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A Surface Energy Analysis of Mucoadhesion: Contact Angle Measurements on Polycarbophil and Pig Intestinal Mucosa in Physiologically Relevant Fluids

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The possible role of surface energy thermodynamics in mucoadhesion was investigated with Polycarbophil and pig intestinal mucosa. In separate experiments, the surface energy parameters of the substrate (mucosa) and the adhesive (polymer film) were determined by contact angle measurements on captive air/octane bubbles in three physiologically relevant test fluids (isotonic saline, artificial gastric fluid, and artificial intestinal fluid). Whereas the swollen Polycarbophil films were relatively hydrophilic as indicated by small water contact angles (22, 23, and 16°), the water contact angles measured on mucosal tissue were significantly larger (61, 48, and 57°). Hence, mucus was found to possess an appreciable hydrophobicity. The measured adhesive performance (force of detachment) between Polycarbophil and pig small intestinal mucosa was highest in nonbuffered saline medium, intermediate in gastric fluid, and minimal in intestinal fluid. In agreement with this trend, the mismatch in surface polarities between substrate and adhesive, calculated from the contact angle data, increased in the same order.

KEY WORDS: captive bubble technique; contact angles; mucoadhesion; mucus; Polycarbophil; surface free energy.

INTRODUCTION

In recent years, various natural and synthetic polymers have been found to possess mucoadhesive properties desirable for the development of bioadhesive drug delivery systems for various routes of application (1). Apart from a better understanding of relevant physiological factors and adequate formulation of such dosage forms, there is a need to improve the intrinsic mucoadhesive properties of those polymers. However, the search for better mucoadhesives has been empirical as the mechanisms of mucoadhesion are not yet understood.

Peppas and Buri (2) reviewed the existing theories to interpret the interaction between polymeric materials and mucosal tissue surfaces. These theories include the adsorption, wetting, diffusion, and fracture theory. Especially the latter two were found to be helpful for a more theoretical analysis of some experimental results (3). However, from adhesion phenomena throughout other fields of application, it is known that no universal theory exists and, further, that the surface properties of the materials involved are important (4–6).

The role of surface energies and wetting for mucoadhesion has already been recognized from a theoretical point of view (2), but experimental proof was lacking. Research on "biomaterials" has recognized these factors early (7). Meanwhile, a growing theoretical and experimental framework proved to be useful in other cases of bioadhesion, such as the adhesion of bacteria to tooth surfaces (8).

Recently, film coating with the mucoadhesive polymer Polycarbophil was found to increase the mean residence time of microspheres in an *in situ*-perfused intestinal loop in the rat (9). Therefore, the adhesion between hydrogels of Polycarbophil and small intestinal mucosa was chosen as a specific example of mucoadhesion in this study. In particular, we investigated to what extent the known pH dependence of the bond strength in this system can be explained by changes in the hydrophilicity or hydrophobicity of the two surfaces involved.

THEORETICAL: CONTACT ANGLE MEASUREMENT OF HYDROGELS

Contact angle measurements provide an appropriate methods to characterize the hydrophilicity/hydrophobicity of solid surfaces. In the case of tissue or polymer surfaces relevant for mucoadhesion, however, particular experimental difficulties are met, since both are hydrogels. These are (i) the mucus as a natural hydrogel of macromolecular glycoproteins and (ii) the mucoadhesive hydrogels which are formed when polymers take up water from the body liquids. It is important to note that, for gastrointestinal application of a bioadhesive drug delivery system (BDDS), the system will probably reach its place of adhesion in a completely swollen state—unless swelling is controlled by further technological measures. This constitutes an important difference from other routes of application (e.g., buccal, nasal, etc.), where the BDDS may be administered as a dry tablet, film, or powder and, furthermore, can be applied by the patient with a certain mechanical pressure. The capillary attraction forces can be considerable when water from the space between polymer and mucosa is taken up by such a dry system. This particular case of "dry" mucoadhesion is not considered here and should be strictly separated from spontaneous "wet" adhesion of already swollen polymers.

Liquid contact angles as measured on dry polymers are difficult to interpret, since they do not reflect an equilibrium state. Contact angle measurements on prehydrated hydrogels in a humid atmosphere of water saturated vapor do not seem to be appropriate either as, from the work of Holly and Refojo (10), it is known that hydrogels are able to adapt their surface properties to the actual environment. This means that the surface properties of a give hydrogel as characterized in an air environment would be different from the surface properties of the same hydrogel in equilibrium with an aqueous environment.

Contact angle experiments with hydrogels being completely immersed and equilibrated with water have been described by Andrade *et al.* (11). They measured contact angles on captive air and octane bubbles according to a method

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originally devised by Hamilton (12). This technique allows determination of the dispersive $\gamma_S{}^d$ and polar $\gamma_S{}^p$ components of the solid surface energy γ_S for hydrophilic surfaces such as swollen hydrogels in equilibrium with an aqueous environment. The essential experimental setup is depicted in Fig. 1.

In separate experiments, a small bubble or droplet of air and *n*-octane, respectively, is "snapped" from a microsyringe onto the down-facing surface of the hydrogel being investigated. The hydrogel itself is completely immersed and equilibrated with an aqueous test medium. The contact angles measured on the air bubbles are considered as water contact angles θ_W at an hydrogel–air interface (i.e., θ_W is usually less than 90°). The contact angles measured on the *n*-octane droplets are considered as octane contact-angles θ_O at a hydrogel–water interface (i.e., θ_O is usually greater than 90°). The two types of contact angles are also shown in Fig. 2.

For a captive air bubble at the gel–water interface, Young's equation can be applied immediately:

$$\gamma_{SV} - \gamma_{SW} = \gamma_{WV}\cos\theta_W \qquad (1)$$

with the subscripts S, V, and W referring to "solid," "vapor," and "water." For a drop of *n*-octane at a solid–water interface the relation becomes

$$\gamma_{SW} - \gamma_{SO} = \gamma_{OW}\cos\theta_O \qquad (2)$$

According to the original concept of Fowkes (13) and its later refinements by Owens and Wendt (14), the interfacial free energy γ between two phases *i* and *j* can be calculated from the dispersive components γ^d and the polar components γ^p of their respective surface free energies by the so-called geometric mean equation:

$$\gamma_{ij} = \gamma_i + \gamma_j - 2(\gamma_i^d\gamma_j^d)^{0.5} - 2(\gamma_i^p\gamma_j^p)^{0.5} \qquad (3)$$

Under certain assumptions discussed below, this approach can be transferred to the situation at a gel–water or a gel–octane interface, by writing

$$\gamma_{SO} \simeq \gamma_{SV} + \gamma_{OV} - 2(\gamma_{SV}^d\gamma_{OV}^d)^{0.5} - 2(\gamma_{SV}^p\gamma_{OV}^p)^{0.5} \qquad (4)$$
$$\gamma_{SW} \simeq \gamma_{SV} + \gamma_{WV} - 2(\gamma_{SV}^d\gamma_{WV}^d)^{0.5} - 2(\gamma_{SV}^p\gamma_{WV}^p)^{0.5} \qquad (5)$$

In these equations, the values for γ_{WV} and γ_{OV} are known, as well as their respective dispersive and polar components. At 25°C, for water γ_{WV} = 72.1 mN/m with $\gamma_{WV}{}^d$ = 21.6 mN/m and $\gamma_{WV}{}^p$ = 50.5 mN/m (11). For octane $\gamma_{OV} = \gamma_{OV}{}^d$ = 21.6 mN/m and $\gamma_{OV}{}^p$ = 0 mN/m, as octane is nonpolar. Remarkably, the numerical values of $\gamma_{WV}{}^d$ and $\gamma_{OV}{}^d$ are identical. Using these values, (4) can be subtracted from (5) and substituted into (2), yielding

$$\gamma_{OW}\cos\theta_O \simeq 50.5 - 2(50.5\gamma_{SV}^p) \qquad (6)$$

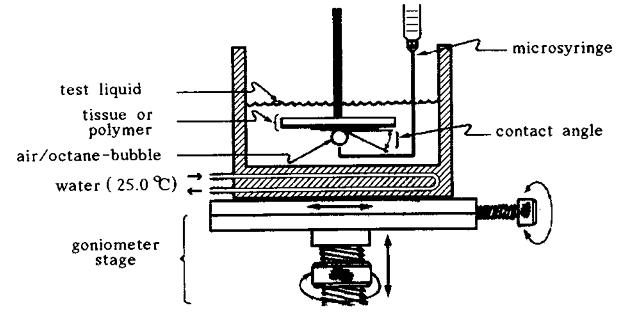

Fig. 1. Experimental setup to characterize hydrogel surfaces in water by the captive bubble technique. Adapted from Andrade *et al.* (11).

Fig. 2. Schematic drawing, indicating contact angle measurements on a hydrogel (e.g. mucosa or polymer) using either an octane drop or an air bubble, in an aqueous medium. The surfaces of interest are facing downward.

The interfacial free energy between octane and water can also be calculated using the geometric mean equation γ_{OW} = 50.5 mN/m, which is in good agreement with reported values from direct measurements [50.8 mN/m at 20°C (15)]. Hence, $\gamma_{SV}{}^p$ is directly obtained from the octane experiment to be

$$\gamma_{SV}^p \simeq \frac{50.5}{4}(1 - \cos\theta_O)^2 \qquad (7)$$

in order to calculate $\gamma_{sv}{}^d$, Eq. (5) is rearranged and substituted with (1) yielding

$$\gamma_{SV}^d \simeq \left[\frac{72.1(1 + \cos\theta_W) - 2(50.5\gamma_{SV}^p)^{0.5}}{9.3}\right]^2 \qquad (8)$$

Equations (7) and (8) have been used to calculate the solid surface energy parameters in the experiments described below.

The approximation in Eqs. (4) and (5) and the use of Young's equation without further corrections are based on the following assumptions (11):

(1) The surface free energy of water-saturated octane is the same as that of pure octane, which seems acceptable because octane mixes with water only in the parts per million range.

(2) There is no relevant difference between the surface free energy of the solid in vacuum γ_S and in saturated vapor γ_{SV}. This assumption means that the surface free energy of the solid is not reduced by adsorbed vapor of the liquid. This is acceptable for a water-saturated hydrogel surface with respect to water and the nonmiscible octane as well. Moreover, a water-saturated hydrogel surface in vacuum would be physically meaningless.

(3) The contact angle induced deformation of the gel-water interface is neglected. Andrade *et al.* (11) showed that the error as a result of this phenomenon will not exceed 3° as long as the measured contact angles are larger than 15°. This has been confirmed experimentally by Yuk and Jhon (16). As we shall see, an error of 3° is negligible indeed in view of the limited accuracy of contact angle measurements on such irregular surfaces as mucosa tissue or swollen polymer films.

(4) The surface free energy of the aqueous test medium is assumed to be the same as that of pure water. To

check this, control measurements have to be performed.

(5) No corrections are made for effects because of surface roughness. Although especially biological surfaces form difficult substrates for contact angle measurements, the magnification of the goniometer microscope allows correction for macroscopic irregularities using the rotating cross-hairs or by tilting the substrate holder. A quantitative treatment of microirregularities is not straightforward, as it requires additional data for surface roughness, which, again, is a particular problem in the case of hydrogels. Nonetheless, the macro contact angles provide valuable quantitative information as long as they can be measured reproducibly.

MATERIALS AND METHODS

Materials Used

Polycarbophil (Carbopol EX-55 resin) has been obtained as a gift from BF Goodrich, Cleveland, Ohio.

Pig intestinal tissue was received from various Dutch research institutions. Good state of health of the animals was confirmed. Usually, a 10- to 20-cm-long piece from the upper part of the small intestines was removed immediately after slaughtering and transported in previously oxygenated Krebs–Ringer buffer. At the laboratory, the tissue was stored until use at 5°C without further oxygenation. Tissue was always used within 2 days.

N-Octane (purity, 99+%) was purchased from Aldrich Chemicals. Isotonic saline, artificial gastric, and intestinal fluids were prepared from bidistilled water according to the respective monographs in the United States-Pharmacopoeia, Ed. XXII, but without adding any enzymes. The pH was 6.6–7.0 for saline, 1.2–1.4 for gastric fluid, and 7.4–7.5 for intestinal fluid.

Preparation of Polymer Films and Measurement of Mucoadhesive Performance

A detailed description of the procedure and apparatus is given elsewhere (9). Briefly, glass coverslips (22 × 22 mm) were coated with Polycarbophil by pipetting an aliquot of 0.300 ml of a 1% methanolic dispersion upon their surface and drying on air. The force of detachment F per unit surface area of pig intestinal mucosa was measured using a modified DuNouy tensiometer. As a standard procedure, both polymer and mucosa were preequilibrated with the test medium at 37°C for 5 min; thereafter they were brought in contact with very slight pressure ($\sim$10 mN/cm^2) and kept in this position for 1 min more.

Contact Angle Measurements

Contact angles were measured using a NRL contact-angle goniometer, Model 100-00 (Ramé-Hart, Mountain Lakes, VA) equipped with an environmental chamber (Model 100-07). After rinsing several times with water, methanol, and bidistilled water, the environmental chamber was mounted on the goniometer stage and filled with the test liquid. Temperature was kept constant at 25 ± 0.5°C, because at this temperature the concise numerical values for the surface free energy of octane and water were known from literature.

Polymer-coated cover glasses were stuck onto the lower side of a Delrin support using a minimum amount of silicone grease. The support was then suspended into the test liquid and equilibrated for at least 5 min. Mucosa samples were mounted in the same way by gluing them onto cover glasses using "Rapid Kleber" (Henkel, FR Germany). Serosa and muscularis layer had been previously stripped away in order to obtain a relatively flat surface. Soluble mucus was removed by washing several times in fresh isotonic saline immediately before gluing.

Octane droplets of approximately 10 μl or air bubbles of about the same size were "snapped" against the hydrogel surface. Several droplets or bubbles were measured per each hydrogel specimen. If possible, two contact angles (left and right) were measured per droplet or bubble. Sometimes, however, the contact points were not clearly distinguishable due to irregularities of the surfaces or "flocks" of mucus.

Surface Free Energy of Test Media

In order to detect significant deviations in the surface free energy of the aqueous test media from that of pure water, a glass stalagmometer (Tamson BV, The Netherlands) was used. A small aliquot of the test medium was aspirated before and after the contact angle measurements directly from the environmental chamber. Hence measurements could be done with a minimum effort and risk of contamination. In addition, we found this method more reproducible than expensive tensiometer instruments, especially in the presence of small impurities. This might be due to the fact that every stalagmometer measurement represents an average of approximately 50 single droplets.

RESULTS AND DISCUSSION

Validation of the Contact Angle Measurements

As discussed above, the validity of the numerical calculation of surface energy parameters from the contact angle data on captive air and octane bubbles strongly depends on the surface free energy of the test liquid, which should be the same as for pure water. In order to check this, surface free energies of the test media were compared before and after each series of measurements with that of bidistilled water using the stalagmometer method. The stalagmometer used reproducibly yielded 54 droplets when filled with bidistilled water as reference. Hence, an increase in that number by one droplet would indicate a reduction in surface free energy due to impurities by approximately 2%, which was considered to provide a sufficient detection limit.

In no case, however, was the number of droplets increased by more than one or two in repeated measurements. This indicates that neither the addition of buffering salts nor possible contaminations during the preparations nor the use of octane and the silicone grease led to dramatic changes in the surface free energy of the test media in comparison to pure water. Nonetheless, the test liquid was renewed after each third tissue specimen. Mikos and Peppas (17) reported a decrease in surface free energy of an aqueous buffer at 37°C from 69.72 to 44.79 mN/m after the addition of 1% (M/V) porcine stomach mucin. These concentrations, however, could hardly be achieved even when the total amount of mucus covering a tissue specimen had been dissolved in the volume of the environmental chamber (approximately 150 ml). Assuming a mucus thickness of 100 μm and a tissue surface of approximately 2 cm^2, the volume of the covering mucus gel is only 20 μl but, again, consists for only about 1–5% of mucin. More recent measurements performed by Baszkin *et al.* (18) also confirmed that the addition of 0.5% (m/v) of bovine submaxillary mucin to water leads only to a very slight and slow decrease in the liquid surface free energy. In summary, the surface free energies of the test media used in this study differed from that of pure water by less than 5%.

The measurement of contact angles by fitting the tangent "by eye" on a droplet is of limited accuracy. However, in contrast to the so-called height-basis method, which allows the calculation of contact angles from measurements on size and shape of the droplets, the former method has the advantage of being independent of the droplet volume and aberrations from the ideal spherical shape. This, however, appeared to be practically unavoidable, especially for air bubbles.

As reported by Neumann and Good (19), trained observers can achieve an accuracy of better than 0.5° on flat, smooth surfaces. Hydrogel surfaces and, especially, mucosa specimens are more difficult to measure, apart from possible "physical" errors due to surface roughness and contact angle deformation. However, when a sufficient number of measurements is performed, the standard deviations were small enough to demonstrate statistically significant effects. In order to confirm the validity of the measurements by independent observers, colleagues working at the same laboratory were asked to measure contact angles on various bubbles and substrates. Eighteen control measurements performed by three different individuals yielded an averaged interindividual error of 2.5° with a maximum of 7°.

Contact Angles in Different Test Media

The contact angle data as measured on Polycarbophil films and mucosa specimens are shown in Fig. 3, each bar representing the mean + standard deviation of $n = 36$–49 readings on 18 droplets/bubbles and 6 mucosa/polymer samples for each case. Obviously, surface properties of both mucosa and polymer films change under the influence of the different test media as indicated by significantly different contact angles (Wilcoxon *U* test).

For poly(acrylic acid) gels, it is known that raising the pH above its pK_a (≈ 4.5) induces increased swelling. When a Polycarbophil film was equilibrated with artificial intestinal fluid buffered at pH 7.5, the water contact angle γ_W was decreased in comparison to both the nonbuffered saline medium and the artificial gastric fluid of pH 1.2. Analogously, the octane angle γ_O was increased. In the pH 7.5 medium the gel appeared to be more hydrophilic and the interfacial free energy of the gel–water interface was reduced, probably due to the pH-dependent dissociation of the COOH groups in the polymer. There was no difference, however, between the contact angles as measured in the acidic buffer and the nonbuffered saline medium. In both media, water contact angles were larger than in the pH 7.5 medium, and the octane contact angles were smaller. Obviously, at pH values lower or equal to the pK_a of the polymer, the COOH groups are not completely ionized and hence keep the gel more hydrophobic. Although a bulk pH of approximately 7 was measured in the saline medium, it can be assumed that in the absence of any other buffering salts, the activity of H_3O^+ ions within the hydrogel and at its gel–water interface is controlled primarily by the weak poly acids of the polymer. This explains the reduced hydrophilicity of the gel–water interface in the nonbuffered saline medium in comparison to the pH 7.5 buffer.

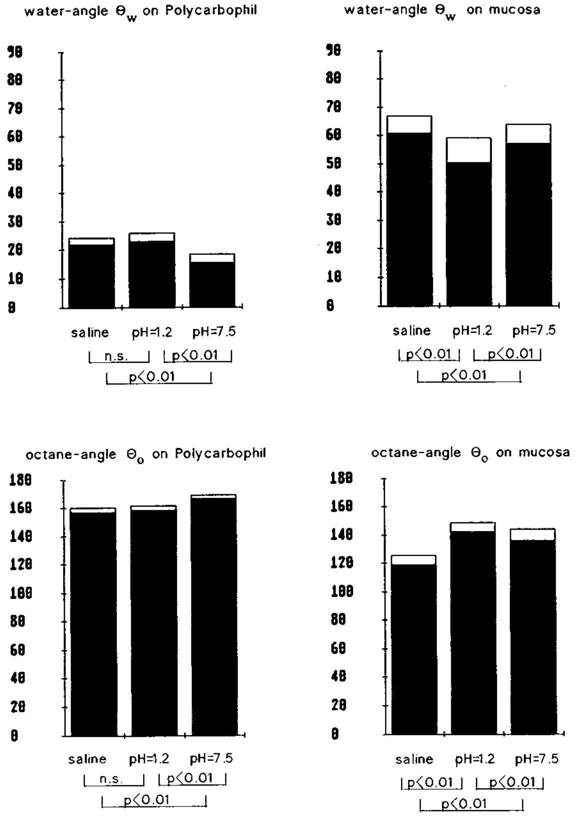

Fig. 3. Results of contact angle measurements. Each bar represents the mean + SD of 36–49 readings. Significance is indicated according to Wilcoxon's *U* test. N.S., not significant.

Compared with Polycarbophil films, the mucus gel surface showed an appreciable hydrophobicity in all three media as indicated by the larger water contact angles. Although the observed contact angles are surprisingly large for such a highly hydrated hydrogel as mucus, this relative hydrophobicity is in good agreement with recent findings of other investigators. Hills *et al.* (20) reported contact angle measurements of saline droplets on dried gastrointestinal mucosa specimens from dogs. They found the highest values for gastric mucosa (50–80°), intermediate values for esophagus and colon (25–35°), and only very small contact angles (<5°) for the duodenum. Spychal *et al.* (21) performed similar experiments on human mucosal biopsies. Their reported water contact angles for stomach, duodenum, and rectum as measured by the sessile drop method on dried tissue in air were comparable with our values for small intestinal mucosa as measured by the captive bubble technique on native tissue in saline.

Surface Free Energy and Mucoadhesion

The dispersive and polar components of both mucosal and Polycarbophil gel surface free energies were calculated from the contact angle data as described in the theoretical section for the three test media, respectively, and are shown in Table I.

The last column in Table I shows the mucoadhesive performance (force of detachment F) of this system in the test medium concerned. The indicated values represent the mean ± SE of $n = 6$–21 measurements. It can be seen that the mucoadhesive bond is the strongest in the nonbuffered saline medium, intermediate in the acidic gastric fluid, and weakest in the neutral buffered intestinal fluid. The pH dependency of the mucoadhesive Polycarbophil has already been investigated earlier by Park and Robinson (22). They explained the decreased bond strength at higher pH values by the increased swelling of the ionized poly(acrylic acid) gel, and consequently its reduced mechanical strength.

Based on the structural similarities between mucus and cross-linked poly(acrylic acid), Leung and Robinson (23,24) discussed four possible mechanisms for the mucoadhesive interaction: (i) electrostatic interactions, (ii) hydrogen bonding, (iii) hydrophobic interactions, and (iv) interdiffusion (interpenetration). In agreement with earlier work of Smart *et al.* (25) and Ponchel *et al.* (3), they concluded that interpenetration should be the prime mechanism of mucoadhesion and all molecular features of a candidate polymer favoring the entanglement with mucus (e.g., flexible chains, expanded network structure, secondary interactions), hence should increase its mucoadhesiveness. Although the occurrence of interpenetration is accepted as a mechanism for adhesion between polymers, it is questionable whether it is the predominant process relevant for the formation of the mucoadhesive interface. In the beginning of our experiments with mucoadhesives of the poly(acrylic acid) type, we frequently observed the almost ubiquitous sticking properties of these polymers even in the hydrated state. The tenacious adherence of polycarbophil-coated microspheres to various surfaces, such as glass or different plastics, not only led to practical problems, but also raised the question of how these adhesion phenomena of the same mucoadhesive polymers on completely different substrates could be explained in terms of the existing theories about mucoadhesion. In addition, Forget *et al.* (26) published a method to characterize muco(!)adhesive properties of candidate polymers by measuring their bond strength on stainless steel grids. Interestingly, the tensile stress necessary to detach tablets containing poly(acrylic acid) from such an inert model substrate was of the same scale as data reported by Ponchel *et al.* (3) for adhesion of similar tablets on mucosal tissue. It seems difficult to accept interpenetration as the common basic mechanism of all these adhesion phenomena involving flat and inert substrates as well.

Table I. Surface Free Energy γ_s(mN/m) of Pig Intestinal Mucosa and Polycarbophil Gels as well as Their Dispersive $\gamma_s{}^d$(mN/m) and Polar $\gamma_s{}^p$(mN/m) Components as Calculated from the Contact Angle Data[a]

Medium	$\gamma_s{}^d$	$\gamma_s{}^p$	γ_s	P	ΔP	F
Saline (not buffered)						
Mucosa	12	28	40	0.70	0.01	17.6 ± 1.3
Polycarbophil	21	46	67	0.69		
Gastric fluid, pH = 1.2						
Mucosa	9	41	50	0.80	0.10	13.5 ± 1.6
Polycarbophil	20	47	67	0.70		
Intestinal fluid, pH = 7.5						
Mucosa	7	37	44	0.84	0.14	8.0 ± 1.4
Polycarbophil	21	49	70	0.70		

[a] P is the fractional polarity $\gamma_s{}^p/\gamma_s$, ΔP its difference between mucosa and Polycarbophil in the medium concerned, and F(mN/cm^2) the force of detachment for the mucoadhesive bond as measured in the same medium.

In contrast to interpenetration, free surface energies and spreading coefficients are general thermodynamic parameters for adhesion, irrespective of the chemical nature of the adhesive or the substrate. Analogous to Arrhenius' *simile* principle, de Bruyne (1939) stated the simple rule that polar/nonpolar pairs will never form strong adhesive joints (27). The polarity of a solid surface can be described by the fractional polarity P, which is given by the ratio $\gamma_S{}^p/\gamma_S$. The corresponding values for mucosa and Polycarbophil have been calculated in Table I. It is striking that the decrease in adhesive performance in terms of the measured force of detachment between the tissue and the polymer is parallel with an increasing mismatch between the fractional polarities of the respective substrate and adhesion in response to the aqueous test medium. As a more quantitative criterium to predict adhesion between two polymers from their surface energies, Wu (27) has proposed a so-called interaction parameter. In mucoadhesion, however, the interrelations are more complex, as the interstitial third phase is an aqueous medium rather than air. A quantitative treatment of this problem would be beyond the scope of this article. At least in a qualitative sense, however, the data presented here are suited to support the hypothesis that, besides molecular interactions between the two hydrogel phases involved in mucoadhesion, the thermodynamic balance of surface free energies also plays an important role. In order to avoid possible misunderstandings, we should like to note that these findings in no way exclude the occurrence of interpenetration. Our results rather support the model presented earlier by Boddé (28). Herein mucoadhesion is understood as a two-step process, in which the first adsorptive contact is governed primarily by surface energy effects and spreading processes. In a later phase of mucoadhesion, polymer chains might interdiffuse across the interface and hence enhance the final bond.

CONCLUSIONS

In this study, the surface properties of pig intestinal mucosa and films of Polycarbophil have been studied in different physiologically relevant fluids. The applied captive bubble technique permitted the quantitative determination of surface energy parameters of such hydrogel surfaces without the need to remove surface water. Hence, the hydrogel–water interface could be studied in equilibrium with the interstitial medium concerned.

The fractional polarity of both the swollen Polycarbophil films and those of pig small intestinal mucus gel changed in response to the pH or the buffer capacity of the test fluids. In contrast to the hydrophilic polymer films, intestinal mucus possessed an appreciable hydrophobicity in all three media. This finding is in good agreement with recent physiological models about the nature and composition of the gastrointestinal mucosal linings.

The adhesive performance (force of detachment) of the mucoadhesive bond between mucosal tissue and Polycarbophil followed the same trend as the mismatch in fractional surface polarity between substrate and adhesive, respectively. Such behavior was in agreement with other cases of polymer adhesion. Hence, the results give a first qualitative indication that—besides interpenetration—interfacial energies play an important role in mucoadhesion.

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