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Modelling Mucoadhesion by Use of Surface Energy Terms Obtained from the Lewis Acid–Lewis Base Approach. II. Studies on Anionic, Cationic, and Unionisable Polymers

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Surface energies of carbopol, chitosan, hydroxypropyl cellulose (HPC) and poly(HEMA) were assessed from contact angle and surface tension experiments. The surface energy was considered in terms of an apolar Lifshitz-van der Waals term and a polar acid-base term, which in turn is divided into electron donor and electron receptor (Lewis acid-Lewis base) contributions. Using these surface energy terms the interaction of dry and hydrated polymer with mucin in the presence of either artificial gastric or intestinal fluid, or saline was predicted. The predictions were related to measured forces of detachment. There was a significant difference between the surface energy on dry and hydrated HPC and also for carbopol; for the other polymers either the surface energy of the hydrated material was not detectable, or the effect of hydration was minimal. There were good correlations between mucoadhesive strength and the calculated free energies of interaction between mucin and polymer in the presence of each of the fluids, for each individual polymer. Thus, two trends were observed, one for unionisable and the other for ionisable polymers. It is argued that the increased mucoadhesion seen with ionisable polymers (compared with the predicted value based on results of unionisable polymers) is a direct result of the ionic interaction. No attempt has been made to correct for the ionisation effect, but the surface energy predictions provide insight into the mechanism of the mucoadhesion process. This approach is useful for understanding and predicting interactions between different materials and biological components.

KEY WORDS: surface energy; Lewis acid-Lewis base; contact angle; mucoadhesion; mucin; carbopol; chitosan; cellulose; p(HEMA); biocompatibility.

INTRODUCTION

Mucoadhesion is an interaction of a polymer with mucous in the presence of a biological fluid. Interfacial interactions have been acknowledged as being an important aspect in the control of mucoadhesion (e.g. 1). Indeed Lehr et al (2) have modelled the mucoadhesive behaviour of polycarbophil by considering the polar and dispersive components of surface energy of the polymer and of mucous. The use of polar and dispersive terms to describe surface energies of materials stems from the early work of Fowkes (3). However, it has been shown that such a simplistic data treatment (i.e. splitting surface energies into polar and dispersive forces) is inadequate for many practical situations (4).

We recently assessed the mucoadhesive performance of carbopol using a more rigorous treatment of interfacial forces (5). The theory (e.g. 6), considers the importance of acid-base (AB) interactions in surface and interfacial tensions. It is noted that interactions are dominated by the ability of compounds to either act as electron donors or electron acceptors (Lewis theory). Surfaces can be completely characterized by three parameters γ^{LW}, γ^{+} and γ^{-} representing the apolar (Lifshitz-van der Waals), electron acceptor and electron donor parameters, respectively. Quantitative information on these new surface energy parameters can be obtained by contact angle measurements with three adequate liquids (of which one must be apolar) on the solid of interest.

For a liquid once the total surface tension is known, the γ^{LW} component of the surface tension can be found by contact angle (θ) measurement on a completely apolar surface such as Teflon, by using equation 1:

$$\gamma_L(1+\cos\theta) = 2\,(\sqrt{\gamma_S^{LW}\,\gamma_L^{LW}}) \qquad (1)$$

The γ^{LW} component of the surface tension of solids can similarly be determined by contact angle measurement with apolar liquids for which $\gamma_L = \gamma^{LW}$ using the equation

$$1+\cos\theta = 2\,(\sqrt{\gamma_S^{LW}/\gamma_L}) \qquad (2)$$

According to the Dupre' equation, the apolar interaction energy (ΔG_{132}^{LW}) between materials 1 and 2 immersed in a liquid 3 is:

$$\Delta G_{132}^{LW} = \gamma_{12}^{LW} - \gamma_{13}^{LW} - \gamma_{23}^{LW} \qquad (3)$$

where

$$\gamma_{12}^{LW} = (\sqrt{\gamma_1^{LW}} - \sqrt{\gamma_2^{LW}})^2 \qquad (4)$$

It is clear that $\Delta G_{132}^{LW} < 0$ only when $\gamma_3^{LW} > \gamma_1^{LW}$ and $\gamma_3^{LW} > \gamma_2^{LW}$ or when $\gamma_3^{LW} < \gamma_1^{LW}$ and $\gamma_3^{LW} < \gamma_2^{LW}$. Similarly $\Delta G_{132}^{LW} > 0$ when $\gamma_1^{LW} > \gamma_3^{LW} > \gamma_2^{LW}$ or when $\gamma_1^{LW} < \gamma_3^{LW} < \gamma_2^{LW}$. The last two conditions result in repulsive Lifshiftz – van der Waals forces, thus when two different materials 1 and 2 interact, immersed in a liquid 3, and when $\gamma_1^{LW} \neq \gamma_2^{LW}$ and the last two conditions prevail an apolar repulsion exists.

In addition to apolar interactions, polar interactions of, for example, the hydrogen bonding type often occur. The polar component of the free energy of interaction between two materials 1 and 2 can be expressed as

$$\Delta G^{AB} = \gamma_{12}^{AB} - \gamma_1^{AB} - \gamma_2^{AB} \qquad (5)$$

where

$$\gamma_{12}^{AB} = 2(\sqrt{\gamma_1^{+}\gamma_1^{-}} + \sqrt{\gamma_2^{+}\gamma_2^{-}} - \sqrt{\gamma_1^{+}\gamma_2^{-}} - \sqrt{\gamma_1^{-}\gamma_2^{+}}) \qquad (6)$$

and

$$\gamma_1^{AB} = 2\,\sqrt{\gamma_1^{+}\gamma_1^{-}} \qquad (7)$$

Expressing the Young-Dupre' equation as

$$(1+\cos\theta)\gamma_L = -\Delta G^{TOT} \qquad (8)$$

and considering that

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$$\Delta G^{TOT} = \Delta G^{LW} + \Delta G^{AB} \tag{9}$$

we obtain

$$(1+\cos\theta)\gamma_L = -\Delta G^{LW} - \Delta G^{AB} \tag{10}$$

which becomes

$$(1+\cos\theta)\gamma_L = 2(\sqrt{\gamma_S^{LW}\gamma_L^{LW}} + \sqrt{\gamma_S^{+}\gamma_L^{-}} + \sqrt{\gamma_S^{-}\gamma_L^{+}}) \tag{11}$$

Thus by contact angle (θ) measurement with three different liquids (of which two must be polar) with known γ_L^{LW}, γ_L^{+} and γ_L^{-} values, using the last equation three times the γ_S^{LW}, γ_S^{+} and γ_S^{-} of any solid can be determined. Similarly by contact angle measurement of a liquid on various solids (of which two must be polar) the γ_L^{LW}, γ_L^{+} and γ_L^{-} can be determined.

Once all the parameters are determined for two different materials 1 and 2, their interfacial tension γ_{12} is

$$\gamma_{12} = (\sqrt{\gamma_1^{LW}} - \gamma_2^{LW})^2 + 2(\sqrt{\gamma_1^{+}\gamma_1^{-}} + \sqrt{\gamma_2^{+}\gamma_2^{-}} - \sqrt{\gamma_1^{+}\gamma_2^{-}} - \sqrt{\gamma_1^{-}\gamma_2^{+}}) \tag{12}$$

According to the Dupre' equation for interactions between particles or molecules 1 and 2 in a liquid 3

$$\Delta G_{132}^{TOT} = \gamma_{12} - \gamma_{13} - \gamma_{23} \tag{13}$$

$$\begin{aligned}\Delta G_{132}^{TOT} = {} & \gamma_{12}^{LW} - \gamma_{12}^{LW} - \gamma_{23}^{LW} \\ & + 2[\sqrt{\gamma_3^{+}}(\sqrt{\gamma_1^{+}} + \sqrt{\gamma_2^{-}} - \sqrt{\gamma_3^{-}}) \\ & + \sqrt{\gamma_3^{-}}(\sqrt{\gamma_1^{+}} + \sqrt{\gamma_2^{+}} - \sqrt{\gamma_3^{+}}) \\ & - \sqrt{\gamma_1^{+}\gamma_2^{-}} - \sqrt{\gamma_1^{-}\gamma_2^{+}}]\end{aligned} \tag{14}$$

A negative value for the free energy of interaction will result in a net attraction between substance 1 and 2 immersed in a liquid 3.

A number of polymer characteristics are known to be necessary for mucoadhesion: strong hydrogen bonding groups, strong anionic charges, high molecular weight, sufficient chain flexibility, surface energy properties favouring spreading onto mucous, presence of carboxyl groups. Poly(acrylic acid) type polymers have many of the properties in this list and are known for their good mucoadhesive performance. However positively charged polymers could possibly develop molecular attraction forces by electrostatic interactions with negatively charged mucosal surfaces (7).

The purpose of this work is to develop our study on the interaction between one polymer and mucin in the presence of different fluids (5), by comparing estimates of interfacial energy with measured mucoadhesive performance for different types of polymer, the polymers selected are examples of cationic, anionic and non-ionic materials.

MATERIALS AND METHODS

Carbopol 934 and porcine gastric mucin type III used as received without further purification as purchased from Sigma Chemical Co. Chitosan (PM average 325,000 g/mol, degree of deacetylation 77%) was received from Pronova Biopolymer LTD. Hydroxypropylcellulose (HPC) Klucel low viscosity grade was purchased from Hercules Inc.. p(HEMA) was received from Sigma Chemical Co. Diiodomethane, glycerol, ethanol, were all of commercial purity grade. Isotonic saline, artificial gastric and intestinal fluid were prepared from distilled water according to USP XXII Ed. without adding any enzymes. The pH was 6.4 for saline, 7.5 for intestinal fluid and 1.2 for gastric fluid.

Preparation of Mucin

Dried mucin was hydrated with phosphate buffer pH 6.4 by stirring at room temperature up to complete hydration (30 min). A dispersion of mucin 50% (w/v) was used for the force of detachment experiments.

Preparation of Polymers

Carbopol 934 was dispersed in distilled water (1% w/v) and magnetically stirred at room temperature up to complete polymer hydration (12 hours). Polymer films were prepared by dipping microscope cover glasses (24×32 mm) in the 1% dispersion and drying on air. The coated slides were used for contact angle and force of detachment experiments. To assess the surface energy and the Lifshitz van der Waals and electron donor / receptor contributions to the surface energy of the polymer, dispersions of Carbopol 934 in saline, gastric and intestinal fluid were prepared with different polymer concentrations, ranging from 0.5 to 6% (w/v). Surface tension measurements were performed on these solutions using a glass cover slide. The region of surface tension-concentration independence was found for all the samples. In this window the contact angle measurements were then obtained using solids of known surface energy. A similar approach was used to determine the surface energies for the other polymers, from the solutions prepared as detailed below.

Chitosan (1% w/v) was dissolved in dilute acetic acid (1%v/v) (7). The solution was filtered before being used to cast films of chitosan on glass plates (for contact angle assessment of the dry polymer). A solution of chitosan was also prepared in artificial gastric fluid (1% w/v) for assessment of the surface energy of the hydrated polymer. However, chitosan could not be hydrated (i.e. swollen) nor dissolved in saline or artificial intestinal fluid.

HPC (1% w/v) was dissolved in distilled water and used to cast films onto glass plates for surface energy assessment of the dry polymer. Dispersions of HPC in distilled water in different concentration (range 0.5–6% w/v) were also prepared in order to find the region of surface tension-concentration independence (in practice over 1% W/V); the surface energy of a 1 % solution was assessed as characteristic of the hydrated polymer. As HPC is non-ionic, no attempt was made to assess the surface energy in different pH conditions.

p(HEMA) (1% w/v) was dissolved in ethanol 95 %, from which films were cast onto glass slides for contact angle assessment. As for HPC, no attempt was made to consider surface energies in differing pH fluids as this polymer is non-ionic.

Contact Angle Measurement (to Assess the Surface Energy of the Dry Polymers)

The measurement of contact angle was performed using the Dynamic Contact Analyzer (DCA System 312, Cahn Instruments Inc.-USA). For all experiments undertaken using the DCA the results are means of 5 replicate determinations,

Table 1. (a) Mean Contact Angle Data for Polymers (Slides Coated with 1% w/v of Polymer Dispersions) on Water, Diiodomethane and Glycerol

Sample	COSθ Water	COSθ Diiodomethane	COSθ Glycerol
CARBOPOL 934[1]	0.27 ± 0.07	0.75 ± 0.06	0.370 ± 0.05
p(HEMA)	0.09 ± 0.03	0.50 ± 0.03	0.192 ± 0.05
CHITOSAN	0.20 ± 0.04	0.57 ± 0.03	0.359 ± 0.04
HPC (dry)	0.49 ± 0.01	0.56 ± 0.07	0.331 ± 10.02

[1] From (5).

unless otherwise stated in the text. The polymer coated glass slides were suspended on an electro-microbalance in the DCA by means of a metal clip. The liquid was poured into a cleaned glass beaker positioned on the platform below the slide. The slide was than allowed to come into contact with the liquid by raising the platform, immersing the plate to a depth of 10 mm at a speed of 157 μm/sec. Changes in the force acting on the plate were recorded to produce a force-immersion profile which was analyzed to give the advancing contact angle.

Three different test liquids, one apolar and two polar (of known polar i.e. γ^- and γ^+ and dispersive i.e. γ^{LW} nature) (Table 1) were required for the calculation of the surface energy components of the unknown materials. Diiodomethane was chosen as apolar with water and glycerol as polar liquids. The surface tensions of each of the liquids were checked by use of a flame cleaned glass plate attached to the DCA and were found to argee with literature values (the absolute values obtained for the measured surface tensions have been reported elsewhere (8)).

To Assess the Surface Energy of the Hydrated Polymer

The solutions of the polymer in the liquid of relevant pH were prepared in the first region of concentration independence for the surface tension (i.e. solutions of increasing concentration were prepared until the surface tension did not decrease with increasing polymer load). The surface energy and its component parts were then calculated by use of the surface tension and contact angles values between the polymer surface and two known solids (of which one was apolar i.e Teflon (PTFE) and one had known surface energy and polarity (polymethylmethacrylate, PMMA)). Surface energies were calculated at different pH values for the soluble ionisable polymer (carbopol, chitosan), but at one pH only if unionisable (HPC),[4] in the solid state only if insoluble (p(HEMA), chitosan at non-acidic pH).

Mucoadhesion Measurement

The DCA equipment was used in order to measure the strength of adhesive bonding of polymers when brought in contact with mucin in different media. The mucin layer (50% w/v in phosphate buffer solution pH 6.4), previously hydrated, was placed on a metal block, then covered with a cap with a central hole of 1.4 cm diameter. The mucin surface exposed to the polymer was 1.54 cm^2. The block was than transferred into a 50 mL beaker containing 30 mL of the test fluid.

A coated slide was stuck onto the lower side of a support, using a minimum amount of silicone grease, so that its flat face would contact the mucin gel. The support was hung on the arm of the balance (of the DCA). By raising the beaker using the moving platform, the slide was imbibed in the test liquid until it almost touched the mucin gel. The force on the balance was then set to zero. Then the platform was raised 3 mm at 151.7 μm/sec, giving contact between the polymer coated slide and the mucin gel. This situation was maintained for 1 or 5 minutes. The mucous surface was subsequently pulled down continuously at a constant rate of 151.7 μm/sec until the polymer was detached. Each sample of polymer and mucin was only used for one measurement. Every experiment was carried at least 5 times.

RESULTS AND DISCUSSION

Contact Angles on Dry Polymers

The contact angle values obtained for the slides coated with each polymer are reported in Table 1 (a). p(HEMA) is the most hydrophobic and HPC is the most hydrophilic of the polymers tested in this study.

Contact Angle on Hydrated Polymer

The contact angle data for Chitosan (1% w/v) hydrated in gastric fluid and for HPC (1% w/v) hydrated in water are reported in Table 1 (b). No data are reported concerning

Table 1. (b) Mean Contact Angle Data for HPC Hydrated in Water and Chitosan Hydrated in pH 1.2 with Teflon and PMMA. The Surface Tension is Obtained Against Glass (Data are Means ± SD)[1]

Sample	% (w/v)	γ^{TOT} (mN · m^{-1}) GLASS	COSθ TEFLON	COSθ PMMA
CHITOSAN (hydrated)	1	37.25 ± 0.16	0.20 ± 0.01	0.93 ± 0.01
HPC (hydrated)	1	39.50 ± 0.11	−0.42 ± 0.03	0.46 ± 0.03

[1] Data for carbopol have been reported previously (5).

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[4] Any possible effect of changes in pH, and/or ionic strength of the fluid used, on the swelling of unionisable polymers has not been investigated in relation to either surface energy of the polymer or the mucoadhesive performance. Such investigations will form the basis of further work.

Table 2. Components of the Surface Energies of the Test Fluids, Mucin and Polymers

Sample	pH	γ^{TOT} (mJ/m^{-2})	γ^{LW} (mJ/m^{-2})	γ^{AB} (mJ/m^{-2})	γ^{+} (mJ/m^{-2})	γ^{-} (mJ/m^{-2})
MUCIN[1]	/	46.2	6.9	39.3	49.2	7.8
GASTRIC F.[1]	1.2	56.4	17.1	39.4	45.0	8.6
SALINE[1]	6.4	71.7	33.7	38.0	27.4	13.2
INTESTINAL F.[1]	7.5	66.8	32.7	34.1	38.2	7.6
CARBOPOL (DRY)[1]	/	40.3	38.9	1.4	8.0	0.1
CARBOPOL (HYD)[1]	1.2	48.0	6.3	41.7	42.7	10.2
CARBOPOL (HYD)[1]	6.4	46.9	6.0	41.0	42.3	9.9
CARBOPOL (HYD)[1]	7.5	63.7	32.6	31.1	21.1	11.5
p(HEMA)	/	33.4	33.1	0.3	0.0	6.7
CHITOSAN	/	35.2	31.2	4.00	0.5	8.0
CHITOSAN (HYD)	1.2	37.3	26.8	10.5	7.5	3.7
HPC (dry)	/	32.6	30.9	1.7	0.02	33.1
HPC (HYD)	/	39.5	7.2	32.3	25.9	10.0

[1] As reported previously (5).

Chitosan dissolved in artificial intestinal fluid and in saline, as in these cases the polymer was completely insoluble.

Surface Energies of the Test Fluids

The surface energies for the test liquids (i.e. saline, artificial gastric and intestinal fluid) were as reported previously (5) and are presented in Table 2. It is surprising that the surface tension measured for the buffer at gastric pH was significantly lower than water (considering that the additives may be expected to raise the pH). It must be assumed that some impurity has lowered the surface energy, this is not deemed to be significant as the buffer is not physiologically relevant. True gastric fluid will contain bile salt surfactants which will certainly lower the surface energy of the fluid. The important considerations for this study are that the fluid is of known pH and of known surface energy; these criteria are satisfied.

Surface Free Energy of Dry Polymers

The surface parameters of the polymers and test media were calculated from the contact angle data as described above. The results are shown in Table 2. Each of the polymers have a substantial value for γ^{LW}, in contrast to mucin which has a predominantly polar surface nature (which does not change with the pH (9,5)). This is highlighted in Table 3, where the data are presented in terms of fractional polarity ($P = \gamma^{AB}/\gamma^{TOT}$).

Table 3. Fractional Polarity of Polymers and Mucin

Sample	P (γ^{AB} / γ^{TOT})
MUCIN	0.85
CARBOPOL (HYD) (SALINE)	0.87
CARBOPOL (HYD) (GASTRIC FLUID)	0.87
CARBOPOL (HYD) (INTESTINAL FLUID)	0.49
p(HEMA)	0.01
CHITOSAN	0.11
CHITOSAN (HYD) (GASTRIC FLUID)	0.28
HPC (dry)	0.05
HPC (hydrated)	0.82

It has been shown (5) for carbopol 934 that the greater the difference between the fractional polarity (P) of polymer and mucin the lower the force of detachment (i.e. the worse the mucoadhesive performance). In this respect p(HEMA) would be predicted to be the least mucoadhesive polymer, followed by HPC (dry) and chitosan. However, there is not a perfect correlation between fractional polarity and mucoadhesion.

The total free energy of interaction (ΔG_{132}^{TOT}) between the three phases (polymer, mucin and test fluid), and the contributing polar (ΔG_{132}^{AB}) and apolar (ΔG_{132}^{LW}) components for each system can be calculated (as described above). The results are reported in Table 4.

For the surface energy data calculated on the dry polymers, there was some similarity between the trends obtained for p(HEMA), HPC and chitosan, in that the lowest value in terms of total free energy of interaction (ΔG_{132}^{TOT}) was found for the systems polymer-mucin-saline, where the highest value was for polymer-mucin-gastric fluid, in each case. A totally different ranking was seen for carbopol.

The apolar contribution (ΔG_{132}^{LW}) to the total free energy obtained for carbopol (dry) in gastric fluid, artificial intestinal fluid and in saline is larger (more positive, less favoured interaction) than that of p(HEMA), Chitosan or HPC.

Surface Free Energy of Hydrated Polymer

Values for the surface energy components and ΔG_{132}^{TOT}, ΔG_{132}^{LW} and ΔG_{132}^{AB} calculated for chitosan (1% w/v) hydrated in gastric fluid and for HPC hydrated in water (1% w/v) are reported in Tables 2 and 4.

After hydration the polar component of the surface energy (γ^{AB}) for HPC increased (Table 3) such that the polymer is predominantly polar. The reduced mismatch in terms of fractional polarity between polymer and mucin indicates that HPC will be significantly more mucoadhesive (2,5) when hydrated than when dry. Furthermore ΔG_{132}^{TOT} and ΔG_{132}^{LW} for HPC hydrated are lower than that of the dry polymer (although ΔG_{132}^{AB} is higher). The decreased values in terms of total free energy and its apolar contribution after the hydration of the polymer favour the mucoadhesion of the hydrated polymer.

Table 4. Total Free Energy of Interaction Between the Three Phases (Polymer-Mucin-Test Medium), Apolar and Polar Components Contributing[1]

Sample	pH	ΔG_{132}^{LW} (mJ/m^{-2})	ΔG_{132}^{AB} (mJ/m^{-2})	ΔG_{132}^{TOT} (mJ/m^{-2})
CARBOPOL 934(HYD)-MUCIN[1]	1.2	−4.9	0.1	−5.0
	6.4	−21.4	3.8	−15.7
	7.5	0	−0.9	−0.9
p(HEMA)-MUCIN	1.2	4.9	−1.0	3.8
	6.4	−0.4	−4.8	−5.2
	7.5	9.7	−9.1	0.7
CHITOSAN-MUCIN	1.2	4.4	−1.5	2.9
	6.4	−1.4	−4.6	−6.0
	7.5	−0.7	0.3	−0.4
CHITOSAN(HYD)-MUCIN	1.2	3.1	−1.0	2.2
HPC(dry)-MUCIN	1.2	4.5	−3.5	1.0
	6.4	−1.7	−16.0	−17.7
	7.5	−0.8	−4.5	−5.3
HPC(HYD)-MUCIN	1.2	−4.3	−0.6	−4.9
	6.4	−19.8	1.4	−18.5
	7.5	−18.6	−0.6	−19.2

[1] From (5).

Hydrated chitosan shows an increased value of γ^{AB} and γ^{+}, and γ^{LW} is slightly decreased compared to the values obtained for the dry polymer. The changes in the surface parameters between the dry and hydrated state of the polymer are more significant for HPC than for Chitosan. The fractional polarity (P) for the two forms of chitosan (dry and hydrated) differ by a factor of less then three, whilst for HPC the difference between dry and hydrated is a factor of 16.4 (Table 3). There is a reasonable correlation between mucoadhesive strength and fractional polarity when the surface energy data for the hydrated polymers are compared (Tables 3 and 5) (i.e. the values for carbopol in each fluid, chitosan in gastric fluid and HPC). However, there is no obvious reason as to why the data for the hydrated systems should be separated out, thus fractional polarity is related to the mucoadhesive performance, but is not sufficient to explain all the observed behaviour.

Table 5. Mean Force of Detachment Values Recorded After 1 and 5 Minutes of Contact Time Between Polymer and Mucin in Different Media (Data Mean ± SD)[1]

Sample	pH	FORCE (mg) after 1 min	FORCE (mg) after 5 min
Carbopol 934[1]	1.2	7451 ± 1094	16505 ± 1194
	6.4	5723 ± 167	19627 ± 1817
	7.5	5759 ± 1131	10190 ± 778
p(HEMA)	1.2	4198 ± 1614	9826 ± 1644
	6.4	7374 ± 820	9683 ± 3570
	7.5	5097 ± 901	11970 ± 1968
CHITOSAN	1.2	9408 ± 1119	8856 ± 1837
	6.4	5928 ± 626	12651 ± 1889
	7.5	5729 ± 470	13599 ± 2800
HPC	1.2	5654 ± 1368	8983 ± 673
	6.4	7727 ± 277	16088 ± 1261
	7.5	7361 ± 1681	17489 ± 1424

[1] From (5).

Surface Free Energy and Mucoadhesion

The data from the force of detachment experiments are reported in Table 5. The best mucoadhesive performance for Chitosan and HPC was in intestinal fluid, and the lowest force for both the polymers has been recorded in artificial gastric fluid (comparing data recorded after 5 minutes contact time in the different fluids tested). Carbopol showed the greatest mucoadhesive behaviour in saline. The mucoadhesive performance of cationic and non-ionic polymers is superior to that of anionic for high pH values. The mucoadhesive performance of HPC was found to be better than that of Chitosan, even though HPC high viscosity grade was found not to show mucoadhesion at all (7). The weak bioadhesiveness of high viscosity cellulose was related to the low rate of water transport (10), which will not be so for the low viscosity grade of HPC (which can act as a tablet disintegrant).

The ability of materials to displace water from a biological surface is known as a prerequisite for bioadhesion (10). In this respect the poor bioadhesive performance of p(HEMA) can be related to its hydrophobic character.

In Figure 1 the force of detachment for each of the polymers after 5 minutes contact time is plotted against ΔG_{132}^{TOT}. A correlation can be seen for each of the polymers individually, and a general trend is observed for all the polymers collectively, but, the results do not all fit to one common straight line. However, the data can reasonably be fitted to 2 separate lines (Figure 2), one for the ionisable and the other for the non-ionisable polymers. It is notable that the correlation coefficient is much better for the non-ionisable polymers ($r = 0.99$) than the ionisable ($r = 0.84$). It is probable that there is a need for a correction in the measured free energy terms to account for the electrostatic free energies that will contribute to the interactive behaviour of the ionisable polymers. The electrostatic free energy of repulsion ΔG^{EL} between spheres has been described by van Oss and Costanzo (11) as being:

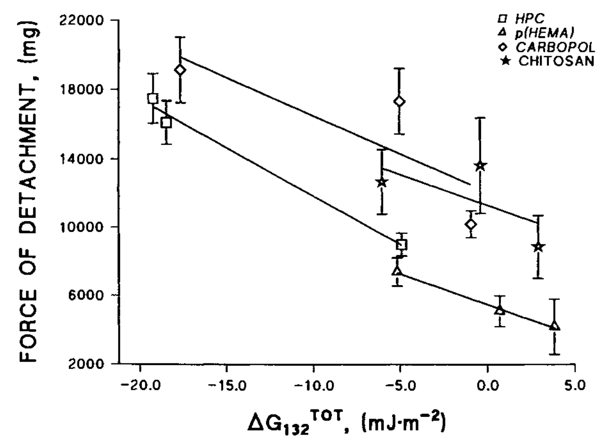

Figure 1: The relationship between the total free energy of interaction between polymer (1) and mucin (2) in the presence of each of the three test fluids (3) (ΔG_{132}^{TOT}) and the force of detachment in the mucoadhesion experiment. The responses for each separate polymer are highlighted.

$$\Delta G^{EL} = 0.5\, \epsilon\, R\, \varphi_o^2 \ln[1 + \exp(-\kappa l)] \qquad (15)$$

where ϵ is the dielectric constant of the liquid medium, R is the radius of the sphere, φ_o is the surface potential, κ is the double layer thickness and l is the distance between the outer shells of the spheres. The comparatively poor correlation coefficient ($r = 0.84$) for the ionisable polymers can be expected to be due to the fact that differences in electrostatic interactions will occur in the different fluids (each of different ionic strength), and at different ionisation of both the polymer and the mucin. Carbopol (pKa = 4.75), for example, will be highly ionised at pH 6.4 and 7.5 (ca. 97.8 % and 99.8 % respectively), but hardly ionised at all at pH 1.2, equally the sialic acid groups of the mucin will be unionised in acid, but highly ionised at higher pH. From this it is not surprising that the carbopol data in Figure 2 show a closer fit to the line for the pH independent polymers when the mucoadhesion in acidic conditions are considered, but deviate significantly from the pH independent line at both the higher pH values (when ionisation will play a more significant role). At present we do not have the necessary information on the polymers to correct the total surface energy for these electrostatic factors. However, despite the inability to correct for electrostatic behaviour, the fit in Figure 2 is very encouraging as it does show a clear interfacial relationship between mucoadhesion and surface energy terms. From Figures 2 and 3, it can be argued that the surface energy interactions provide an excellent model for mucoadhesive behaviour and consequently it should be possible to use such data to both explain and predict interactions between biomaterials and biological surfaces.

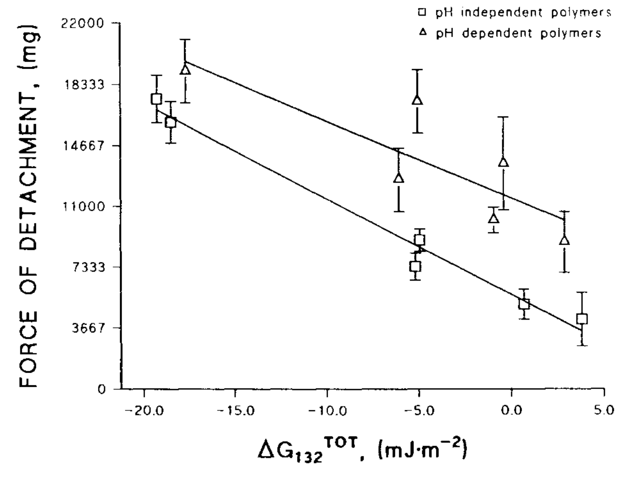

Figure 2: The relationship between the total free energy of interaction between polymer (1) and mucin (2) in the presence of each of the three test fluids (3) (ΔG_{132}^{TOT}) and the force of detachment in the mucoadhesion experiment. The difference between ionisable and unionisable polymers is highlighted.

A similar plot to that obtained in Figure 2 is seen when the force of detachment is plotted as a function of the Lifshitz-van der Waals free energy of interaction between the mucin and polymer in the presence of fluid (Figure 3). The relationship is not so clear for the acid-base interaction (not shown). Surprisingly, this would indicate that the mucoadhesive interaction has a major contribution which is due to non-polar interactions.

A further reason for possible deviation from the relationship between the free energy of interaction and the force of detachment (Figure 2) is that some of the surface energy data were obtained from contact angles on dry polymer plates, whilst other data are obtained from polymer solutions. It is possible that the method by which the surface energies are calculated will influence the absolute values obtained. It was an experimental necessity that the method used to calculate the surface energy terms differed for each system. However, the high correlation coefficient for the pH independent polymers, which includes some data on dry and some on hydrated samples, would tend to indicate that the choice of experimental method is not a major cause for concern.

In conclusion the bioadhesive performance of different polymers show reasonable correlation to predictions that are made on the basis of surface energy terms. The ionisable materials deviate from a common relationship, presumably due to a contribution from electrostatic forces. The surprisingly good correlations for different materials is encouraging

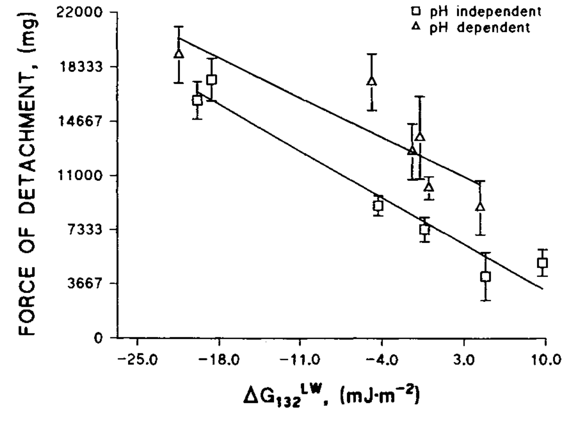

Figure 3: The relationship between the Lifshitz-van der Waals free energy of interaction between polymer (1) and mucin (2) in the presence of each of the three test fluids (3) (ΔG_{132}^{LW}) and the force of detachment in the mucoadhesion experiment. The difference between ionisable and unionisable polymers is highlighted.

and shows that interfacial considerations play a very significant role in the mucoadhesive process.

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