

## Modelling mucoadhesion by use of surface energy terms obtained by the Lewis acid-Lewis base approach

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### Abstract

The surface energies of carbopol and mucin have been assessed from contact angle and surface tension measurements. The surface energy has been considered in terms of an apolar Litshitz-van der Waals term and a polar acid-base term, which in turn is divided into electron donor and electron acceptor (Lewis acid-Lewis base) contributions. Using these surface energy components, the interaction of dry polymer, and hydrated polymer in the presence of simulated gastric fluid, intestinal fluid and saline, with mucin gel has been predicted. The predicted behaviour has been compared with measured mucoadhesion performance. It was found that the surface energy of the carbopol changed when hydrated. The surface energy of the dry polymer gave a better correlation with mucoadhesive strength after a short contact time. The surface energy of the hydrated polymer was found to give the best correlation with mucoadhesion after a longer contact time. This implies that the interpenetration stage of mucoadhesion has a driving force which is related to interfacial phenomena. The carbopol, but not the mucin, was found to show changes in surface energy as a function of pH. These differential changes correlated with changes in mucoadhesive behaviour in the different model media.

*Keywords:* Surface energy; Lewis acid-Lewis base; Contact angle; Mucoadhesion; Mucin; Carbopol

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### 1. Introduction

Interfacial interactions have been acknowledged as being an important aspect in the control of mucoadhesion (e.g., Peppas and Buri, 1985). Indeed, Lehr et al. (1993) have modelled the mucoadhesive behaviour of polycarboxophil 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 (1964). Polar and dispersive contributions to surface energy of a solid can be determined by measuring contact angles on that solid for two liquids of known surface energy and polarity. The calculation of the polar and dispersive terms can then be undertaken by either a harmonic or a geometric mean method. Even though the absolute difference in results obtained is often not huge, Wu's harmonic mean is normally regarded as the preferred method (Wu,

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1971). However, it has been shown that such a simplistic treatment (i.e., splitting surface energies into polar and dispersive forces) of data is inadequate to model many practical situations (Fowkes et al., 1990). Correlations between predictions made using polar and dispersive contributions to surface energy and observed interactions between materials are regarded as being fortuitous.

A more rigorous treatment of interfacial forces has been presented by Van Oss et al. (1988), who pointed out the importance of acid-base (AB) interactions in surface and interfacial tensions. They note 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  $\gamma^{LW}$ ,  $\gamma^+$  and  $\gamma^-$  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  $\gamma^{LW}$  component of the surface tension can be found by contact angle ( $\theta$ ) measurement on a completely apolar surface such as Teflon, using Eq. 1:

$$\gamma_L(1 + \cos\theta) = 2\left(\sqrt{\gamma_S^{LW}\gamma_L^{LW}}\right) \quad (1)$$

The  $\gamma^{LW}$  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:

$$1 + \cos\theta = 2\left(\sqrt{\gamma_S^{LW}/\gamma_L}\right) \quad (2)$$

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

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

where

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

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  $\gamma_1^{LW} > \gamma_3^{LW} > \gamma_2^{LW}$  and when  $\gamma_1^{LW} < \gamma_3^{LW} < \gamma_2^{LW}$ . The last two conditions result in repulsive Lifshitz-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:

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

where

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

and

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

Expressing the Young-Dupre' equation as:

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

and considering that

$$\Delta G^{TOT} = \Delta G^{LW} + \Delta G^{AB} \quad (9)$$

we obtain

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

which becomes

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

Thus, by contact angle ( $\theta$ ) measurement with three different liquids (of which two must be polar) with known  $\gamma_L^{LW}$ ,  $\gamma_L^+$  and  $\gamma_L^-$  values, using the last equation three times the  $\gamma_S^{LW}$ ,  $\gamma_S^+$  and  $\gamma_S^-$  of any solid can be determined. Similarly, by contact angle measurement of a liquid on various solids (of which two must be polar) the  $\gamma_L^{LW}$ ,  $\gamma_L^+$  and  $\gamma_L^-$  can be determined. Once all the parameters are determined for two different materials 1 and 2, their interfacial tension  $\gamma_{12}$  is:

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

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

$$\Delta G_{132}^{\text{TOT}} = \gamma_{12} - \gamma_{13} - \gamma_{23} \quad (13)$$

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

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.

The acid-base approach has been used to model many interfacial situations, including some which have pharmaceutical relevance (see, for example, Chandaria and Buckton, 1993; Mittal, 1993).

It follows that a more exacting surface energy treatment is available than has been used in any previous study in this field, with which it should be possible to consider the interaction between a mucoadhesive polymer and mucous in the presence of different fluids. The purpose of this work is to consider the interaction between one polymer and mucin in the presence of different fluids, by measurement of the mucoadhesive force, and by considerations of interfacial energy in terms of the acid-base method.

## 2. Materials and methods

Carbopol 934 and porcine gastric mucin type III were used as received from Sigma Chemical Co. Diiodomethane and glycerol were of commercial purity grade. Isotonic saline, artificial gastric and intestinal fluid were prepared from distilled water according to USP XXII Edn, without adding any enzymes. The pH was 6.4 for saline, 1.2 for gastric fluid and 7.5 for intestinal fluid.

### 2.1. Preparation of mucin

Dried mucin was hydrated with phosphate buffer (pH 6.4) by stirring at room temperature

up to complete hydration. Dispersions of mucin with different concentrations were prepared (for contact angle measurement 1% (w/v), for force of detachment experiments 50% (w/v)). Dispersions were also obtained hydrating mucin with gastric and intestinal fluid.

### 2.2. Preparation of polymer

Carbopol 934 was dispersed in distilled water (1% w/v) and magnetically stirred at room temperature up to complete polymer hydration (12 h). 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 surface energy for 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 region the contact angle measurements were than obtained using solids of known surface energy.

### 2.3. Contact angle measurement

The measurement of contact angle was performed using the Dynamic Contact Analyzer (DCA System 312, Cahn Instruments Inc., USA). The polymer coated 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  $\mu\text{m/s}$ . Changes in the force acting on the plate were recorded to produce a force-immersion profile which was analysed to give the advancing contact angle.

Three different test liquids, one apolar and

Table 1  
Surface parameters of the liquids and solids used for contact angle determinations

Sample	$\gamma^{\text{TOT}}$ (mJ m <sup>-2</sup> )	$\gamma^{\text{LW}}$ (mJ m <sup>-2</sup> )	$\gamma^{\text{AB}}$ (mJ m <sup>-2</sup> )	$\gamma^+$ (mJ m <sup>-2</sup> )	$\gamma^-$ (mJ m <sup>-2</sup> )
Diiodomethane	50.8	50.8	–	–	–
Water	72.8	21.8	51.0	25.5	25.5
Glycerol	64.0	34.0	30.0	3.92	57.4
Teflon	18.5	18.5	–	–	–
PMMA	42.7	42.7	0	0	20.4

two polar (of known polar, i.e.,  $\gamma^-$  and  $\gamma^+$  and dispersive, i.e.,  $\gamma^{\text{LW}}$  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. Three different solids were used to characterise unknown liquids, of which one was apolar (Teflon or PTFE) and one had known surface energy and polarity (polymethylmethacrylate, PMMA). The total surface tension for the liquids was obtained with the glass slide.

#### 2.4. 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 provided with a central hole of 1.4 cm diameter. The mucin surface exposed to the polymer was 1.54 cm<sup>2</sup>. The block was then transferred into a 50 ml beaker containing 30 ml of the test fluid (based on the method used by Lehr et al., 1992).

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 now set to zero. Then the platform was raised 3 mm at 151.7  $\mu\text{m/s}$ , giving contact between the polymer coated slide and the mucin gel. This situation was maintained for 1, 5, or 10 min. The mucous surface was subsequently pulled down continuously at a constant rate of 151.7  $\mu\text{m/s}$  until the polymer was detached. Each sample of polymer and mucin was only used for one measurement. Every experiment was carried at least five times.

### 3. Results and discussion

#### 3.1. Contact angle

##### 3.1.1. Calculating surface energy terms for the liquids

The contact angle measurements for the test liquids are listed in Table 2. Dispersions of mucin

Table 2  
Mean contact angle data for mucin, simulated gastric fluid, saline and simulated intestinal fluid on Teflon and PMMA, with the surface tension measured against glass

Sample	$\gamma^{\text{TOT}}$ (glass) (mJ m <sup>-2</sup> )	Cos $\theta$	
		Teflon	PMMA
Mucin	47.05 $\pm$ 1.9	-0.51 $\pm$ 0.08	0.56 $\pm$ 0.05
Gastric fluid	54.6 $\pm$ 1.49	-0.28 $\pm$ 0.12	0.44 $\pm$ 0.06
Saline	71.6 $\pm$ 2.3	-0.24 $\pm$ 0.08	0.25 $\pm$ 0.08
Intestinal fluid	66.8 $\pm$ 2.2	-0.26 $\pm$ 0.05	0.39 $\pm$ 0.1

Each value is the average of five measurements.

Table 3

Mean contact angle data for mucin (1% w/v) hydrated in artificial gastric and intestinal fluid on Teflon and PMMA with the surface tension measured against glass

Sample	$\gamma^{\text{TOT}}$ (glass) ( $\text{mJ m}^{-2}$ )	Cos $\theta$	
		Teflon	PMMA
Mucin pH 1.2	47.9 $\pm$ 2.1	-0.397 $\pm$ 0.09	0.439 $\pm$ 0.08
Mucin pH 7.5	46.4 $\pm$ 2.3	-0.416 $\pm$ 0.05	0.428 $\pm$ 0.02

of different concentration were also prepared and their surface energies were measured. It is known (Mikos and Peppas, 1989) that the total surface tension of mucin is not affected by its concentration. The role of the pH on the surface tension parameters of mucin was investigated by hydrating mucin (1% w/v) in gastric and intestinal fluid and performing contact angle determination on these solutions. The results (reported in Table 3) reveal that for mucin the pH does not affect either the total surface tension or its single components.

### 3.1.2. Contact angle on polymer

**3.1.2.1. Dry polymer.** The contact angle values obtained for the slides coated with Carbopol 934 are reported in Table 4.

**3.1.2.2. Hydrated polymer.** The role of polymer concentration and pH on the surface tension was investigated. The surface tension values of Carbopol 934 in different media are presented in Fig. 1 as a function of polymer concentration. A region of surface tension-concentration independence can be found for the polymer hydrated in each medium (Fig. 1). These concentrations (i.e., 1% in gastric fluid, 1.5% in saline and 6% (w/v) in intestinal fluid) were chosen for contact angle measurement against PTFE and PMMA, in order

Table 4

Mean contact angle data for Carbopol 934 dry (slides coated with 1% w/v of polymer solution) on water, diiodomethane and glycerol

Sample	Cos $\theta$		
	Water	Diiodomethane	Glycerol
Carbopol 934	0.273 $\pm$ 0.07	0.754 $\pm$ 0.06	0.370 $\pm$ 0.05

to calculate the surface energy components for the carbopol hydrated in the different fluids. For Carbopol hydrated in intestinal fluid a gel was obtained in the region of surface tension-concentration independence and this gel was used to form a smooth layer on the glass slide, the characterization of which was then conducted as for a solid by using three different liquids. The results are reported in Table 5.

### 3.1.3. Surface free energy

The single components of the surface parameters of mucin, polymer and test media were calculated from the contact angle data as described in the introduction. The results are shown in Table 6. With these parameters the total free energy of interaction between the three phases (i.e., carbopol and mucin in the presence of one of the fluids)  $\Delta G_{132}^{\text{TOT}}$ , and the contributing polar ( $\Delta G_{132}^{\text{AB}}$ ) and apolar ( $\Delta G_{132}^{\text{LW}}$ ) components for each polymer-mucin-fluid combination can be calculated. The results are reported in Table 7, using the

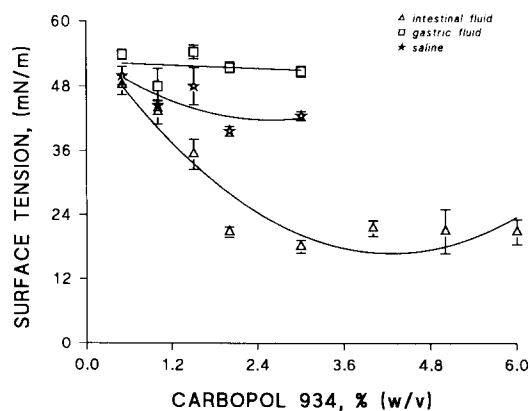


Fig. 1. Region of surface tension independence for Carbopol 934 hydrated in each medium.

surface energy data obtained on both dry and hydrated carbopol samples (as described above). The values in Table 7 for Carbopol 934 dry are higher than those calculated for the hydrated polymer.

The lowest values for the hydrated Carbopol

934 were found using saline or gastric fluid as a test medium. Negative values of  $\Delta G_{132}^{\text{TOT}}$  according to Van Oss et al. (1988) are expected to result in a net attraction between compounds 1 and 2 immersed in a liquid 3. Based on the apolar (LW) interactions and on the  $\Delta G_{132}^{\text{LW}}$  calculations a net

Table 5

Mean contact angle data for Carbopol 934 hydrated in (a) artificial gastric fluid and saline on Teflon and PMMA with the surface tension against glass and (b) intestinal fluid on water, diiodomethane and glycerol

Sample	pH	Polymer % (w/v)	$\gamma^{\text{TOT}}$ glass ( $\text{mJ m}^{-2}$ )	Cos $\theta$ (teflon)	Cos $\theta$ (PMMA)
(a) Carbopol 934	1.2	1	$48.03 \pm 3.2$	$-0.55 \pm 0.06$	$0.41 \pm 0.02$
Carbopol 934	6.4	1.5	$46.95 \pm 3.7$	$-0.55 \pm 0.05$	$0.42 \pm 0.03$
			Cos $\theta$ (water)	Cos $\theta$ (diiodomethane)	Cos $\theta$ (glycerol)
(b) Carbopol 934	7.5	6	$0.86 \pm 0.02$	$0.49 \pm 0.02$	$0.92 \pm 0.03$

Table 6

Single components of the surface parameters of mucin, polymer (dry and hydrated), and test media

Sample	pH	$\gamma^{\text{TOT}}$ ( $\text{mJ m}^{-2}$ )	$\gamma^{\text{LW}}$ ( $\text{mJ m}^{-2}$ )	$\gamma^{\text{AB}}$ ( $\text{mJ m}^{-2}$ )	$\gamma^+$ ( $\text{mJ m}^{-2}$ )	$\gamma$ ( $\text{mJ m}^{-2}$ )
Mucin	–	46.2	6.92	39.28	49.17	7.84
Gastric fluid	1.2	56.4	17.09	39.35	44.95	8.61
Saline	6.4	71.1	33.72	37.97	27.36	13.18
Intestinal fluid	7.5	66.8	32.66	34.14	38.2	7.63
Carbopol 934 (dry)	–	40.3	38.89	1.428	7.997	0.06
Carbopol 934 (hydrated)	1.2	48.0	6.33	41.67	42.72	10.16
Carbopol 934 (hydrated)	6.4	46.9	5.98	40.97	42.26	9.93
Carbopol 934 (hydrated)	7.5	63.7	32.63	31.09	21.12	11.45

Table 7

Total free energy of interaction between the three phases, apolar and polar components contributing for Carbopol 934 dry and hydrated

Sample	pH	$\Delta G_{132}^{\text{AB}}$ ( $\text{mJ m}^{-2}$ )	$\Delta G_{132}^{\text{LW}}$ ( $\text{mJ m}^{-2}$ )	$\Delta G_{132}^{\text{TOT}}$ ( $\text{mJ m}^{-2}$ )
Carbopol 934 (dry)	1.2	0.56	6.16	6.72
	6.4	8	2.74	10.74
	7.5	4.38	3.26	7.64
Carbopol 934 (hydrated)	1.2	9.87	–4.85	–5.02
	6.4	3.78	–21.43	–17.65
	7.5	–0.94	0	–0.94

Table 8

Interfacial tension values between Carbopol 934 hydrated in different media and mucin

System	$\gamma_{12}^{\text{LW}}$ ( $\text{mJ m}^{-2}$ )	$\gamma_{12}^{\text{AB}}$ ( $\text{mJ m}^{-2}$ )	$\gamma_{12}^{\text{TOT}}$ ( $\text{mJ m}^{-2}$ )
Carbopol (pH 1.2)-mucin	0.012	–0.37	–0.36
Carbopol (pH 6.4)-mucin	0.036	–0.36	–0.32
Carbopol (pH 7.5)-mucin	9.49	–2.79	6.7

Table 9

Mean force of detachment values recorded after 1, 5 and 10 min of contact time between polymer and mucin in different media

Sample	pH	Force (mg)		
		After 1 min	After 5 min	After 10 min
Carbopol 934	1.2	7451 ± 1094	16505 ± 1194	14809 ± 2476
Carbopol 934	6.4	5723 ± 167	19627 ± 1817	16697 ± 2851
Carbopol 934	7.5	5759 ± 1131	10190 ± 778	6793 ± 928

attraction can also be predicted for the systems Carbopol(hydr.)-mucin-saline and Carbopol(hydr.)-mucin-gastric fluid as the conditions  $\gamma_1^{LW} \neq \gamma_2^{LW}$  and  $\gamma_1^{LW} > \gamma_3^{LW} > \gamma_2^{LW}$  are not respected.

Similarly, the interfacial tension ( $\gamma_{12}$ ) between Carbopol 934 and mucin in different media can be calculated from the surface tension parameters (Van Oss et al., 1988) (Table 8, Eq. 6). The lowest values for  $\gamma_{12}^{TOT}$  were found for the system Carbopol-mucin by using the surface parameters concerning the polymer hydrated in gastric fluid and in saline. Thus a good affinity between these two surfaces should be expected, where the high value for the interfacial tension between mucin and the polymer hydrated in intestinal fluid is indicative of a decreased affinity of the two surfaces.

### 3.2. Mucoadhesion

#### 3.2.1. Influence of pH and contact time

The results concerning the mucoadhesion experiments are shown in Table 9 and in Fig. 2. After 1 min of contact time the highest force of detachment was found in artificial gastric fluid (pH 1.2). For  $\text{pH} > \text{p}K_a$  (4.75 for Carbopol 934) both polymer and mucin are highly ionized, above pH 5 negative charge repulsion is considerably increased in the polymer-mucin interaction. By increasing the contact time from 1 to 5 min, the role of polymer hydration becomes more important than the charge sign (Leung and Robinson, 1988). All the force of detachment results recorded after a 5 min contact time were higher than those after 1 min. After 5 min contact the highest force of detachment was obtained when saline was the surrounding fluid. The mucoadhe-

sion profile is almost the same as the 5 min data when the contact time is increased up to 10 min.

The mucoadhesive performance seems to follow the characteristic hydration profile of the polymer of the acrylic acid. In fact in acid conditions up to pH 4 the swelling of the polymer is slight, swelling is more significant between pH 4 and pH 5 and continues to increase at pH 6 and pH 7 whereas it reduces at more alkaline levels (Ch'ng et al., 1985).

#### 3.2.2. Surface free energy and mucoadhesion

In Fig. 3 and 4 the force of detachment after 1 and 5 min of contact time is plotted as a function of the total free energy of the system calculated using the value for the dry and hydrated polymer respectively. Correlations exist between the force of detachment (mucoadhesion) and the calculated free energy of interaction (the higher the force of detachment the lower the  $\Delta G_{132}^{TOT}$ ). It can be seen that the use of surface energy values

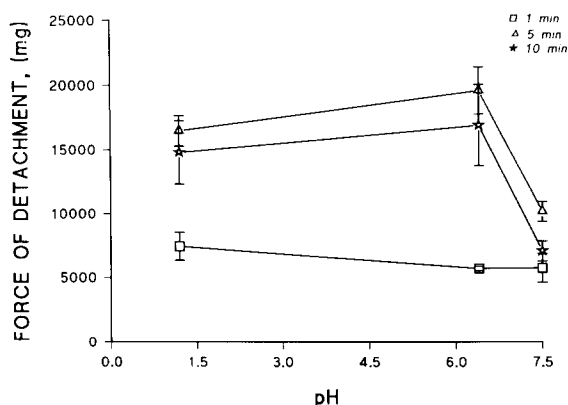


Fig. 2. Mucoadhesion of Carbopol 934 after different contact times as a function of pH.

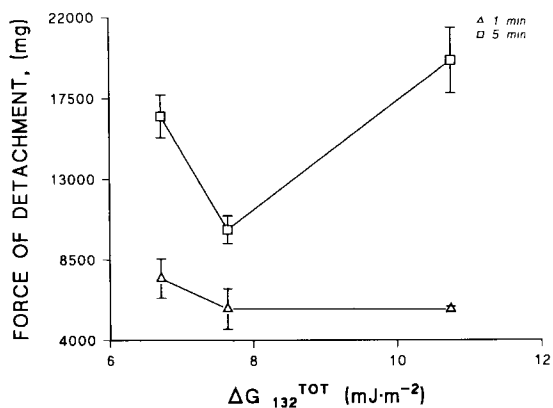


Fig. 3. Total free energy of adhesion between Carbopol 934 (measured in the dry state) and mucin, in the presence of each of the different fluids, as a function of force of detachment after different contact times.

calculated on the dry polymer seem to provide the best correlation for 1 min contact time, whilst the surface energy terms calculated for the hydrated polymer provide a better correlation for mucoadhesive strength after 5 min contact (Fig. 3 and 4 respectively). This is a logical observation, given that the hydration of the carbopol is not instantaneous, and implies that the changing surface energy of the carbopol during hydration has an influence on the mucoadhesive behaviour. A similar conclusion can be made from Fig. 5 and 6,

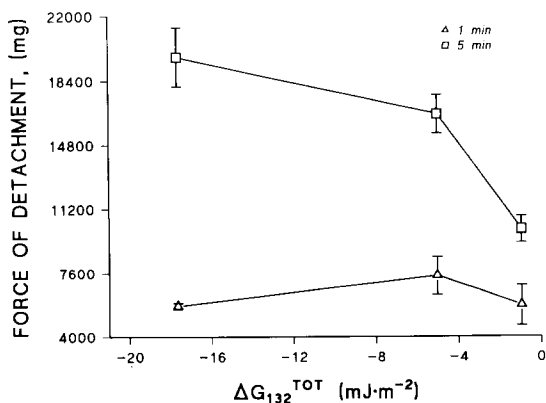


Fig. 4. Total free energy of adhesion between Carbopol 934 (measured in the hydrated state) and mucin, in the presence of each of the different fluids, as a function of force of detachment after different contact times.

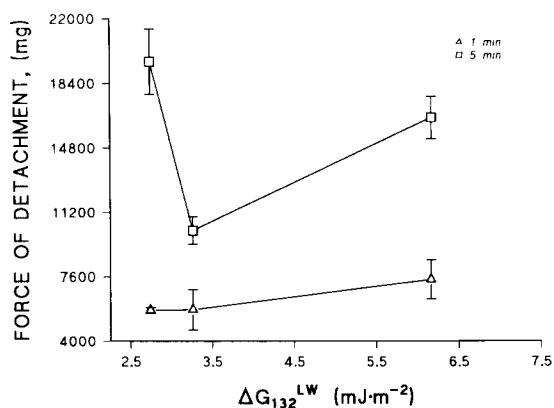


Fig. 5. Apolar free energy of Carbopol (dry state) as a function of the force of detachment from the mucin gel, after different contact times.

where the apolar contribution to the interaction is considered ( $\Delta G_{132}^{LW}$ ).

No simple correlation was found between  $\Delta G^{AB}$  and the mucoadhesive performance. It is stated that polar materials will never form strong adhesive joints with non-polar materials (e.g., Lehr et al., 1992). Mucin is predominantly polar under all pH conditions encountered, however, the polarity of Carbopol is seen to change in the different environments. By describing the solid surface by the fractional polarity ( $P = \gamma^{AB} / \gamma^{TOT}$ ) using the values reported in Table 6, the decrease in mucoadhesion found in intestinal fluid can be correlated with the decrease of polarity of Carbopol 934 (see Table 10). As shown by the  $P$  data in Table 10 the force of detachment is high (good mucoadhesion) when both mucin and polymer are characterized by similar polarities.

The change in polarity of Carbopol with the pH is mainly due to a significant decrease in the value of  $\gamma^+$ . In intestinal fluid the  $\gamma^+$  component

Table 10  
Contrast in terms of fractional polarity between polymer hydrated in different media and mucin

Medium	$P(\gamma^{AB} / \gamma^{TOT})$	
	Carbopol	Mucin
Saline	0.87	0.85
Gastric fluid	0.87	0.85
Intestinal fluid	0.49	0.85



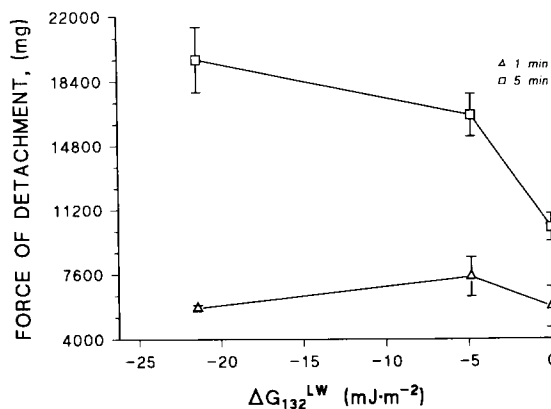


Fig. 6. Apolar free energy of Carbopol (hydrated state) as a function of the force of detachment from the mucin gel, after different contact times.

of the apolar surface tension is less than twice (1.8) the  $\gamma^-$  while in gastric fluid and in saline  $\gamma^+$  is 4 times larger than  $\gamma^-$ . In pH 7.5 the polar and apolar characteristics of the polymer are similar whereas in pH 1.2 and 6.4 the polymer is predominantly polar (see Fig. 7). Mucin, on the other hand, maintains its polar characteristics in all the media, thus the polar-polar affinity in the mucin-carbopol interaction is respected only for the low pH.

The force of detachment decreases as  $\gamma^-$  for the carbopol increases (Fig. 8). There is less of a correlation between the force of detachment and  $\gamma^+$  and  $\gamma^{AB}$  for the carbopol in different media, even though the polarity seems important in the mucoadhesion process (Table 10).

### 3.3. General discussion

As this work is being used to probe the principles of mucoadhesion, and especially the role of underlying interfacial phenomena, the choice of mucin as a model (and the question of how good a model for mucous covered tissue mucin gel is) is not a significant issue. It can be assumed that any other surface can be tested for surface energy and used in the same way as has that reported here for the mucin gel.

The use of the acid-base approach to surface energy analysis provides a good insight into the mucoadhesion process. Not only are there corre-

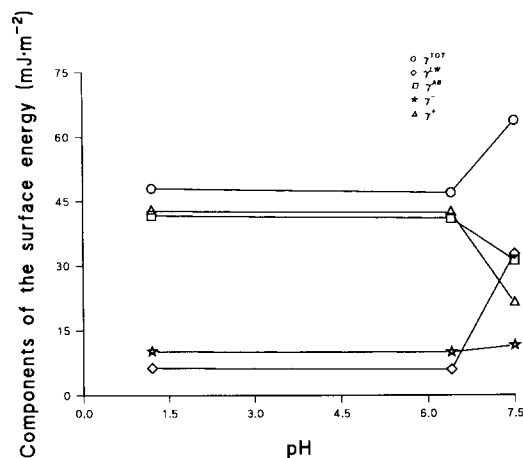


Fig. 7. Variation in surface energy terms of Carbopol 934 as a function of pH.

lations between predicted interfacial interactions and the measured mucoadhesion behaviour, but also the reasons for these correlations can be identified. It is notable that the carbopol shows changes in surface energy as it is hydrated. These changes on hydration correlate with the difference between the mucoadhesion after 1 and 5 or 10 min contact time. This can be taken to imply that the interpenetration mechanism that is described for long contact times has an interfacial energy driving mechanism. This driving mechanism relates to the interaction between the mucin

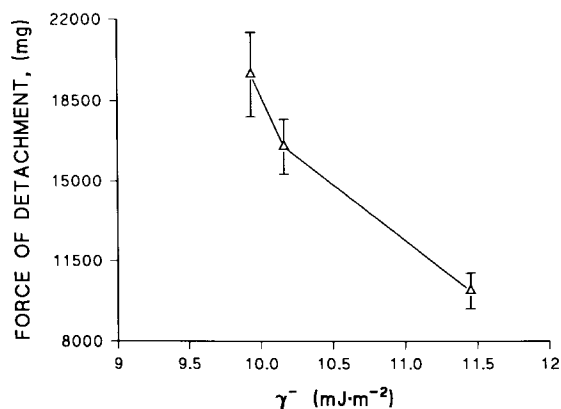


Fig. 8. Force of detachment from the mucin gel after 5 min contact as a function of the  $\gamma^-$  component of the surface energy of Carbopol, at each pH.

and the hydrated polymer in the presence of the physiological fluid in the mucoadhesive region.

The carbopol has different surface energies, whilst the mucin remains largely unchanged, in fluids of different pH. These relative changes in surface energy correlate well with the observed changes in mucoadhesive behaviour in different model media.

Interfacial models of mucoadhesion, especially those using the acid-base interaction principle appear to be a valuable tool in studies of these complex interaction processes.

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