

# Investigation of Correlations between Mucoadhesion and Surface Energy Properties of Mucoadhesives

Jun Xiang,\* Xiaoling Li

Department of Pharmaceutics and Medicinal Chemistry, Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific, Stockton, CA 95211

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**ABSTRACT:** To explore the correlations between mucoadhesion and the surface properties of mucoadhesive polymers, a series of polymer, poly[acrylic acid-co-poly(ethylene glycol) monomethylether monomethacrylate-co-dimethylaminoethyl methacrylate], poly(AA-PEGMM-DMEMA), was designed and synthesized as a model mucoadhesive in this study. Poly(AA-PEGMM-DMEMA) was prepared by free radical polymerization. The composition of the polymer was varied by changing the content of DMEMA from 0 to 2.9 mol %, while keeping the mole ratio of AA to PEGMM at constant 9:1. The contact angles of water, glycerol (GL), or diiodomethane (DIM) on the surface of polymers with different hydration levels were measured, respectively. Surface energy components of the Lifshitz-van der Waals and the Lewis acid-base interactions for the polymer were calculated, based on the measured contact angles of water, GL, and DIM. The free energy of mucoadhesion ( $\Delta G$ ) of the polymer on the buccal surface was estimated by interfacial free energy

of a ternary system, consisting of mucin, polymer, and normal saline. The mucoadhesion of the polymer was measured after prehydration for 0, 5, and 180 min. It was found that Lewis acid-base interactions and Lifshitz-van der Waals interactions played different roles in the process of mucoadhesion. Increasing Lewis acid-base interaction between the polymer and the buccal mucosa led to a thermodynamically favorable adhesion process. Hydration could greatly affect mucoadhesion by changing the thermodynamic properties of the surface. Restricted hydration promoted the formation of mucoadhesive joints. The force of mucoadhesion was correlated mathematically with the effects of various interactions involved in the process of mucoadhesion. © 2006 Wiley Periodicals, Inc. *J Appl Polym Sci* 102: 2608–2615, 2006

**Key words:** adhesion; drug delivery systems; surfaces; thermodynamics

## INTRODUCTION

Mucoadhesion, which refers to the adhesion formed between the surface of a polymer and the mucus layer, is crucial in the development of mucoadhesive drug delivery systems, because the delivery systems must be retained at the site of application for a desired period of time. A better understanding of mucoadhesion is important for pharmaceutical scientists to design and develop biomaterials with optimal mucoadhesive properties. In the past few decades, several theories have been developed to describe the adhesion phenomena. Such theories include electronic theory,<sup>1</sup> adsorption theory,<sup>2</sup> wetting theory,<sup>3</sup> and diffusion theory.<sup>4</sup> While no individual theory alone is able to completely describe the formation of mucoadhesion, a combination of these theories has been used to interpret interactions between biological tissues and bioadhesive substrates.<sup>5</sup> In general, the process of forming adhesion involves three major steps of inter-

actions: wetting to form an intimate surface contact, formation of intermolecular interactions, and interpenetration and entanglement.<sup>6</sup> Among various approaches to explain the mucoadhesion phenomena, diffusion theory and thermodynamic principle were commonly applied.

According to the diffusion theory,<sup>4</sup> mucoadhesion is initiated by the intimate contact between the mucoadhesive polymer and the surface of mucosa. Then, the polymer chains diffuse into the surface of mucosa, and the glycoprotein chains in mucus diffuse into the polymer because of the concentration gradient across the interface. The chains that diffuse across the interface act as anchors to secure the adherence of the mucoadhesive to the surface of mucosa.<sup>7</sup> The diffusion theory has been supported by the ATR-FTIR spectroscopy study, which revealed chain interpenetration across the interface of poly(acrylic acid)-mucin.<sup>8</sup>

Thermodynamic analysis was applied to study the driving force of mucoadhesion. Lehr et al. determined the polar and dispersive components of surface energy of polycarbophil and mucosa by measuring the contact angles of captive air/octane bubbles.<sup>9</sup> The predicted and the measured mucoadhesion can be correlated by a spreading coefficient, based on polar and dispersive surface energy components.<sup>10</sup> How-

\*Present address: Biological Products Division, Bayer HealthCare LLC, 800 Dwight Way, Berkeley, CA 94701.

Correspondence to: X. Li (xli@pacific.edu).

ever, simply dividing surface energy into polar and dispersive components did not give proper attention to the Lewis acid–base (AB) interaction, and was inadequate for some practical situations.<sup>11</sup> An AB approach was presented by van Oss et al.<sup>12</sup> to better describe the interactions at interface. By introducing AB interaction into surface energy analysis, thermodynamic properties of surfaces can be more precisely characterized by using the surface energy parameters related to Lifshitz–van der Waals (LW) interaction, Lewis acid, and Lewis base. Rilossi and Buckton<sup>13,14</sup> assessed surface energies of carbopol, chitosan, poly(2-hydroxyethyl methacrylate), and hydroxypropyl cellulose in different test fluids by using the AB surface energy analysis. A good correlation was found between the values of the total free energy of adhesion and the measured force of mucoadhesion. However, the specific effects of AB interaction and LW interaction on the mucoadhesion were not explicitly explained in their studies.

To further explore the correlations between mucoadhesion and the thermodynamic properties of mucoadhesive polymers, a series of polymer, poly [acrylic acid-*co*-poly(ethylene glycol) monomethylether monomethacrylate-*co*-dimethylaminoethyl methacrylate], poly(AA-PEGMM-DMEMA), was designed and synthesized in this study. Poly(AA-PEGMM-DMEMA) contained both negatively charged carboxylate groups and positively charged amino groups, and was used as the model mucoadhesive to study the correlations between mucoadhesion and the thermodynamic properties of the polymer through the approach of AB surface energy analysis. The effects of various interactions involved in the process of mucoadhesion on the force of mucoadhesion of poly(AA-PEGMM-DMEMA) were also investigated.

### Theory of surface energy analysis

The interfacial interactions can be characterized by using the surface energy analysis. When AB interaction is included in the surface energy analysis, the surface energy ( $\gamma$ ) consists of two components: AB interactions and LW interactions.<sup>12,15</sup> The surface energy of these two types of interactions can be generally expressed as follows:

$$\gamma = \gamma^{\text{LW}} + \gamma^{\text{AB}} \quad (1)$$

For a pure substance, the value of  $\gamma^{\text{AB}}$  can be calculated by the following equation:

$$\gamma^{\text{AB}} = 2\sqrt{\gamma^+ \gamma^-} \quad (2)$$

where “+” and “-” denote the Lewis acid (electron acceptor) and Lewis base (electron donor) components, respectively.

When a liquid ( $l$ ) is placed on the surface of a solid ( $s$ ), the AB component and LW component across the interface can be calculated as follows:

$$\begin{aligned} \gamma_{\text{sl}}^{\text{AB}} &= 2\left(\sqrt{\gamma_s^+ \gamma_s^-} + \sqrt{\gamma_l^+ \gamma_l^-} - \sqrt{\gamma_s^+ \gamma_l^-} - \sqrt{\gamma_s^- \gamma_l^+}\right) \\ &= 2\left(\sqrt{\gamma_s^+} - \sqrt{\gamma_l^+}\right)\left(\sqrt{\gamma_s^-} - \sqrt{\gamma_l^-}\right) \end{aligned} \quad (3)$$

$$\gamma_{\text{sl}}^{\text{LW}} = \left(\sqrt{\gamma_s^{\text{LW}}} - \sqrt{\gamma_l^{\text{LW}}}\right)^2 \quad (4)$$

The free energy of adhesion across the interface ( $\Delta G_{\text{sl}}^{\text{a}}$ ) can be determined by measuring the contact angle ( $\theta$ ) of the liquid on the surface of the solid:

$$\begin{aligned} \Delta G_{\text{sl}}^{\text{a}} &= -\gamma_l(1 + \cos \theta) \\ &= -2\left(\sqrt{\gamma_s^{\text{LW}} \gamma_l^{\text{LW}}} + \sqrt{\gamma_s^+ \gamma_l^-} + \sqrt{\gamma_s^- \gamma_l^+}\right) \end{aligned} \quad (5)$$

If liquids form nonzero contact angles on the surface of a solid, a set of general contact angle equations can be obtained for three different liquids on the same solid surface as follows.

$$\gamma_l(1 + \cos \theta_1) = 2\left(\sqrt{\gamma_s^{\text{LW}} \gamma_l^{\text{LW}}} + \sqrt{\gamma_s^+ \gamma_l^-} + \sqrt{\gamma_s^- \gamma_l^+}\right) \quad (6a)$$

$$\gamma_l(1 + \cos \theta_2) = 2\left(\sqrt{\gamma_s^{\text{LW}} \gamma_l^{\text{LW}}} + \sqrt{\gamma_s^+ \gamma_l^-} + \sqrt{\gamma_s^- \gamma_l^+}\right) \quad (6b)$$

$$\gamma_l(1 + \cos \theta_3) = 2\left(\sqrt{\gamma_s^{\text{LW}} \gamma_l^{\text{LW}}} + \sqrt{\gamma_s^+ \gamma_l^-} + \sqrt{\gamma_s^- \gamma_l^+}\right) \quad (6c)$$

where  $l_1$ ,  $l_2$ , and  $l_3$  refer to liquid 1, liquid 2, and liquid 3,  $\theta_i$  ( $i = 1, 2, 3$ ) is the contact angle of the liquids on the solid surface.

The surface energy of the solid surface ( $\gamma_s^{\text{LW}}$ ,  $\gamma_s^+$ , and  $\gamma_s^-$ ) can be solved from eqs. (6a)–(6c) by measuring the contact angles of the three liquids on the solid surface if the surface energy ( $\gamma_l^{\text{LW}}$ ,  $\gamma_l^+$ , and  $\gamma_l^-$ ) of the three liquids are known. For an apolar liquid  $l_1$ ,  $\gamma_s^{\text{LW}}$  can be obtained by using eq. (6a):

$$\gamma_s^{\text{LW}} = \gamma_{l_1}^{\text{LW}} \frac{(1 + \cos \theta_1)^2}{4} \quad (7)$$

Combining eqs. (6b), (6c), and (7) the values of  $\gamma_s^+$  and  $\gamma_s^-$  can be solved:

$$\sqrt{\gamma_s^+} = \frac{A\sqrt{\gamma_{l_3}^+} - B\sqrt{\gamma_{l_2}^+}}{2\sqrt{\gamma_{l_2}^- \gamma_{l_3}^+} - 2\sqrt{\gamma_{l_2}^+ \gamma_{l_3}^-}} \quad (8)$$

$$\sqrt{\gamma_s^-} = \frac{B\sqrt{\gamma_{l_2}^-} - A\sqrt{\gamma_{l_3}^-}}{2\sqrt{\gamma_{l_2}^+\gamma_{l_3}^+} - 2\sqrt{\gamma_{l_2}^+\gamma_{l_3}^-}} \quad (9)$$

where

$$A = \gamma_{l_2}(1 + \cos \theta_2) - 2\sqrt{\gamma_s^{LW}\gamma_{l_2}^{LW}} \quad (10)$$

$$B = \gamma_{l_3}(1 + \cos \theta_3) - 2\sqrt{\gamma_s^{LW}\gamma_{l_3}^{LW}} \quad (11)$$

When the surface of the Material (1) (e.g., adhesive) is placed on the surface of the Material (2) (e.g., mucous membrane) immersed in a Liquid (3) (e.g., saliva), the free energy of the adhesion involved in LW and AB interactions can be calculated by the following equations.<sup>13</sup>

$$\begin{aligned} \Delta G^{LW} &= \gamma_{12}^{LW} - \gamma_{13}^{LW} - \gamma_{23}^{LW} \\ &= \left( \sqrt{\gamma_1^{LW}} - \sqrt{\gamma_2^{LW}} \right)^2 - \left( \sqrt{\gamma_1^{LW}} - \sqrt{\gamma_3^{LW}} \right)^2 \\ &\quad - \left( \sqrt{\gamma_2^{LW}} - \sqrt{\gamma_3^{LW}} \right)^2 \end{aligned} \quad (12)$$

$$\begin{aligned} \Delta G^{AB} &= \gamma_{12}^{AB} - \gamma_{13}^{AB} - \gamma_{23}^{AB} \\ &= 2 \left[ \sqrt{\gamma_3^+} \left( \sqrt{\gamma_1^-} + \sqrt{\gamma_2^-} - \sqrt{\gamma_3^-} \right) + \sqrt{\gamma_3^-} \left( \sqrt{\gamma_1^+} \right. \right. \\ &\quad \left. \left. + \sqrt{\gamma_2^+} - \sqrt{\gamma_3^+} \right) - \sqrt{\gamma_1^+\gamma_2^-} - \sqrt{\gamma_1^-\gamma_2^+} \right] \end{aligned} \quad (13)$$

Thus, the total free energy of adhesion can be obtained:

$$\begin{aligned} \Delta G^{TOT} &= \Delta G^{LW} + \Delta G^{AB} \\ &= \gamma_{12} - \gamma_{13} - \gamma_{23} \\ &= \gamma_{12}^{LW} - \gamma_{13}^{LW} - \gamma_{23}^{LW} + 2 \left[ \sqrt{\gamma_3^+} \left( \sqrt{\gamma_1^-} + \sqrt{\gamma_2^-} - \sqrt{\gamma_3^-} \right) \right. \\ &\quad \left. + \sqrt{\gamma_3^-} \left( \sqrt{\gamma_1^+} + \sqrt{\gamma_2^+} - \sqrt{\gamma_3^+} \right) - \sqrt{\gamma_1^+\gamma_2^-} - \sqrt{\gamma_1^-\gamma_2^+} \right] \end{aligned} \quad (14)$$

A negative value of  $\Delta G^{TOT}$  indicates that the spontaneous attraction could be formed between the two surfaces of Material (1) and (2) when they are immersed in a Liquid (3).

## METHODS

### Synthesis of buccal mucoadhesive polymers

Poly(ethylene glycol) monomethylether monomethacrylate (PEGMM) (PEG unit = 200, Polysciences, PA), acrylic acid (AA, Milwaukee, WI), and dime-

thylaminoethyl methacrylate (DMEMA, Polysciences) were dehibited by Dehibit 100 ion-exchange resin for 24 h, prior to polymerization. The compositions of the polymers were varied by changing the content of DMEMA from 0 to 2.9 mol %, while keeping the mole ratio of AA to PEGMM at constant 9:1. The monomer solution with the initiator 2,2'-azobisisobutyronitrile [M]/[I] ratio = 1000:1 was purged with nitrogen and then degassed by a vacuum pump. The degassed solution was filled into a mold that was constructed with two glass plates and a silicone rod as the spacer. The polymerization was carried out in the oven at 80°C for 18 h. The polymerized film was washed in deionized water for 48 h, and water was frequently changed.

### Contact angle measurement

The contact angle measurement was conducted by using a goniometer (model G-I, Kernco Instruments, El Paso, TX). The advancing contact angles were measured by applying an aliquot (10  $\mu$ L) of water, glycerol (GL), or diiodomethane (DIM), respectively, on the surfaces of the polymers. The polymers were prehydrated in normal saline for 0, 5, and 180 min, respectively, prior to contact angle measurement. Surface energy components of the LW and the AB interactions of the polymers were calculated based on the contact angles of the two polar liquids (water and GL) and one apolar liquid (DIM), according to eqs. (6)–(11). The free energy of mucoadhesion of the polymers on the buccal surface was estimated by calculating interfacial free energy of a ternary system, consisting of mucin, polymer, and normal saline, according to eqs. (12)–(14). The surface energy parameters of water, GL, DIM, normal saline, and mucin applied in calculation were listed in Table I.

### Tissue preparation

Porcine buccal tissue was obtained immediately after pigs were slaughtered (Long Ranch, Manteca, CA) and stored in normal saline at 4°C. Buccal mucosa was separated from underlying tissue by surgical scissors. The mucosa was used within 2 h after slaughtering. To measure the force of mucoadhesion,

TABLE I  
Surface Energy Parameters (in mJ/m<sup>2</sup>) of  
Various Materials<sup>13,15</sup>

	$\gamma$	$\gamma^{LW}$	$\gamma^{AB}$	$\gamma^+$	$\gamma^-$
Water (W)	72.8	21.8	51	25.5	25.5
Glycerol (GL)	64	34	30	3.92	57.4
Diiodomethane (DIM)	50.8	50.8	0		
Mucin	46.2	6.92	39.28	49.17	7.84
Saline	71.1	33.72	37.97	27.36	13.18

a  $1.5 \times 5 \text{ cm}^2$  piece of buccal mucosa was secured onto a plastic holder stage, and fresh mucosa was used in each measurement. The buccal mucosa was maintained at  $(37 \pm 1)^\circ\text{C}$  during measurement.

### Force of mucoadhesion measurement

The polymer film discs were affixed onto a glass slide (Arthur H. Thomas Co., Philadelphia, PA) by super glue (Super Duper, ITW Devcon, Danvers, MA). The polymer film discs were hydrated in the normal saline at  $(37 \pm 1)^\circ\text{C}$  for 0, 5, and 180 min, before adhering to the buccal mucosal surface. The glass slide with nonhydrated or hydrated polymer was fixed on a sample holder that connected to a load cell (GS-500, Transducer Techniques, Temecula, CA). The polymer film disc was placed in contact with porcine buccal surface, and an external force of 50 g (including weight of the sample holder and the glass slide) was applied. The contact was maintained for 1 min. The sample holder was then raised at a constant speed of 0.3 mm/s driven by a precision motor. An analog/digital converter (model 500A, Keithley Metrabyte, Taunton, MA) was used to convert the analog signals generated by the load cell into digital signals. The digital signals were acquired and analyzed by a personal computer with EasyLX software (Keithley Metrabyte). The maximum detachment force, which was required to separate the polymer from the buccal mucosa, was recorded as the force of mucoadhesion. The detection system was calibrated by standard weights (Permas<sup>®</sup>, Fisher Scientific) before measurement. The detached buccal tissues and the polymers were examined under a microscope for any possible cohesive failure. The measurements were carried out in triplicate.

## RESULTS AND DISCUSSION

The measured forces of mucoadhesion of poly(AA-PEGMM-DMEMA) at different hydration levels were shown in Table II. No cohesive failure was observed within the buccal mucosa and all hydrated polymers during the mucoadhesion measurement. The mucoadhesion of poly(AA-PEGMM) decreased as hydration increased, and the maximum mucoadhesion was obtained from the polymer without prehydration. The mucoadhesion of polymers with DMEMA reached the maximum after prehydrating for 5 min. Without prehydration, the mucoadhesion of the polymer without DMEMA was not significantly (ANOVA,  $P > 0.05$ ) different from those with 0.5–2.9% DMEMA. However, the mucoadhesion of prehydrated polymers with 1.0 and 1.5% DMEMA was significantly (ANOVA,  $P < 0.05$ ) greater than that of poly(AA-PEGMM). The polymer with 2.9% DMEMA did not show significant (ANOVA,  $P$

**TABLE II**  
Measured Force of Mucoadhesion of Poly(AA-PEGMM-DMEMA) in Contact with Porcine Buccal Mucosa at Different Hydration Levels

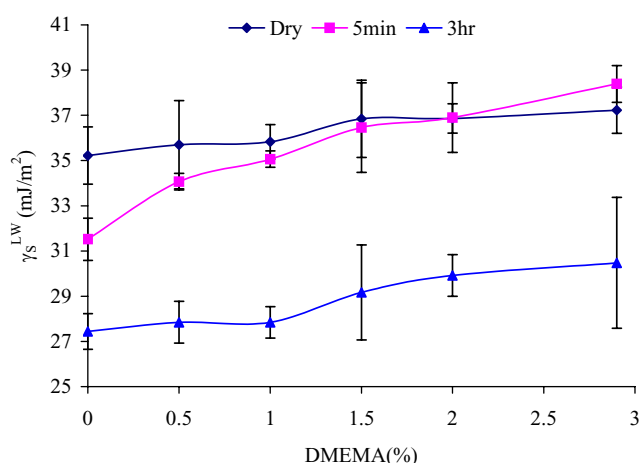
DMEMA (mol %)	Force of mucoadhesion (N/cm <sup>2</sup> )		
	No prehydration	5-min prehydration	3-h prehydration
0	0.27 ± 0.02	0.23 ± 0.02	0.19 ± 0.01
0.5	0.30 ± 0.04	0.32 ± 0.01	0.20 ± 0.03
1	0.34 ± 0.03	0.44 ± 0.04	0.21 ± 0.01
1.5	0.29 ± 0.02	0.33 ± 0.03	0.23 ± 0.01
2	0.27 ± 0.02	0.30 ± 0.05	0.23 ± 0.01
2.9	0.24 ± 0.04	0.29 ± 0.01	0.18 ± 0.02

Values given are mean ± SD.

> 0.05) mucoadhesion improvement at all hydration levels compared to poly(AA-PEGMM).

The influence of hydration on the mucoadhesion of adhesive materials has been studied earlier.<sup>16</sup> In a mucoadhesive joint, the mucosal epithelial cells and the mucoadhesive are intermediated by a layer of mucus gel. The primary compositions of the mucus gel are water and mucin. Water movement from the mucus gel to the dry or partially hydrated mucoadhesive could result in a substantial increase in the cohesive and adhesive properties of the mucus gel, which in turn would lead to strengthening of the mucoadhesive joint. Restricted hydration was found to be crucial to prolong mucoadhesion.<sup>17</sup> Changing the crosslinking of the mucoadhesive or introducing hydrophobic entities are two possible ways to restrict the hydration of mucoadhesive. In this study, the high mucoadhesion of polymers at low hydration level could be attributed to the increased polymer chain mobility for interpenetration/entanglement and the dehydration of mucus gel to form a strong adhesive joint. As the hydration increased, the dehydration capabilities of the polymers decreased. The polymer chain segments could also be over extended at high hydration level, which decreased the capability of interpenetration and entanglement of polymer chains.<sup>18</sup> In addition, the volume of the hydrated polymers increased greatly at high hydration level, which resulted in the lower density of interaction sites between the mucoadhesive and the buccal mucosa to form the adhesive joint. Therefore, the mucoadhesion of the polymers with high hydration decreased. The decline of mucoadhesion when increasing the content of DMEMA in the polymers was due to the decreased polymer chain mobility, resulting from the intrapolymer interaction between the amino group in DMEMA and carboxyl group in AA.<sup>19</sup>

AB surface energy analysis for poly(AA-PEGMM-DMEMA) was carried out based on the contact angle measurement. As shown in Figure 1, the polymers with prehydration for 3 h had significantly (ANOVA,  $P < 0.05$ ) lower  $\gamma_s^{\text{LW}}$  than the polymers prehydrated



**Figure 1** Effect of DMEMA on the LW component of surface energy of poly(AA-PEGMM-DMEMA). (◆) Prehydrated for 0 min (Dry); (■): Prehydrated for 5 min; (▲) Prehydrated for 3 h. Error bars represent standard deviations,  $n = 5$ . [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

for 0 and 5 min. The  $\gamma_s^{LW}$  values for the polymers without prehydration was not significantly different (ANOVA,  $P > 0.05$ ) from those with 5-min prehydration, except for poly(AA-PEGMM). In contrast, the  $\gamma_s^{AB}$  values for polymers with 0.5%, 1%, and 1.5% DMEMA prehydrated for 3 h were significantly (ANOVA,  $P < 0.05$ ) greater than those prehydrated for 0 and 5 min (shown in Fig. 2). Polymer with 1% DMEMA had the lowest  $\gamma_s^{AB}$  value at low hydration levels. Figures 1 and 2 revealed that hydration could increase the value of  $\gamma_s^{AB}$ , but decrease the value of  $\gamma_s^{LW}$ .

It was noticed that  $\gamma_s^{AB}$  values were negative for poly(AA-PEGMM-DMEMA) prehydrated for 0 and 5 min, except for poly(AA-PEGMM) without prehydration. The negative value of  $\gamma_s^{AB}$  was attributed to the negative value of  $\sqrt{\gamma_s^+}$ . Although the negative values of  $\sqrt{\gamma_s^+}$  might be explained as the experimental errors in the contact angle measurements, this explanation could not be applied to a series of negative  $\sqrt{\gamma_s^+}$  values found in poly(AA-PEGMM-DMEMA). Good and van Oss<sup>20</sup> found that negative values of  $\sqrt{\gamma_s^+}$  occurred more frequently in experiments using AB approach to obtain  $\gamma_s^+$ . Rillosi and Buckton<sup>13,14</sup> also obtained negative  $\gamma_s^{AB}$  using AB approach in the study of surface energy of Carbopol 934 hydrated in different media. The negative values of  $\sqrt{\gamma_s^+}$  could be interpreted as the negative contribution of the acid character to  $\gamma_s^{TOT}$  of the surface according to Good and coworkers<sup>12,15</sup>. Under this circumstance, eq. (2) must be written in an operational form:

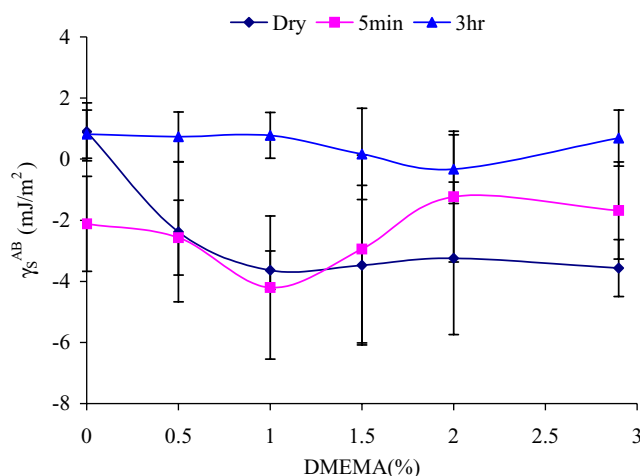
$$\gamma_s^{AB} = 2\sqrt{\gamma_s^+}\sqrt{\gamma_s^-} \quad (2b)$$

The result of  $\gamma_s^{AB}$  using this equation was a negative value. For a mechanically stable condensed phase, it is

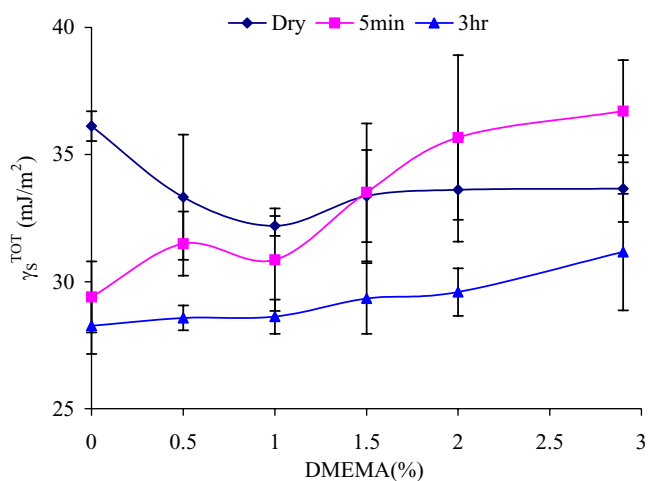
possible to have the negative value of  $\gamma_s^{AB}$  if  $\gamma_s^{AB} < \gamma_s^{LW}$ . This is because the total surface free energy  $\gamma_s^{TOT}$  remained positive. For poly(AA-PEGMM-DMEMA),  $\gamma_s^{AB}$  values were lower than  $\gamma_s^{LW}$  values, which resulted in positive  $\gamma_s^{TOT}$  for all compositions of the polymer at all hydration levels (shown in Fig. 3).

The free energy of AB interactions, the free energy of LW interactions, and the total free energy of adhesion in the polymer–mucin–saline system were shown in Figures 4–6. The  $\Delta G^{AB}$  of poly(AA-PEGMM-DMEMA) prehydrated for 5 min was significantly (ANOVA,  $P < 0.05$ ) lower than that prehydrated for 3 h. The minimum value of  $\Delta G^{AB}$  was observed when the polymer with 1% DMEMA was prehydrated for 5 min. The  $\Delta G^{LW}$  of the polymers decreased as the hydration increased. It should be noticed that the  $\Delta G^{AB}$  values for the polymers were negative at all hydration levels but the  $\Delta G^{LW}$  values were negative mainly at 3-h hydration level. Negative value of  $\Delta G$  indicated the spontaneous formation of adhesive joint. Lower negative values of  $\Delta G$  would result in the higher potential to form adhesive joint. In this study, the AB interaction could drive the spontaneous formation of adhesive joints at all hydration levels for the polymers, while the LW interaction had this capability only at high hydration level.  $\Delta G^{TOT}$  was the result of combining the effects of these two interactions. As shown in Figure 6, the negative  $\Delta G^{TOT}$  values for poly(AA-PEGMM-DMEMA) at all hydration levels indicated that the AB interaction was critical for good mucoadhesion.

The relationships between  $\Delta G^{TOT}$  and the measured force of mucoadhesion for poly(AA-PEGMM-DMEMA) at various hydration levels were plotted in Figures 7–9. The measured force of mucoadhesion increased as the  $\Delta G^{TOT}$  value decreased, but both pa-

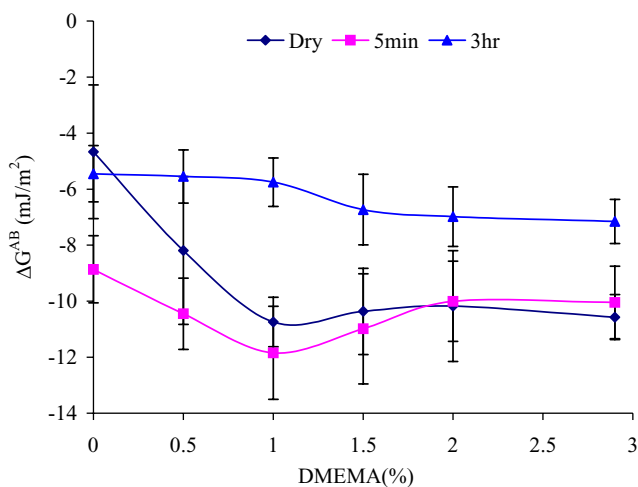


**Figure 2** Effect of DMEMA on the AB component of surface energy of poly(AA-PEGMM-DMEMA). (◆) Prehydrated for 0 min (Dry); (■): Prehydrated for 5 min; (▲) Prehydrated for 3 h. Error bars represent standard deviations,  $n = 5$ . [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

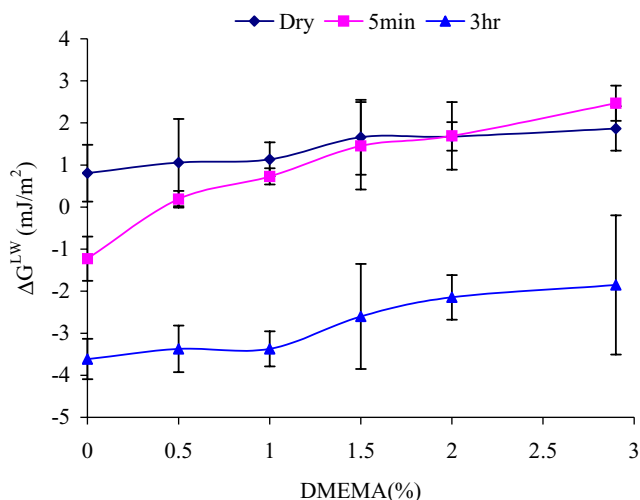


**Figure 3** Effect of DMEMA on the total surface energy of poly(AA-PEGMM-DMEMA). (◆) Prehydrated for 0 min (Dry); (■): Prehydrated for 5 min; (▲) Prehydrated for 3 h. Error bars represent standard deviations,  $n = 5$ . [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

rameters were not linearly changed with the variation of DMEMA content. Previous study<sup>19</sup> conducted in our lab revealed that increasing the DMEMA content in poly(AA-PEGMM-DMEMA) could result in two opposite mucoadhesion behaviors of the polymer. Increasing DMEMA content could promote the mucoadhesion of the polymer by increasing the intersurface interactions between the polymer and the buccal mucosa. However, increasing DMEMA content could also increase the inter- or intramolecular interactions within the polymer and lead to a

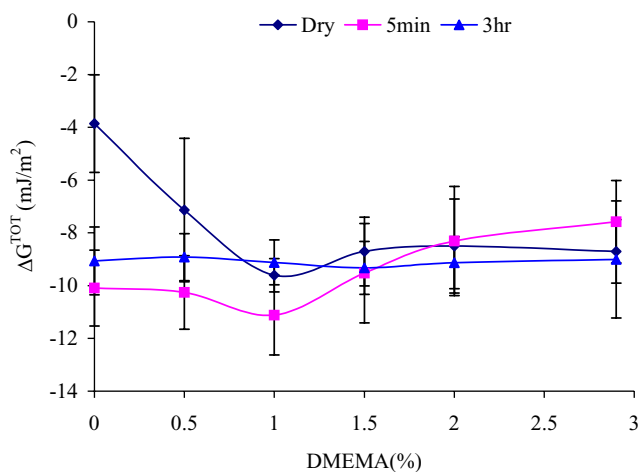


**Figure 4** Effect of DMEMA on the AB component of free energy of interaction between poly(AA-PEGMM-DMEMA) and mucin in normal saline. (◆) Prehydrated for 0 min (Dry); (■): Prehydrated for 5 min; (▲) Prehydrated for 3 h. Error bars represent standard deviations,  $n = 5$ . [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

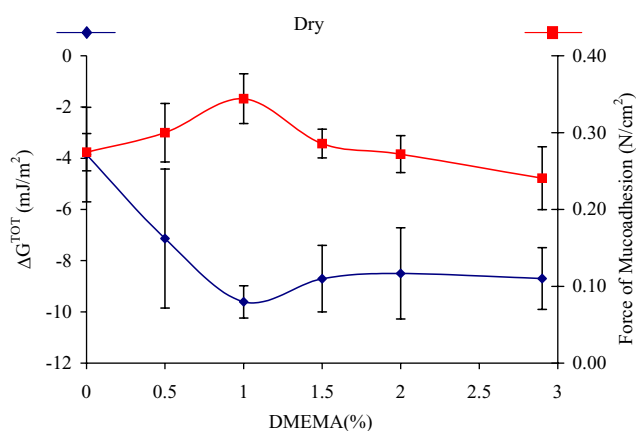


**Figure 5** Effect of DMEMA on the LW component of free energy of interaction between poly(AA-PEGMM-DMEMA) and mucin in normal saline. (◆) Prehydrated for 0 min (Dry); (■): Prehydrated for 5 min; (▲) Prehydrated for 3 h. Error bars represent standard deviations,  $n = 5$ . [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

decrease in mucoadhesion. When the effect of interactions between the polymer and the buccal surface outweighed that of inter- or intrapolymer interactions, high mucoadhesion was observed. When inter- or intrapolymer interactions were dominant, low mucoadhesion was exhibited. The polymer containing 1.0% DMEMA showed that the interactions between the polymer and the buccal mucosa surface were dominant, which also reflected in the surface energy analysis. The polymer with 1.0% DMEMA



**Figure 6** Effect of DMEMA on the total free energy of interaction between poly(AA-PEGMM-DMEMA) and mucin in normal saline. (◆) Prehydrated for 0 min (Dry); (■): Prehydrated for 5 min; (▲) Prehydrated for 3 h. Error bars represent standard deviations,  $n = 5$ . [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]



**Figure 7** Relationship between the total free energy of interaction (◆) and the measured force of mucoadhesion (■). Polymers were not prehydrated. Error bars represent standard deviations,  $n = 5$  for  $\Delta G^{\text{TOT}}$  and  $n = 3$  for force of mucoadhesion. [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

prehydrated for 5 min had the highest force of mucoadhesion and the lowest  $\Delta G^{\text{TOT}}$  value among the polymers, at all hydration levels. The result shown in Figures 7–9 demonstrated that a general trend of mucoadhesion of the polymer with the same hydration level could be predicted by  $\Delta G^{\text{TOT}}$  using the AB surface energy analysis approach.

To quantitatively describe the relationship between the mucoadhesion and the thermodynamic properties of poly(AA-PEGMM-DMEMA), the mucoadhesion was assumed to be the sum of individual effect of all interactions involved in the process of forming adhesion. Then the force of mucoadhesion could be expressed by the following equation:

$$F = aW + bR + cI + d \quad (15)$$

where  $F$  stands for the force of mucoadhesion;  $W$ ,  $R$ , and  $I$  are the physicochemical parameters representing the effects associated with wetting, intermolecular interactions, and interpenetration and entanglement, respectively;  $a$ ,  $b$ , and  $c$  are the coefficients for  $W$ ,  $R$ , and  $I$ , respectively; and  $d$  is a constant. The constant  $d$  represents the effects of other interactions besides  $W$ ,  $R$ , and  $I$  on the force of mucoadhesion.

In this study, the effects associated with wetting can be expressed from the thermodynamic aspect by using the surface energy. Since AB interactions and LW interactions played different roles at different hydration levels, both  $\gamma_s^{\text{AB}}$  and  $\gamma_s^{\text{LW}}$  were used to express the effects of wetting in the equation. The coefficient  $a$  was then divided into  $a_1$  and  $a_2$  for  $\gamma_s^{\text{AB}}$  and  $\gamma_s^{\text{LW}}$ , respectively. The total free energy of adhesion  $\Delta G^{\text{TOT}}$  was a result of intermolecular interactions and, therefore, was used to represent the effects of these interactions in the equation. Hydration ( $H$ ) was used to represent the effects associated with interpenetration and entan-

glement, since the mobility and extension of polymer chains changed with the polymer hydration, which would affect the interpenetration and entanglement capability of the polymer. With these assumptions, the eq. (15) could be rewritten as follows:

$$F = a_1\gamma_s^{\text{AB}} + a_2\gamma_s^{\text{LW}} + b\Delta G^{\text{TOT}} + cH + d \quad (16)$$

Regression was performed by using Minitab™ software (Minitab, State College, PA) to calculate the values of  $a_1$ ,  $a_2$ ,  $b$ ,  $c$ , and  $d$  in eq. (16) at three different hydration levels. For the force of mucoadhesion measured without prehydration, 1-min hydration was used in the calculation, because the polymer was contacted with the hydrated buccal mucosa for 1 min, before the measurement was conducted. The hydration of poly(AA-PEGMM-DMEMA) at different hydration times had been studied previously.<sup>19</sup> The obtained values of the coefficients in eq. (16) is shown in the following:

Without prehydration:

$$F = 185\gamma_s^{\text{AB}} - 2475\gamma_s^{\text{LW}} - 1501\Delta G^{\text{TOT}} + 15438H + 461$$

$$R^2 = 0.967 \quad (17a)$$

After 5-min prehydration:

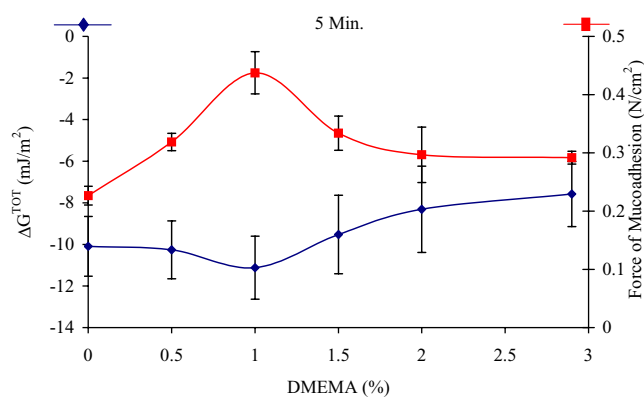
$$F = -5766\gamma_s^{\text{AB}} + 1140\gamma_s^{\text{LW}} - 12164\Delta G^{\text{TOT}} - 27104H + 3974$$

$$R^2 = 1.000 \quad (17b)$$

After 3-h prehydration:

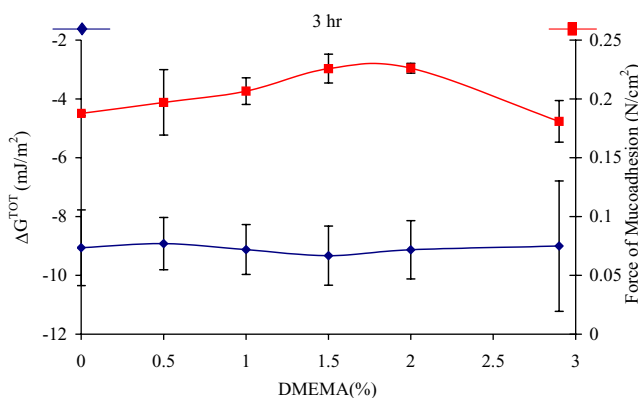
$$F = -4198\gamma_s^{\text{AB}} - 1750\gamma_s^{\text{LW}} - 3825\Delta G^{\text{TOT}} - 412H + 621$$

$$R^2 = 0.952 \quad (17c)$$



**Figure 8** Relationship between the total free energy of interaction (◆) and the measured force of mucoadhesion (■). Polymers were prehydrated for 5 min. Error bars represent standard deviations,  $n = 5$  for  $\Delta G^{\text{TOT}}$  and  $n = 3$  for force of mucoadhesion. [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]





**Figure 9** Relationship between the total free energy of interaction (◆) and the measured force of mucoadhesion (■). Polymers were prehydrated for 3 h. Error bars represent standard deviations,  $n = 5$  for  $\Delta G^{\text{TOT}}$  and  $n = 3$  for force of mucoadhesion. [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

where the unit for  $F$  is  $\text{mN}/\text{cm}^2$ ; the units for  $\gamma_s^{\text{AB}}$ ,  $\gamma_s^{\text{LW}}$ , and  $\Delta G^{\text{TOT}}$  are  $\text{mN}/\text{cm}$ ,  $H$  is dimensionless, the units for the coefficients of  $a_1$ ,  $a_2$ , and  $b$  are  $\text{cm}^{-1}$ , and the units for coefficient  $c$  and constant  $d$  are  $\text{mN}/\text{cm}^2$ .

The  $R^2$  values of eqs. (17a), (17b), and (17c) demonstrated that the force of mucoadhesion of poly (AA-PEGMM-DMEMA) could be well expressed by  $\gamma_s^{\text{AB}}$ ,  $\gamma_s^{\text{LW}}$ ,  $\Delta G^{\text{TOT}}$ , and  $H$ . The values of coefficient  $b$  for  $\Delta G^{\text{TOT}}$  at all hydration levels were negative. This indicated that decreasing  $\Delta G^{\text{TOT}}$  led to the increase of mucoadhesion, which conformed to the results shown in Figures 7–9. The values of coefficient  $a_1$  and  $a_2$  in eq. (17a), (17b), and (17c) revealed that  $\gamma_s^{\text{AB}}$  and  $\gamma_s^{\text{LW}}$  played different roles in the force of mucoadhesion at different hydration levels. As shown in Figures 1 and 2,  $\gamma_s^{\text{LW}}$  values of the polymers were positive at all hydration levels, and  $\gamma_s^{\text{AB}}$  values were negative for the polymers prehydrated for 0 and 5 min, but positive after 3-h prehydration. The term  $a_1\gamma_s^{\text{AB}}$  and  $a_2\gamma_s^{\text{LW}}$  had positive effects on the force of mucoadhesion at 5-min prehydration level, but negative at 0-min and 3-h prehydration level. This result conformed to the early statement that it was favorable to develop the intimate surface contact between the buccal mucosa and the polymers with restricted hydration. Since the effect of the restricted hydration on mucoadhesion was greatly different from that of no/little hydration and overhydration, it was difficult to incorporate three different hydration levels into one equation with a good fitting. The values of coefficient  $c$  in eqs. (17a), (17b), and (17c) also revealed such great difference. The negative  $c$  value in eq. (17b) cannot be fully interpreted, which could result from the high impact of surface energy and total free energy in the equation. Nevertheless, the correlation between the force of mucoadhesion

and the effects of various interactions involved in the process of mucoadhesion could be well expressed by eq. (16). This equation remains to be further verified by polymers and vigorous theoretical derivation.

## CONCLUSIONS

Thermodynamic analysis reveals that AB interactions and LW interactions played different roles in the process of mucoadhesion. Increasing AB interaction between the polymer and the buccal mucosa leads to a thermodynamically favorable adhesion process. Hydration can greatly affect mucoadhesion by changing the thermodynamic properties of the polymer surface. Restricted hydration promotes the formation of mucoadhesive joints. The relationship between the force of mucoadhesion and the effects of various interactions involved in the process of mucoadhesion could be quantitatively described. The results of this study can be applied in the design mucoadhesive polymers with optimal thermodynamic properties.

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