An evaluation of the adhesion of solid oral dosage form coatings to the oesophagus

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Abstract

There is a requirement for the development of oral dosage forms that are adhesive and allow extended oesophageal residence time for localised therapies, or are non-adhesive for ease of swallowing. This study provides an initial assessment of the in vitro oesophageal retention characteristics of several widely utilised pharmaceutical coating materials. To this end, a previously described apparatus has been used to measure the force required to pull a coated disc-shaped model tablet across a section of excised oesophageal tissue. Of the materials tested, the well-studied mucoadhesive polymer sodium alginate was found to be associated with significant oesophageal adhesion properties that was capable of ‘self-repairing’. Hydroxypropylmethylcellulose exhibited less pronounced bioadhesive behaviour and blending this with plasticiser or with low molecular weight polymers and surfactants did not significantly affect this. Low molecular weight water soluble polymers, were found to behave similarly to the uncoated glass control disc. Polysorbates exhibited bioadhesion behaviour that was majorly influenced by the nature of the surfactant. The insoluble polymer ethylcellulose, and the relatively lipophilic surfactant sorbitan monooleate were seen to move more readily than the uncoated disc, suggesting that these may have a role as ‘easy-to-swallow’ coatings.

Keywords: oesophageal adhesion, easy-to-swallow, mucoadhesion, non-adhesive coatings.
1. Introduction

Despite the major effort over several decades by pharmaceutical scientists to develop a range of advanced drug delivery systems, the majority of drugs are still administered in the form of tablets and capsules. These are swallowed and need to pass through the oesophagus to reach the stomach and small intestine where the drug is absorbed. The adhesion of such solid formulations in the oesophagus has been widely implicated in medication-induced injury to this organ. A high local concentration of mucosal irritants (e.g. emepronium bromide, apple-cider vinegar, alendronate sodium, tetracycline, potassium chloride) within the oesophagus may lead to oesophageal damage (Hill et al., 2005; Jaspersen, 2000; Ueda et al., 2011). In addition, the extended retention of therapeutic formulations in the oesophagus may impact on the bioavailability and the pharmacokinetics profile of the active. Formulation size, shape and surface characteristics have been identified as factors that influence the adhesion of dosage forms in the oesophagus during swallowing (Channer and Virjee, 1985; Marvola et al., 1982; Perkins et al., 2001).

The adhesion of solid dosage forms to the oesophagus is often desirable, however, since it may provide the means for anchoring formulations designed for the local treatment of gastrooesophageal reflux disease (Batchelor et al., 2002) or for pain and inflammation (Mako et al., 2009), or for delivering diagnostic agents (Collaud et al., 2007).

In a previous study, an in vitro apparatus was developed and validated that allowed adhesive interactions to be assessed in terms of the force needed to pull a disc coated with a test material over a flattened section of oesophageal mucosa when applying a physiologically relevant shear stress (Smart et al. 2013). In this study the adhesion/antiadherent properties of a range of
pharmaceutical coating materials along with various additives will be evaluated, with regard to their likely effect on oesophageal transit.

2. Materials and methods

2.1 Materials

Hydroxypropylmethylcellulose (HPMC), under the trade names Pharmacoat 615 was supplied by Harke Group, Muelheim an der Ruhr, Germany; The Pluronic™ copolymers F127, F98 and F38 were supplied by BASF PLC, Cheadle, Cheshire. Poly(ethylene glycol) (PEG) 6,000 MW grade (PEG) and Paraffin wax (high melting point, ca. 60°C) was purchased from B.D.H Chemicals Ltd, Poole. Polyethylene glycol (PEG) (1,450 mw grade and 200 mw grade), Gelatin (type B, from bovine skin), sodium alginate (medium viscosity grade from Mactocystis pyrifera) fluorescein, Type III partially purified mucin, from porcine stomach, triacetin and sorbitan monopalmitate (Span 40) purchased from Sigma-Aldrich Chemical Company, Poole, Dorset. Polyvinyl alcohol (PVA) 15,000 mw grade and ethylcellulose (Ethocel, 10 mPas) were supplied by Fluka Chemicals, Gillingham. LustreClear™ (a microcrystalline cellulose/carrageenan/polyethylene oxide based coating), FMC Biopolymer, Brussels, Belgium.

Poly(ethylene oxide), under trade name PolyOx™ (NF grade, WSR N10 mw 100,000) were supplied by Dow Chemical Company, Belfast.

2.2 Preparation of solutions

Polymer solution concentrations were chosen for their ease of use in the spin-casting process, determined in preliminary investigations. Dispersions of HPMC (7% w/w), PEG (15 %w/w), sodium alginate (1.5% w/w), gelatin (8% w/w), Fl27 (10% w/w), Lustraclear™ (9% w/w) and PVA (4% w/w)
were all prepared by adding the appropriate mass of polymer to rapidly vortexing (magnetic stirrer) de-ionised water. Mixes were prepared in the proportions of HPMC 7.5% / triacetin 1.5%; HPMC 3% / triacetin 1.5%; HPMC 7.5% PEG 200 1.5%; HPMC 3.75%, triacetin 1.5%, F127 3.75%; PVA 4%, F127 1%. Ethyl cellulose (5% w/w) and sorbitan monopalmitate (7% w/w) were prepared by dissolving in ethanol and isopropanol respectively. All solutions were stored with stirring overnight before use.

Simulated saliva, as used in our previous studies (Kockisch et al 2004, Smart et al 2013), was prepared by dissolving 0.9 % sodium chloride solution in deionised water. To simulate the presence of salivary mucin, 0.5% gastric mucin was added and this stirred using a magnetic stirrer for 1 h at 4°C before use.

2.3 Preparation of test discs

Test discs (8mm diameter providing a film surface area of 50.3mm²) were prepared by casting films from the aqueous polymer solutions using a spin casting technique. The majority of the films were spun at a speed of ca. 1000 rpm for 30 seconds, however, the more viscous solutions of HPMC blends and sodium alginate required a higher rotation speed of ca. 2000 rpm for 50 seconds. The films were then air-dried (at ambient temperature) and weighed; further applications were applied until a dry constant weight of between 1.50 - 2.00 mg was achieved. Paraffin wax and PEG (melt) were melted over a beaker of boiling water. Once molten the glass discs were coated by dipping the surface of each into the molten wax using tweezers and were then allowed to set at room temperature. The films were stored in a dessicator over silica gel and used within 1 week to avoid any discrepancies that may result from physical ageing.

2.4 Experimental
The apparatus consisted of the porcine oesophageal mucoadhesion test system described by Smart 
et al. (2013). Effectively the disc coated with the test material on its lower surface and with a 2 g 
weight placed on the upper surface is pulled off a PTFE ‘non-stick’ launch then pulled for 290 s 
across a distance of 59.5 mm on a flat section of frozen and thawed pig oesophageal mucosa at a 10° 
age with a flow of simulated saliva (1 mL min\(^{-1}\)) along the tissue (Fig. 1). The force required to 
move the disc was recorded, and only one test was completed on each tissue. To take into account 
tissue variances an identical uncoated roughened glass disc was tested on each tissue before 
adhesion testing with the coated test disc. Each material was tested six times on six different tissues 
and the corresponding values of the roughened glass controls are also included for each material. 
Statistical differences were tested using Analysis of Variance with a Multiple comparison - Tukey’s 
HSD, p < 0.05.

3. Results

This apparatus measures the resistance to movement of the test disc across the oesophageal mucosa. 
Two parameters were evaluated: the Maximum Detachment Force (greatest resistance force to 
movement across the tissue; most often this corresponded with the force associated with resistance 
to initiate movement across the tissue); and, the work done (area under the force-distance curve 
over 59.5 mm. To account for differences related to tissue topography, measurements were taken 
first with the uncoated plate followed by a plate coated with the test material on the same tissue 
sample. A ‘normalized’ value was calculated by dividing the coated-, by the uncoated plate value, to 
yield the adhesion and detachment ratios.

Bioadhesion data for the range of coatings tested is presented on Table 1 and Fig. 2. Of the range of 
coating materials that have been evaluated sodium alginate and HPMC were found to exhibit the 
greatest resistance to movement. Interestingly, one of the least adhesive materials was
Lustraclear™, which exhibited an initial detachment force that was significantly higher than that seen for the glass plate control. Coatings of PVA or gelatin exhibited behavior that was very similar to that of the uncoated glass plate. The higher molecular weight polyethylene oxide (PolyOx) was characterized by a high resistance to movement, while the structurally related lower molecular weight PEGs behaved similarly to the glass plate controls (Table 2, Fig 3). The method of coating, from solution or as a melt, had little effect. The mode of deposition (from the melt or from solution) of the PEG 1450 coating had little effect on the resistance-to-movement value measured.

Of the three Pluronics tested, only F127 showed a significantly larger adhesion ratio than the control (Table 3, Fig 4), while the PVA F127 mix exhibited bioadhesion behaviour that was akin to that of the glass plate. F38 was characterized by its very low resistance to the onset of movement, as were the water insoluble materials ethylcellulose and sorbitan monooleate, both of displayed lower resistance to movement than the glass plate (Table 4, Fig. 5).

The mixing of HPMC with triacetin (a plasticizer), a pluronic and PEG did not induce a significant effect on the measured biadhesive properties as compared with those determined for HPMC alone (Table 5, Fig. 6).

4. Discussion

The aim of this study was to use a previously developed test system to evaluate the adhesion of solid oral dosage form coatings to oesophageal mucosa using physiologically relevant shear stresses. In a typical force-distance plot, there would be an initial increase (from zero) in the force measured as tension is applied to the disc. If adhesion is similar to that of controls, the force measured corresponds to the frictional force of pulling the disc across the mucosa. Bioadhesion is deemed to occur when there is a marked increase in the force measured relative to that for the control. A
reduction in the force required to move the coated plate relative to that needed to move the roughened glass plate identifies the coating material as non–adhesive/lubricating.

In accord with findings from a previous study, sodium alginate is a material that becomes bioadhesive on hydration (Mortazavi and Smart 1994, Smart 2014). In addition to exhibiting significant bioadhesion, if dislodged this material was seen to self-repair the adhesive joint by re-adhering at the next contact point.

In accord with previous reports and owing to the absence of ionisable structural moieties, HPMC, which is employed widely as a tablet coating and also as a bioadhesive in some buccal formulations (e.g. Suscard Buccal™), is confirmed to be a weaker oesophageal bioadhesive than sodium alginate (Smart 2014). Gelatin, a protein that is the main component of many soft and hard capsules, exhibited little evidence of bioadhesive behaviour. Also in accord with previous reports (Mortazavi and Smart 1995), PVAs, the hydrophilic non-ionic polymers often used as tablet coatings, were found to behave in a similar fashion to the uncoated disc control. LustreClear™, the microcrystalline cellulose/carrageenan/polyethylene oxide based coating that is marketed as a coating with an ‘unparalleled ease of swallowing’, behaved similarly in that it showed some bioadhesive properties on application to the tissue (i.e. some force was required to start movement) but the average work done to pull the plate across the oesophagus was not significantly different from that obtained for the uncoated glass plate. This bioadhesive behaviour may be explained in terms of the mucoadhesive component (carrageenan; Mortazavi and Smart 1995) of the coating formulation.

Characterised by the dual capability to mask materials for parenteral administration and to prevent bacterial biofilm formation (Arciola et al 2012, Teixeira and Gomes 2015), PEGylation may also be reasonably assumed to result in materials that hydrate rapidly and form a lubricating ‘slippery mucilage’ between the disc and mucosa. Under the testing protocol employed in this study,
however, the behaviour of PEGs was little different to that of the uncoated disc (Table 2, Fig. 3). It is assumed that this behavior is consequent to the PEG coating being rapidly removed in an aqueous test environment. Relatively high molecular weight polyethylene oxide coatings, which have been used as mucoadhesives (Mortazavi and Smart 1995), required an initial strong detachment force to get the disc moving but adhesion ratios were similar to those of the glass-plate control. Blending the Pluronic™ F127 with a low molecular weight water soluble polymer, such as PVA, reduced the resistance to initial movement to close to that of the glass plate control. Since Pluronic™ surfactants consist of two blocks of hydrophilic polyoxethylene flanking a central hydrophobic polyoxypropylene block, it may be assumed that in aqueous environments the hydrophilic components orientate themselves such that that they become projected outwards from the film to form a hydrated lubricating coating. F38 (average molecular weight, 4700; HLB, 16.1) exhibited bioadhesion behaviour that was insignificantly different to that of the glass plate control. It is possible that it this material is rapidly removed from the glass substrate that it coats. F98 (average molecular weight, 13000; HLB, 16) showed some adhesion, notably in the initial detachment force. The less hydrophilic F127 (average molecular weight, 12,600; HLB, 13.8) exhibited significant bioadhesive properties, indicating its unsuitability for use as an ‘easy to swallow’ tablet coating. Adhesive failure often arises from a cohesive failure of the weakest component of the adhesive joint (Smart 2014) and F127 is known to have thermogelation properties on heating to body temperature (Escobar-Chavez et al 2006). It is therefore possible that the ability of the polyoxyethylene components to form bioadhesive bonds, along with that of the F127 to form stronger gels on exposure to the aqueous environment and temperature of this test system, explains its more adhesive nature.

Amongst the materials under evaluation, ethylcellulose, an insoluble tablet coating material, exhibited one of the lowest resistance-to-movement values, presumably by providing a smooth water-repellent coating to glass disc that glides on interfacial water. Similarly, coatings of sorbitan monopalmitate, a sparingly water soluble hydrophobic surfactant with a low HLB value (6.7) also
showed a very reduced resistance to movement across the mucosa. The hypothesis of the lubricant effect of water repelling materials was further tested with paraffin wax (Drake et al., 2002). As expected, the maximum detachment force and corresponding work done were directionally lower but not significantly different to those obtained with the uncoated glass disc.

The incorporation of a plasticizer (e.g. triacetin; commonly used in pharmaceutical coatings) in HPMC (Table 5, Fig. 6) or the mixing of HPMC with a low molecular weight PEG or with a pluronic surfactant did not alter the bioadhesive properties of corresponding coatings.

This work evaluated a range of coating materials for their capability to influence the residence time of a solid dosage form in the oesophagus. A lipophilic surfactant and a water-insoluble polymer have been shown to promote rapid transit, suggesting their suitability as candidate coating materials for easy-to-swallow solid oral formulations. By contrast, known mucoadhesive materials used as coatings slowed the transit of a coated modelled tablet. The work identifies promising oesophageal coating materials, especially for easy-to-swallow solid dosage forms.

References


Table 1. Average work done (WD) and maximum detachment forces (MDF) for polymer coatings relative to roughened glass controls, evaluated in the *in vitro* test system.

<table>
<thead>
<tr>
<th>Material</th>
<th>Film weight / mg (s.d.)</th>
<th>WD /μJ (n=6, s.d.)</th>
<th>MDF / mN (n=6, s.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium alginate</td>
<td>1.96 (0.09)</td>
<td>4154.03 (1379.01)</td>
<td>263.42 (111.39)</td>
</tr>
<tr>
<td>Glass control</td>
<td></td>
<td>666.35 (72.71)</td>
<td>13.72 (1.11)</td>
</tr>
<tr>
<td>HPMC</td>
<td>1.73 (0.18)</td>
<td>1209.28 (339.70)</td>
<td>95.14 (43.68)</td>
</tr>
<tr>
<td>Glass control</td>
<td></td>
<td>665.01 (118.83)</td>
<td>14.52 (2.52)</td>
</tr>
<tr>
<td>LustreClear</td>
<td>1.74 (0.04)</td>
<td>900.91 (44.45)</td>
<td>71.52 (32.46)</td>
</tr>
<tr>
<td>Glass control</td>
<td></td>
<td>801.25 (127.64)</td>
<td>17.31 (2.26)</td>
</tr>
<tr>
<td>PVA</td>
<td>1.92 (0.10)</td>
<td>625.23 (57.00)</td>
<td>29.11 (8.36)</td>
</tr>
<tr>
<td>Glass control</td>
<td></td>
<td>628.94 (73.54)</td>
<td>13.44 (2.99)</td>
</tr>
<tr>
<td>Gelatin</td>
<td>1.89 (0.20)</td>
<td>575.25 (76.02)</td>
<td>19.83 (7.61)</td>
</tr>
<tr>
<td>Glass control</td>
<td></td>
<td>605.51 (70.79)</td>
<td>12.58 (2.03)</td>
</tr>
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Table 2. Average work done (WD) and maximum detachment forces (MDF) for polyoxyethylene polymer coatings relative to roughened glass controls evaluated in the in vitro test system.

<table>
<thead>
<tr>
<th>Material</th>
<th>Film weight / mg (s.d.)</th>
<th>WD /μJ (n=6, s.d.)</th>
<th>MDF /mN (n=6, s.d.)</th>
</tr>
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<tr>
<td>PolyOx</td>
<td>1.98 (0.15)</td>
<td>744.51 (80.71)</td>
<td>48.98 (16.34)</td>
</tr>
<tr>
<td>Glass control</td>
<td></td>
<td>705.08 (47.05)</td>
<td>14.77 (0.70)</td>
</tr>
<tr>
<td>PEG 1,450 (solution)</td>
<td>1.90 (0.70)</td>
<td>653.96 (91.05)</td>
<td>14.37 (2.47)</td>
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<tr>
<td>Glass control</td>
<td></td>
<td>586.04 (71.61)</td>
<td>13.00 (1.57)</td>
</tr>
<tr>
<td>PEG 1,450 (Melt)</td>
<td>3.26 (0.15)</td>
<td>611.23 (74.51)</td>
<td>16.66 (1.80)</td>
</tr>
<tr>
<td>Glass control</td>
<td></td>
<td>559.70 (47.38)</td>
<td>12.35 (2.38)</td>
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<tr>
<td>PEG 6,000</td>
<td>1.83 (0.16)</td>
<td>591.50 (98.85)</td>
<td>12.70 (1.84)</td>
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<tr>
<td>Glass control</td>
<td></td>
<td>585.49 (54.69)</td>
<td>12.86 (2.05)</td>
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Table 3. Average work done (WD) and maximum detachment forces (MDF) for Pluronic™ copolymers coatings relative to roughened glass controls evaluated in the *in vitro* test system.

<table>
<thead>
<tr>
<th>Material</th>
<th>Film weight / mg (s.d.)</th>
<th>WD /μJ (n = 6, s.d.)</th>
<th>MDF / mN (n = 6, s.d.)</th>
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<tbody>
<tr>
<td>F127</td>
<td>1.82 (0.17)</td>
<td>1121.57 (361.05)</td>
<td>81.85 (37.57)</td>
</tr>
<tr>
<td>Glass control</td>
<td></td>
<td>526.20 (59.86)</td>
<td>11.56 (1.92)</td>
</tr>
<tr>
<td>F98</td>
<td>1.88 (0.18)</td>
<td>782.82 (83.72)</td>
<td>48.67 (14.67)</td>
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<tr>
<td>Glass control</td>
<td></td>
<td>480.26 (59.94)</td>
<td>9.98 (1.11)</td>
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<tr>
<td>f38</td>
<td>1.81 (0.18)</td>
<td>572.16 (65.89)</td>
<td>13.19 (2.34)</td>
</tr>
<tr>
<td>Glass control</td>
<td></td>
<td>575.21 (85.14)</td>
<td>12.49 (2.33)</td>
</tr>
<tr>
<td>PVA/F127</td>
<td>1.67 (0.20)</td>
<td>505.29 (43.09)</td>
<td>20.36 (5.21)</td>
</tr>
<tr>
<td>Glass control</td>
<td></td>
<td>513.65 (92.52)</td>
<td>10.78 (1.84)</td>
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Table 4. Average work done (WD) and maximum detachment force (MDF) values for Hydrophobic coatings and roughened glass controls evaluated in the *in vitro* test system.

<table>
<thead>
<tr>
<th>Material</th>
<th>Film weight / mg (s.d.)</th>
<th>WD /μJ (n = 6, s.d.)</th>
<th>MDF / mN (n = 6, s.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethylcellulose</td>
<td>1.76 (0.23)</td>
<td>438.52 (22.72)</td>
<td>8.59 (0.59)</td>
</tr>
<tr>
<td>Glass control</td>
<td></td>
<td>734.46 (59.01)</td>
<td>16.01 (2.03)</td>
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<tr>
<td>Paraffin wax</td>
<td>3.5 (0.20)</td>
<td>416.44 (54.84)</td>
<td>8.61 (1.35)</td>
</tr>
<tr>
<td>Glass control</td>
<td></td>
<td>532.32 (57.52)</td>
<td>10.60 (1.42)</td>
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<tr>
<td>Sorbitan monopalmitate</td>
<td>1.98 (0.20)</td>
<td>339.01 (29.82)</td>
<td>7.01 (0.85)</td>
</tr>
<tr>
<td>Glass control</td>
<td></td>
<td>608.10 (89.89)</td>
<td>13.07 (2.05)</td>
</tr>
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</table>
Table 5. Average work done (WD) and maximum detachment force (MDF) values for polymer blend coatings relative to roughened glass controls evaluated in the in vitro test system.

<table>
<thead>
<tr>
<th>Material</th>
<th>Film weight / mg (s.d.)</th>
<th>WD /μJ (n = 6, s.d.)</th>
<th>MDF / mN (n = 6, s.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPMC/triacetin (2:1)</td>
<td>1.93 (0.32)</td>
<td>1095.91 (338.49)</td>
<td>51.46 (22.70)</td>
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<td>Glass control</td>
<td></td>
<td>570.00 (43.67)</td>
<td>12.09 (1.32)</td>
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<tr>
<td>HPMC/triacetin (5:1)</td>
<td>1.86 (0.17)</td>
<td>1244.75 (275.32)</td>
<td>108.49 (35.00)</td>
</tr>
<tr>
<td>Glass control</td>
<td></td>
<td>603.48 (75.18)</td>
<td>13.21 (3.18)</td>
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<tr>
<td>HPMC/PEG 200 (5:1)</td>
<td>1.72 (0.27)</td>
<td>1196.05 (169.03)</td>
<td>74.05 (18.72)</td>
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<td>Glass control</td>
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<td>688.51 (37.50)</td>
<td>15.71 (0.90)</td>
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<tr>
<td>HPMC/triacetin/F127 (2.5:1.0:2.5)</td>
<td>1.93 (0.14)</td>
<td>1297.67 (281.96)</td>
<td>77.64 (29.53)</td>
</tr>
<tr>
<td>Glass control</td>
<td></td>
<td>625.60 (109.85)</td>
<td>13.71 (2.35)</td>
</tr>
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</table>
Fig. 1. Schematic diagram of the in vitro oesophageal adhesion model

Fig. 2. Adhesion and detachment ratios calculated for various coating materials evaluated in the in vitro test system (n = 6, s.d. bars).

Fig. 3. Adhesion and detachment ratios for the hydrophilic polymers (n=6, s.d. bars)

Fig. 4. Adhesion and detachment ratios for the pluronic polymers (n=6, s.d. bars)

Fig. 5. Adhesion and detachment ratios for the hydrophobic/insoluble polymers (n=6, s.d. bars)

Fig. 6. Adhesion and detachment ratios calculated for polymer blends relative to HPMC (n = 6, s.d. bars).
Fig 1

Fig. 2

- Sodium alginate
- HPMC
- LustreClear
- PVA
- Gelatin

![Graph showing adhesion and detachment ratios for different materials.](image-url)
Fig. 3

![Graph showing adhesion and detachment ratios for various samples.]

Fig. 4

![Graph showing adhesion and detachment ratios for different samples.]

- **Adhesion Ratio**
- **Detachment Ratio**
Fig. 5

![Graph showing the adhesion and detachment ratios for different materials.]

- Ethylcellulose
- Paraffin wax
- Sorbitan monopalmitate

- Adhesion Ratio
- Detachment Ratio

Fig. 6

![Graph showing the adhesion and detachment ratios for different formulations.]

- HPMC
- HPMC/triacetin (2:1)
- HPMC/triacetin (5:1)
- HPMC/PEG
- HPMC/triacetin/F127

- Adhesion Ratio
- Detachment Ratio