disc was attached to a 1.5g weight suspended from a top-pan balance. The disc and weight were lowered onto the surface of a model mucosa (a section of rat small intestine) mounted on a platform in an isotonic buffer (pH 6.8) at 37^0c. After 2min the platform was lowered at a rate of 1mm/min until the disc pulled clear of the mucosa, and the breaking force of the adhesive bond recorded. The results were calculated in terms of a standard $1cm^2$ adhesive contact area.

TABLE 1.

An Investigation of the Stability of Some Mucosa-adhesive Granules (n = 3)

Formulation	Observed Stability	% Swelling (S.D.)	Time (min) to Max. Swelling
Carb934P	Yes	386 (58)	90
Carb934P 1:1 EC	No	102 (30)	120
Carb934P 1:1 HPMC	Yes	156 (51)	90
Carb934P 7:3 $CaCl_2$	Yes	80 (22)	90
Carb934P 4:1 $CaCl_2$	Yes	71 (26)	30
Carb934P 1:1 SA	Yes	154 (49)	20
SCMC	No	94 (22)	10
Carb1342	Yes	71 (26)	30
CarbEX55	Yes	251 (91)	120

RESULTS AND DISCUSSION

In the initial screening study Carb934P granules were seen to rapidly swell and form a clear gel. All strategies adopted to reduce the degree of swelling were seen to be relatively successful (Table 1), although the EC containing granules were unstable. CarbEX55 (polycarbophil) is more densely crosslinked than Carb934P and Carb1342 is a hydrophobically modified Carbopol i.e. it is a block copolymer containing hydrophillic polyacrylic acid and hydrophobic methacrylate

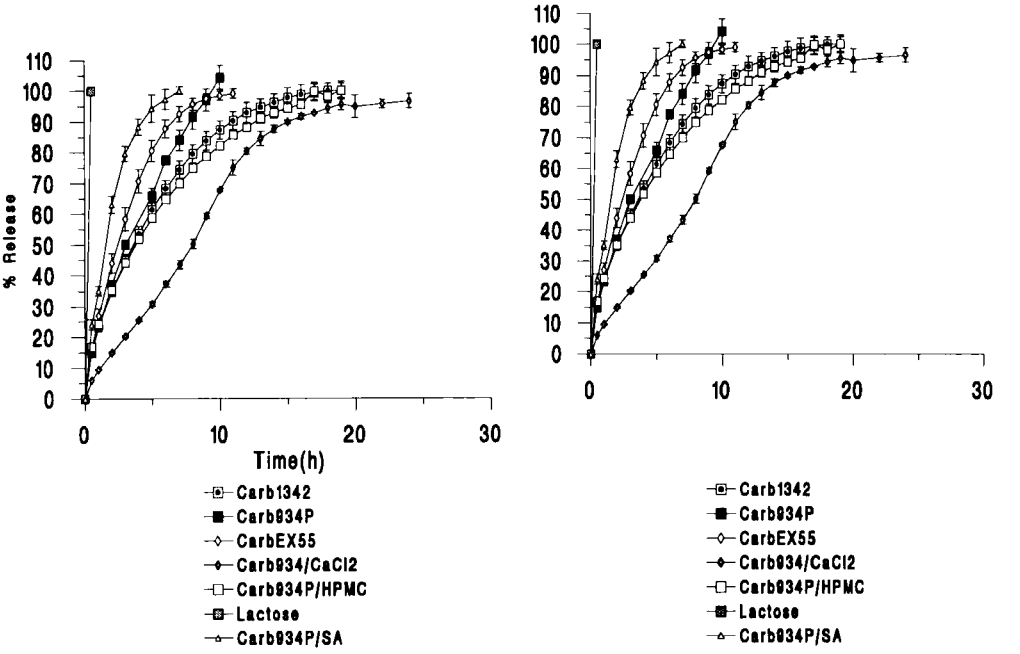

FIGURE 1.
Drug Release from Bioadhesive Matrices

components. Calcium ions were added to Carb934P to act as a simple crosslinking agent i.e. the divalent cations may interact with the carboxyl groups and form bridges between polymer chains. HPMC was included as a sparingly soluble component and SA as a hydrophobic component of the formulation. Granules containing SCMC as a mucosa-adhesive material disintegrated on contact with the saline solution, and all strategies to stabilise the granule were unsuccessful.

All the formulations selected from the initial study demonstrated sustained release relative to the control lactose formulation (Fig 1, Table 2). The inclusion of HPMC and $CaCl_2$ in the formulation was successful in extending drug release from a Carb934P matrix. The $CaCl_2$ containing formulation gave release kinetics

TABLE 2.

Release of a Model Drug from Polyacrylic Acid Matrices

Matrix Formulation	n	$T_{50\%}$ (h) (S.D.)	$T_{75\%}$ (h) (S.D.)	n value
Carb934P 0.35g	5	3.12 (0.15)	5.68 (0.41)	0.625
Carb1342 0.35g	6	3.57 (0.25)	7.15 (0.41)	0.613
CarbEX55 0.35g	6	2.40 0.24)	4.42 (0.38)	0.562
Carb934P 0.175g/ HPMC 0.175g	5	3.73 (0.12)	8.06 (0.17)	0.597
Carb934P 390g/ $CaCl_2$ 0.90g	5	7.77 (0.24)	10.90 (0.16)	0.830
Carb934P 0.175g/ SA 0.175g	5	1.68 (0.24)	2.95 (0.47)	0.581
Lactose 0.35g (Control)	6	<10	<10	-

nearest to the ideal zero order. However the comparatively low loading of the model drug may explain in part this result. The inclusion of a hydrophobic material (SA), although observed to reduce the extent of swelling, increased the rate of drug release. This may have resulted from inhibition of the initial surface gelling required to reduce the rate of drug release. CarbEX55 and Carb1342 formulations both showed prolonged near Higuchi like release.

All the formulations were found to be strongly adhesive and the inclusion of a relatively high drug loading in the matrix did not inhibit adhesion (Table 3).

TABLE 3.

The Adhesive Force Between Discs of Mucosa-adhesive and a Model Mucous Membrane (n = 5)

Formulation	Mean force (Ncm^{-2})	S.D.
Carb 934P 35mg, Saccharin Na 15mg	3.09	0.71
Carb EX55 35mg, Saccharin Na 15mg	4.17	1.09
Carb 1342 35mg, Saccharin Na 15mg	3.86	0.54
Carb 934P 17.5mg, HPMC 17.5mg Saccharin Na 15mg	3.01	0.83
Carb 934P 39mg, $CaCl_2$ 9mg, tartrazine 2mg	3.36	1.00

The forces obtained with the Carb934 and CarbEX55 formulations are similar to those obtained in previous investigations that used discs containing only the mucosa-adhesive[13].

There were no significant differences ($P > 0.05$, one way analysis of variance) between different formulations, although in other studies it has been reported that the presence of calcium ions can affect the adhesive force[14].

All the formulations developed in this study were both bioadhesive and gave a sustained release of the model drug. The formulation containing $CaCl_2$ with Carb934P was particularly successful and may warrant further investigation. It may be concluded that prolonged drug delivery of water soluble drugs, even in

comparatively high loadings, from a mucosa-adhesive matrix is achievable, and this may provide the way forward in the development of new bioadhesive controlled drug delivery systems.

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