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Factors affecting in vitro gastric mucoadhesion IV. Influence of tablet excipients, surfactants and salts on the observed mucoadhesion of polymers

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Abstract

The influence of a range of commonly used tabletting excipients, and other materials, on the observed mucoadhesion of Carbopol® 934P and in some cases, xanthan gum, has been tested. It is found that the hydrophobic lubricant magnesium stearate has the ability, at 5% concentration, to hinder the formation of a strong mucoadhesive bond between both of the mucoadhesive polymers and the pig gastric mucosae. However, other commonly used flow aids and lubricant did not share this property. A number of cyclodextrins are demonstrated, at 5% concentration, to have no significant influence on mucoadhesion. Tablet diluents, however, do appear to have a significant influence on the observed mucoadhesion in this system. The effect of a range of surfactants, non-ionic, cationic and anionic, on mucoadhesion is quantified, as is the influence of some salts and a chelating agent. It is concluded that the addition of additives to gastric mucoadhesive formulations can crucially influence the ability of the dosage form to bind to the porcine stomach in this test system.

Keywords: Excipients; Formulation; Gastric tissue; Hydrogen bonding; Mucoadhesion; Polyacrylic acid; Texture analyzer

1. Introduction

It has recently been demonstrated that method dependent parameters can influence the observed mucoadhesion in a particular test system [1]. Further, the physical properties of the polymers used can be demonstrated to have a significant influence on the observed mucoadhesion of systems manufactured from them [2].

To date, only some limited studies have been carried out on the optimization of mucoadhesive formulations, however, no systematic studies in this area have been published [3–5]. More recently it has been shown, for the first time, that the addition of small amounts of certain polymers, some of which are used in tablet formulation, to a mucoadhesive formulation can lead to a substantial decrease in observed mucoadhesion in an in vitro test system, which suggests that formulation of these systems could be crucial in developing successful dosage forms [6].

Although some studies have been carried out on the formulation of mucoadhesive systems there have been no published rationale for the arrival at the formulation used, suggesting that much work remains to be done in this area.

The aim of this study is to investigate the effects, if any, of common tablet excipients and other materials on the observed in vitro mucoadhesion of two representative polymers and to make inferences on the possible mechanisms of actions of the mucoadhesives, and those materials which interact with them.

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2. Methods and materials

2.1. Materials

Carbopol® 934P (Batch B230119, ex BF Goodrich, Hounslow, UK) and xanthan gum (Keltrol GF, Batch 079537K, ex-Kelco, London, UK) were used as representative polymers, previously demonstrated to be mucoadhesive in a range test systems.

Table 1 gives a list of additives and their suppliers. None of these materials had any significant mucoadhesive potential in the test method used [7].

2.2. Methods

The mucoadhesion of polymers was tested according to the method previously described [1]. Mucoadhesive tablets were prepared by compressing 100 mg of polymeric material in a 13 mm IR press for 30 s at a pressure of 5 T. Previous validation indicated that this high force did not cause a diminution of the observed mucoadhesion of tablets in this test system [7]. Where additions were made to the mucoadhesive polymers, mixing was carried out for 5 min prior to compression, as described previously [6].

The test parameters were based on those of Ponchel et al. [8]. Tablets were attached to the mucosa for 600 s with a force of 0.5 N. The instrument probe was then removed at a rate of 0.1 mm/s and the area under the force/distance curve calculated to find the work of adhesion. The development and validation of this test method is described in a previous publication [1].

Pig gastric mucosa (antrum region) was used as the test tissue and the bathing medium was simulated gastric medium (without pepsin). Tablet manufacture and storage has already been documented [1].

2.3. Statistical analysis

Experiments were designed by blocking to allow two way analysis of variance (ANOVA) to be carried out. Statistical analysis was carried out using Excel 4 for Windows (Microsoft Corporation). Post ANOVA analysis was carried out using the Newman–Keuls procedure [9].

Table 1
Additives used in mucoadhesive experiments

Material	Supplier
Magnesium stearate	BDH, Poole, UK
Sterilised talc	BDH, Poole, UK
Colloidal silica (Cab-O-Sil, Grade M5)	Cabot, South Glamorgan, UK
Compressible sucrose (microtal)	Tate and Lyle Ind., London, UK
Dibasic calcium phosphate dihydrate (emcompress)	Mendell, Patterson, NY
Spray dried lactose (DC Lactose 10)	DMV Lactose, Veghel, The Netherlands
Microcrystalline cellulose (Avicel PH 101)	FMC Europe, Brussels, Belgium
β-cyclodextrin	Roquette, Tunbridge, UK
Hydroxypropyl-β-cyclodextrin	Wacker Chemical, Walton-on-Thames, UK
Hydroxypropyl-γ-cyclodextrin	Wacker Chemical, Walton on Thames, UK
Triton X705	Sigma, Poole, UK
Pluronic F87	BASF, Cheadle, UK
Cholesterol	Prolabo, Salford, UK
Span 60	Sigma, Poole, UK
Sodium dodecyl sulphate	BDH Biochemica, Poole, UK
Cetylpyridinium chloride	BDH, Poole, UK
Potassium chloride	Aldrich, Gillingham, UK
Sodium chloride	BDH, Poole, UK
Calcium chloride	Sigma, Poole, UK
EDTA	Sigma, Poole, UK

3. Results and discussion

3.1. Influence of flow aids and lubricants on the observed mucoadhesion of polymers

Table 2 shows the influence of 5% of three common pharmaceutical flow aids on the observed mucoadhesion of Carbopol® 934P, and Table 3 shows the influence of the same materials on the observed mucoadhesion of xanthan gum.

Table 2
Influence of 5% flow aids on the observed mucoadhesion of Carbopol® 934P

Lubricant or gradant	n	Plain tablets		With 5% additive		Statistical significance (paired t-test)
		Mean work of adhesion (mJ)	±S.D.	Mean work of adhesion (mJ)	±S.D.	
Magnesium stearate	10	1.0936	0.256	0.7030	0.204	$P<0.05$
Sterilised talc	10	1.0643	0.321	1.1106	0.289	NS
Colloidal silica	10	1.1329	0.259	1.1165	0.263	NS

Table 3
Influence of 5% flow aids on the observed mucoadhesion of xanthan gum

Lubricant or glidant	n	Plain tablets		With 5% additive		Statistical significance (paired t-test)
		Mean work of adhesion (mJ)	±S.D.	Mean work of adhesion (mJ)	±S.D.	
Magnesium stearate	10	1.2345	0.263	0.9543	0.302	$P<0.01$
Sterilised talc	10	1.2199	0.249	1.2321	0.217	NS
Colloidal silica	10	1.2306	0.314	1.2412	0.294	NS

Magnesium stearate, which is strongly hydrophobic [10,11], probably exerts its negative effect on the mucoadhesion of Carbopol® 934P and xanthan gum by hindering the hydration of the polymer, consequently causing a decrease in the number of chemical groups, in this case carboxylic acid moieties, available for bonding to the mucus. The material may also block the passage of water from mucus to the mucoadhesive, which normally occurs by the mechanism of mucus dehydration [12]. In addition it is known that divalent cations can crosslink polyacrylic acids and this may contribute to the deleterious effects that magnesium stearate has on the observed mucoadhesion. Sterilised talc and colloidal silica, which do not possess the same hydrophobic properties, or have available divalent cations, appear to be viable alternatives to magnesium stearate. One previous study has shown that magnesium stearate does not hinder the formation of the mucoadhesive bond at lower concentrations of the additive, but this was with a lower concentration of the excipient, which may explain the difference in results [13].

3.2. Influence of tablet diluents on the observed mucoadhesion of Carbopol® 934P

Common direct compression diluents were incorporated into blends with Carbopol® 934P in a 1:1 ratio. The results obtained are shown in Table 4.

Two way ANOVA followed by Newman–Keuls analysis showed that all diluted systems showed significantly ($P < 0.01$) lower adhesion than pure Carbopol® 934P and also that tablets containing compressible sucrose had significantly ($P < 0.01$) lower observed mucoadhesion than those containing dibasic calcium phosphate dihydrate and lactose. Tablets containing microcrystalline cellulose had significantly ($P < 0.05$) lower adhesion than lactose or dibasic calcium phosphate dihydrate.

It is notable that those dilutents whose tablets displayed poorer observed mucoadhesion, compressible sucrose and microcrystalline cellulose, both have means to sequester water. The highly soluble disaccharide sucrose, could act to take away water by dissolving in it, making it unavailable for the polyacrylic acid, leading to decreased hydration and consequent bonding. In the case of microcrystalline cellulose this material absorbs water and swells, this may also have the effect of reducing the water content of the mucin/mucoadhesive bond. Mere dilution of the system, to levels approximately half of those obtained for pure polymer, clearly also plays a part.

Higher values, at the same dilution level, are obtained for other diluent additives. Whilst interpretation of this result is speculative it remains clear, that in this test system, they have been shown to be more compatible, in terms of retaining adhesive capacity, with the mucoadhesive polymer. Dibasic calcium phosphate dihydrate, which has poor solubility at low pH, [14] and lactose are less likely to remove water from the system and appear to be more successful diluents for Carbopol® 934P, with regard to influencing mucoadhesion.

Table 4
Influence of 50% diluent on the observed mucoadhesion of Carbopol® 934P tablets

Diluent (50% concentration)	n	Mean work of adhesion (mJ)	±S.D.
None	20	1.0049	0.349
Dibasic calcuium phosphate dihydrate	20	0.7150	0.258
Microcrystalline cellulose	20	0.4986	0.192
Spray dried lactose	20	0.6347	0.170
Compressible sucrose	20	0.4963	0.139

Table 5
Influence of cyclodextrins on the observed mucoadhesion of Carbopol® 934P at 5% concentration

Cyclodextrin additive	*n*	Mean work of adhesion (mJ)	±S.D.
None	20	1.0651	0.293
β-cyclodextrin	20	1.1246	0.306
Hydroxypropyl-β-cyclodextrin	20	1.0002	0.291
Hydroxypropyl-γ-cyclodextrin	20	0.9925	0.257

3.3. Influence of cyclodextrins on the observed mucoadhesion of Carbopol® 934P

Cyclodextrins are large molecular weight oligosaccharides. The materials have the potential for wide use in the pharmaceutical and food industries because of their ability to form water-soluble complexes with hydrophobic agents [15].

The ability of cyclodextrins to hydrogen bond to small molecules allows them to form the complexes with small molecules. As it has already been demonstrated that hydrogen bonding ability allows some polymers to interfere with the formation of the mucoadhesive bond [6] these materials were included in mucoadhesive formulations. The results are given in Table 5. Two way ANOVA demonstrated that there were no significant differences between the groups.

It is perhaps expected that these materials do not hinder the mucoadhesive bond formation between mucoadhesives and mucin, as the polymer would be far too large to form an inclusion complex within the cyclodextrin. This would suggest that materials which are going to hinder the formation of a mucoadhesive bond must, as well as being able to form hydrogen bonds, be able to form a complex with the mucoadhesive polymer, stabilised by such bonds. It has been previously demonstrated that polyvinylpyrrolidone is such a polymer [6].

3.4. Influence of surfactants on the observed mucoadhesion of Carbopol® 934P

There have been several studies into the influence of surface tension on observed mucoadhesion of test materials.

Baszkin et al. noted that the surface properties of poly(methyl methacrylate), which were similar to that of the bovine submaxillary mucin solutions they were being tested against, favoured wetting by the latter [16].

The first fully systematic analysis of the role that surface tension plays in mucoadhesion has been carried out by a group at Leiden University. They used a modified version of the Dupré equation, the geometric mean equation, to describe the interfacial free energy [17,18].

Further developments of the theory, utilising the method of Kaelble, allowed the group at Leiden to elicit a single term which could, in most circumstances, predict mucoadhesive performance [19].

Mikos and Peppas have published data gained from measuring the surface tension of mucus solutions. From this work they claim that surface effects are sufficient to explain the mucoadhesion of weakly adhesive materials such as HPMC but are insufficient to explain the strong adhesion of materials such as polyacrylic acids [20]. Other advances in this area have also been reported by other groups [21–23].

The evidence that surface tension influences observed mucoadhesion in some test systems led to the suggestion that inclusion of surfactants in mucoadhesive formulations would influence observed mucoadhesion to the pig gastric mucosa, and this theory was tested.

Table 6
Influence of 1% surfactant on the observed mucoadhesion of Carbopol® 934P

Surfactant	*n*	Plain Carbopol® 934P tablets		With 1% surfactant		Statistical significance (paired *t*-test)
		Mean work of adhesion (mJ)	±S.D.	Mean work of adhesion (mJ)	±S.D.	
Non-ionic						
Triton X705	12	1.0798	0.281	1.0601	0.356	NS
Pluronic F87	11	1.0809	0.291	1.0539	0.228	NS
Cholesterol	11	1.0873	0.188	1.0609	0.228	NS
Span 60	15	1.0441	0.413	1.0447	0.479	NS
Anionic						
Sodium dodecyl sulphate	12	1.0810	0.185	1.1251	0.214	NS
Cationic						
Cetylpyridinium chloride	12	1.0387	0.193	1.0587	0.226	NS

Table 7
Influence of 5% surfactant on the observed mucoadhesion of Carbopol® 934P

Surfactant	n	Plain Carbopol® 934P tablets		With 5% surfactant		Statistical significance (paired t-test)
		Mean work of adhesion (mJ)	±S.D.	Mean work of adhesion (mJ)	±S.D.	
Non-ionic						
Triton X705	12	1.0533	0.189	1.0712	0.235	NS
Pluronic F87	10	1.0232	0.279	1.0400	0.387	NS
Cholesterol	12	1.0787	0.219	1.0633	0.152	NS
Span 60	12	1.1468	0.126	1.1080	0.144	NS
Anionic						
Sodium dodecyl sulphate	12	1.0462	0.284	1.0598	0.306	NS
Cationic						
Cetylpyridinium chloride	10	0.9212	0.397	0.8052	0.534	NS

The results for surfactants added at 1, 5 and 10% are given in Tables 6–8, respectively.

The results from the experiments carried out with surfactants indicate that, for the materials tested, their presence does not affect the strength of the observed mucoadhesion, with the exception of 10% Pluronic F87, which is discussed below.

The inference that could be made from this is that, contrary to the situation in other parts of the GI tract, that surface activity does not play a substantial role in gastric mucoadhesion. The surface tension of this portion of the GI tract is substantially different from other mucosae [24]. Equally it could be that by studying the surface tension of polymers the workers are, in fact, examining, indirectly, the hydrogen bonding capacity of the polymers, manifested as hydrophillic properties. As discussed by Pritchard the surface tension of a polymer is dependent on its hydrogen bonding capacity [25].

The failure of the surfactants to alter observed mucoadhesion could be due to the fact that, in the region of the mucoadhesive bond—that contains little water—the surfactants are insufficiently soluble to exert an influence. Some of the agents, cholesterol in particular, would be particularly susceptible to this effect. The time course of the experiments may be too short to allow the surfactants to exert their effect. It may also be that, for the charged surfactants tested, that the pH at which the experiments were carried out were not in their charged, active state, thus reducing their effect in the presence of the mucoadhesive.

The one surfactant which did, at the relatively high concentration of 10%, significantly influence observed mucoadhesion of the Carbopol® 934P tablets was Pluronic F87. This might appear to negate much of the foregoing discussion. It may be important that the structure of Pluronic F87, which is a polymer, includes a hydrogen bond accepting group, similar to that found in polyoxyethylene which has already been demon-

Table 8
Influence of 10% surfactant on the observed mucoadhesionof Carbopol® 934P

Surfactant	n	Plain Carbopol® 934P tablets		With 10% surfactant		Statistical significance (paired t-test)
		Mean work of adhesion (mJ)	±S.D.	Mean work of adhesion (mJ)	±S.D.	
Non-ionic						
Triton X705	14	0.8713	0.332	1.1038	0.508	NS
Pluronic F87	12	1.1894	0.524	0.7980	0.368	$P<0.05$
Cholesterol	12	1.1679	0.364	1.3203	0.400	NS
Span 60	12	1.0047	0.350	0.8803	0.335	NS
Anionic						
Sodium dodecyl sulphate	12	0.9265	0.236	0.9401	0.377	NS
Cationic						
Cetylpyridinium chloride	12	0.9829	0.212	1.0377	0.222	NS

Table 9
Influence of salts and EDTA (all at 5%) on the observed mucoadhesion of Carbopol® 934P

Additive	n	Plain tablets		With 5% additive		Statistical significance (paired t-test)
		Mean work of adhesion (mJ)	±S.D.	Mean work of adhesion (mJ)	±S.D.	
Monovalent salts						
NaCl	14	1.1567	0.503	0.8936	0.383	$P<0.05$
KCl	12	1.4214	0.265	1.1097	0.369	$P<0.05$
Divalent salt						
CaCl	12	1.1931	0.323	0.9855	0.244	NS
Chelating agent						
EDTA	12	1.1633	0.322	1.0949	0.276	NS

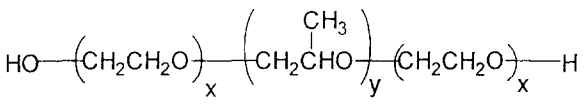

Fig. 1. General structure of pluronic surfactants.

strated as an agent capable of significantly reducing observed mucoadhesion [6]. There is a possibility, therefore, that the ability of this material, the structure of which is given in Fig. 1, to reduce the mucoadhesion of Carbopol® 934P at this concentration is due to this hydrogen bonding capability rather than its surfactant properties.

3.5. Influence of chloride salts and a chelating agent on the observed mucoadhesion of Carbopol® 934P

Two monovalent and one divalent chloride salts were added to Carbopol® 934P. This range may show whether the anions or cations are causing any change in observed mucoadhesion. In addition the calcium chelating agent EDTA was tested. Calcium ions have been shown to have an influence on the mucoadhesive bond [26]. The inclusion of this agent was designed to find whether the calcium ions present in mucus naturally inhibit the strength of the mucoadhesive bond.

The results of the study are shown in Table 9.

The results from the section on addition of salts to the tablets on the observed mucoadhesion are confirmation of the evidence previously published that increasing the ionic strength in the local region of the tablet leads to a decrease in adhesion [27]. The observation that calcium chloride does not significantly affect observed adhesion where sodium and potassium chloride do have the effect, may be an indication that it is not the chloride ions that are exerting the influence but it is the cations that are responsible, the number rather than the overall charge being the important factor. This would be the case if the mucoadhesive interaction involved hydrogen bonding; under these circumstances it is the counter ions to the bonding material that exert the negative influence on the bonding mechanism. The mucoadhesive tested in this circumstance, although uncharged at this pH at which the experiment is carried out, is an anionic polymer.

The result from the addition of EDTA, which was shown to have no influence on the observed mucoadhesion of Carbopol® 934P, may indicate that the calcium ions, an excess of which can hinder the formation of the mucoadhesive bond and are present in mucus, do not have a role in the normal mucoadhesive bond. However, it should be pointed out that the pH at which the experiment is carried out is well below the optimal pH, around 11, at which the agent displays its best chelating ability. The solubility of the material in the environment of the mucoadhesive is also likely to be low.

4. Conclusions

A series of experiments has been carried out which show that the presence of formulation excipients, at concentrations found in pharmaceutical tablets, can affect the observed ex-vivo mucoadhesive bond. This may be of importance in the formulation of tablets for in vivo use.

The cause of these effects on observed mucoadhesion cannot be attributed unambiguously until in vitro evidence of the nature of the bond between mucoadhesives and gastric mucus at low pH is obtained.

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