# Properties of Biomedical Pressure-Sensitive Adhesive Copolymer Films with Pendant Monosaccharides

TAKASHI MIYATA,[1,*] MAYUMI MORIZANE,[1] KATSUHIKO NAKAMAE,[1,†] MASAKAZU OKUMURA,[2] and KEISUKE KINOMURA[2]

[1]Faculty of Engineering, Kobe University, Rokko, Nada, Kobe 657, Japan; [2]Nippon Fine Chemical Co., Ltd., 1-1, 5, Umei, Takasago, Hyogo 676, Japan

SYNOPSIS

Glucosyloxyethyl methacrylate (GEMA) was copolymerized with butyl acrylate (BA) for the preparation of a biomedical pressure-sensitive adhesive with pendant monosaccharides, for possible use in medical applications. The measurements of 180° peel strength, ball tack, and holding power for the GEMA–BA copolymer films revealed that the film at the GEMA content of 5 mol % has excellent pressure-sensitive adhesive properties. Protein adsorption onto the GEMA–BA copolymer film hardly occurred due to very low interfacial free energy between its surface and water. Release profiles of vitamin $B_{12}$ from the GEMA–BA copolymer film suggests that it is useful as a material for a transdermal therapeutic system. © 1995 John Wiley & Sons, Inc.

## INTRODUCTION

Generally, pressure-sensitive adhesives are synthesized by the copolymerization of a main monomer whose polymer has a low glass transition temperature ($T_g$) and a comonomer whose polymer has relatively high $T_g$ so that the pressure-sensitive adhesives can have strong adhesion force, strong cohesion force, and excellent tackiness.[1] For example, butyl acrylate (BA) or butyl methacrylate is often selected as the main monomer, and styrene (St), methyl methacrylate (MMA), etc., as the comonomer. The performance of the pressure-sensitive adhesive can be controlled by the balance among adhesion force, cohesion force, and tackiness. We synthesized graft or block copolymers using BA macromonomer and studied their pressure-sensitive adhesive properties from the viewpoint of surface chemistry.[2,3]

Recently, pressure-sensitive adhesives have been used not only as pressure-sensitive adhesive tapes but as the substrates for drug release in transdermal therapeutic systems.[4–7] The pressure-sensitive adhesives used in biomedical fields must be biocompatible due to concern that the skin might be poisoned by it in the case of a transdermal therapeutic system. Therefore, more advanced functions like biocompatibility as well as excellent pressure-sensitive adhesiveness are required. Furthermore, such pressure-sensitive adhesives must adhere on various surfaces under various environments, including those encountered in the medical field.

Polysaccharides have high potential as materials in biomedical and biotechnological fields and have attracted many workers' attention. Many investigations have been undertaken on the synthesis of polysaccharide-containing polymers and their use as biomaterials.[8–19] Kobayashi et al.[14–17] studied the interactions between polystyrene derivatives with oligosaccharide and liver cells, etc. We also synthesized copolymers with pendant monosaccharides by copolymerizing glycosyloxyethyl methacrylate (GEMA) with St or MMA and studied the surface characteristics of their films.[19–23] The previous studies made it clear that the copolymer surface becomes more hydrophilic with increase in the GEMA content and that proteins are hardly adsorbed onto the surface. Therefore, it is expected that such copolymers can be useful in the medical field. Moreover,

* Present address: Chemical Branch, Faculty of Engineering, Kansai University, Suita, Osaka 564, Japan.

† To whom correspondence should be addressed.

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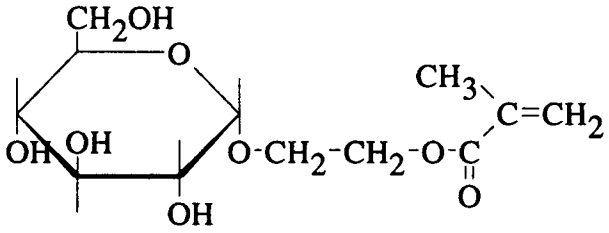
since GEMA is a monomer with a pendant monosaccharide, it can be easily copolymerized with another monomer such as BA. The copolymerization of GEMA and BA may enable us to combine pressure-sensitive adhesion with biocompatibility. Such a pressure-sensitive adhesive can be used as a substrate for drug release in a transdermal therapeutic system.

In this study, we synthesized pressure-sensitive adhesive copolymers with pendant monosaccharides by copolymerizing GEMA with BA and investigated the surface characteristics and the pressure-sensitive adhesive properties of their films. The release profiles of vitamin $B_{12}$ from the copolymer films were also examined as a model of drug release in a transdermal therapeutic system.

## EXPERIMENTAL

### Materials

A monomer with a pendant glucoside (glycosyloxyethyl methacrylate [GEMA]) was synthesized according to our previous method[18]:



GEMA

Butyl acrylate (BA) and styrene (St) were purified by distillation under reduced pressure in a nitrogen atmosphere. 2,2'-Azobisisobutyronitrile (AIBN) recrystallized from benzene solution was used as the initiator. Human fibrinogen was purchased from Kabi Vitrum. Concerning the other solvents and reagents, analytical-grade reagents were used without further purification. The water used was distilled, ion-exchange water.

### Copolymerization of GEMA with BA

GEMA and BA in a typical copolymer composition were dissolved together with AIBN (1.0 wt % relative to the monomers) in dimethyl sulfoxide (DMSO) to make a 10 wt % solution. The mixture was then transferred into a glass tube. The reaction was carried out at 70°C for 12 h under nitrogen atmosphere. The resulting GEMA–BA copolymer was isolated by slow precipitation with water or acetone. It was purified by reprecipitation from DMSO solution into water or acetone and dried at 60°C *in vacuo*. The copolymerization of St and BA was carried out in ethyl acetate, as for the GEMA and BA. Average molecular weights of the GEMA–BA copolymers were determined by gel permeation chromatography (GPC: Waters Model 6000A), equipped with a differential refractometer. Tetrahydrofuran was used as an eluent and the calibration was made with polystyrene standards. The number-average molecular weights of the GEMA–BA copolymers were found to be in the range of about 40,000–80,000.

### Preparation of Pressure-Sensitive Adhesive Films

The GEMA–BA or St–BA copolymers were dissolved in a methanol–water mixture or ethyl acetate in a concentration of 20 wt %. The resulting solution was cast on a poly(ethylene terephthalate) (PET) film that was well washed with water after treatment with a 6*N* aqueous NaOH solution. The amount of the solution cast on the PET film was 30 g/m$^2$. The pressure-sensitive adhesive film was obtained by allowing the solvent to evaporate completely.

### Measurement of Pressure-Sensitive Adhesive Properties

The pressure-sensitive adhesive properties of the GEMA–BA copolymer film were evaluated by the 180° peel strength, ball tack, and holding power tests measured according to JIS Z 0237[24]:

(a) *180° peel strength:* The resulting copolymer film was cut into a strip of 1 in. width. The strip was stuck on a stainless-steel plate (SUS 304), which had been well washed by toluene, by advancing and returning a rubber roller (400 g) on it 10 times. Peel strength of 180° between the film and the stainless-steel plate was measured with a tensile tester (Shimadzu Co., Autograph SD-100) at room temperature with a crosshead speed of 200 mm/min.

(b) *Ball tack:* Ball tack was measured by the method reported by Gainsly and Dow.[25] An iron ball (diameter: $\frac{1}{32}$–$\frac{32}{32}$ in.) was rolled on a slope (30°) with a runway of 10 cm and a 10 cm GEMA–BA copolymer film. Ball tack was represented by the maximum diameter of the ball when it stopped on the pressure-sensitive adhesive.

(c) *Holding power:* The resulting copolymer film (25 × 25 mm) was stuck on the stainless-steel

plate (SUS 304), which had been washed by toluene, by advancing and returning a rubber roller (400 g) on it 10 times. A 1 kg weight was hung perpendicularly on the edge of the film. Then, the holding power was determined by the measurement of the time until the film came off.

## Contact Angle Measurement

The contact angles $\theta$ of methylene iodide and glycerol on the copolymer film surface in air were measured by the method reported previously.[20,26] To evaluate the surface characteristics of the copolymer films in water, the contact angle measurements of methylene iodide and an air bubble on the copolymer films in water were also carried out as shown in Figure 1. When each liquid drop was enlarged and reduced, height $x$ and diameter $\phi$ were measured. The advancing contact angle $\theta_a$, receding contact angle $\theta_r$, and contact angle $\theta$ were calculated with eq. (1) or (2) as follows:

$$\theta_a, \theta_r = \begin{cases} 2\tan^{-1}\left(\dfrac{h}{x}\right) & (x = \phi/2, \theta \le 90) \\ 90 + \cos^{-1}\left(\dfrac{\phi h}{h^2 + x^2}\right) & (x = \phi/2, \theta \ge 90) \end{cases} \quad (1)$$

$$\theta = \cos^{-1}\left(\frac{\cos\theta_a + \cos\theta_r}{2}\right) \quad (2)$$

The surface free energy was calculated from the contact angle $\theta$ which was obtained by $\theta_a$ and $\theta_r$. In this study, the surface free energy in air was obtained with eq. (3), which was proposed by Owens and Wendt[27] as follows:

$$\frac{(1 + \cos\theta)\cdot\gamma_l}{2} = (\gamma_s^d \cdot \gamma_l^d)^{1/2} + (\gamma_s^p \cdot \gamma_l^p)^{1/2}$$

$$\gamma_s = \gamma_s^d + \gamma_s^p \quad (3)$$

where $\gamma_s$ and $\gamma_l$ are the surface free energy of the solid and the liquid, and $\gamma_s^d$, $\gamma_s^p$, $\gamma_l^d$, and $\gamma_l^p$ are the dispersion force components and polar force components of the surface free energy of the solid and the liquid, respectively. The dispersion force component and the polar force component of the surface free energy of glycerol are 37.0 and 26.4 erg/cm$^2$, respectively, and those of methylene iodide were 48.5 and 2.3 erg/cm$^2$, respectively.[28,29]

Furthermore, the surface free energy in water was obtained by substitution of the contact angles in water into eqs. (4)–(6):

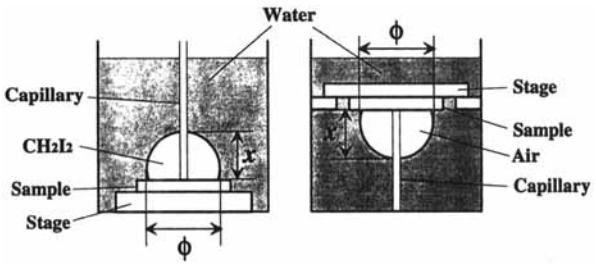



**Figure 1** Contact angle measurement in water.

$$(\gamma_s^d)^{1/2} = \frac{(\gamma_l^p)^{1/2}(\gamma_w\cos\theta' + \gamma_w) - (\gamma_w^p)^{1/2}(\gamma_l + \gamma_{wl}\cos\theta + \gamma_w\cos\theta')}{2[(\gamma_w^d \cdot \gamma_l^p)^{1/2} - (\gamma_l^d \cdot \gamma_w^p)^{1/2}]} \quad (4)$$

$$(\gamma_s^p)^{1/2} = \frac{\gamma_w\cos\theta' + \gamma_w - 2(\gamma_s^d \cdot \gamma_w^p)^{1/2}}{2(\gamma_w^p)^{1/2}} \quad (5)$$

$$\gamma_s = \gamma_s^d + \gamma_s^p \quad (6)$$

where $\gamma_w$, $\gamma_w^d$, and $\gamma_w^p$ are the surface free energy, its dispersion force components, and its polar force components of the surface free energy of water, respectively. The values used for $\gamma_w$, $\gamma_w^d$, and $\gamma_w^p$ are 72.8, 21.8, and 51.0 erg/cm$^2$, respectively.

Moreover, the interfacial free energies between the sample and water are given from the surface free energy in water as follows:

$$\gamma_{sw}^d = \gamma_s^d + \gamma_w^d - 2(\gamma_s^d \cdot \gamma_w^d)^{1/2}$$

$$\gamma_{sw}^p = \gamma_s^p + \gamma_w^p - 2(\gamma_s^p \cdot \gamma_w^p)^{1/2}$$

$$\gamma_{sw} = \gamma_{sw}^d + \gamma_{sw}^p \quad (7)$$

## Measurement of the Amount of Protein Adsorbed on Copolymer Films

The GEMA–BA copolymer films were kept immersed in 0.1$M$ phosphate buffer (pH 7.4) containing 1.0 g/L of human fibrinogen at 37°C for 5 h. Then, the amounts of fibrinogen adsorbed on the copolymer films were determined with a BCA protein assay reagent[30] (Pierce) after the films were adequately rinsed with the phosphate buffer. This protein assay reagent determines the amount of protein on the basis of the reducing reaction of the protein. However, since pendant glucose in GEMA also had a reducing action, the amount of the adsorbed protein was estimated by a comparison with the same film immersed in the phosphate buffer containing no protein.

### Release of Vitamin $B_{12}$ from GEMA–BA Copolymer Film

Vitamin $B_{12}$ was dissolved in an aqueous solution of 10 wt % ethanol containing the GEMA–BA copolymer in a concentration of 10 wt %. Then, the GEMA–BA copolymer film containing vitamin $B_{12}$ was prepared by casting the resulting mixture on a PET film and allowing the solvent to evaporate completely. The amount of vitamin $B_{12}$ in the film was determined by the measurement of its weight.

Release of vitamin $B_{12}$ from the GEMA–BA copolymer film was performed with stirring in a 0.1*M* phosphate buffer (pH 7.4) at 37°C. The amount of released vitamin $B_{12}$ was determined spectrophotometrically at 550 nm with a Hitachi Model 100-50 spectrophotometer.

## RESULTS AND DISCUSSION

### Pressure-sensitive Adhesive Properties of GEMA–BA Copolymer

Pressure-sensitive adhesive properties depend on adhesion force, cohesion force, and tackiness.[1] Generally, they are evaluated by the measurements as follows: (1) *adhesion force:* peel strength between a pressure-sensitive adhesive and an adherend after sufficiently getting the latter wet with the former; (2) *cohesion force:* holding power that is represented by the time until a weight falls or by the migration distance of a weight after a pressure-sensitive adhesive is stuck on an adherend and a weight is hung; and (3) *tackiness:* ball tack that is represented by the maximum diameter of ball when a ball is rolled

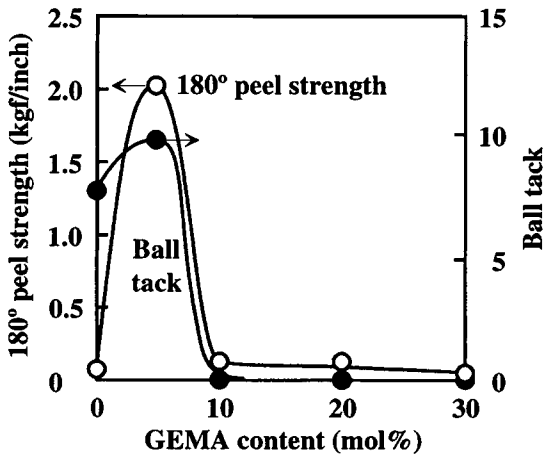



**Figure 2** Effects of GEMA content on (○) 180° peel strength and (●) J. Dow ball tack in GEMA–BA copolymer.

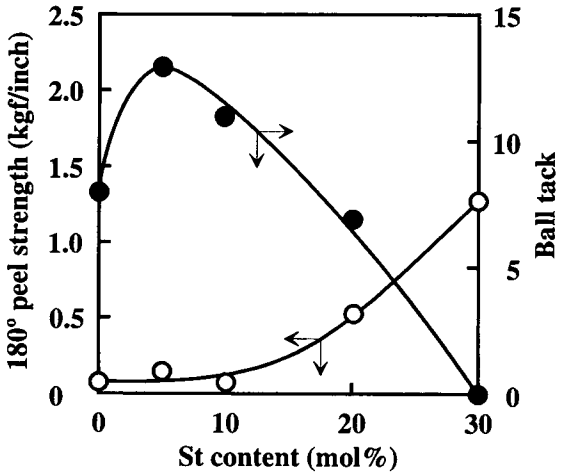



**Figure 3** Effects of St content on (○) 180° peel strength and (●) J. Dow ball tack in St–BA copolymer.

and stops on the pressure-sensitive adhesive. In the present study, we investigated the pressure-sensitive adhesive properties of the GEMA–BA copolymer film by the measurement of 180° peel strength, ball tack, and holding power.

Figures 2 and 3 show the effects of the GEMA and St content on 180° peel strength and ball tack for the GEMA–BA and St–BA copolymer films, respectively. The peel strength of the St–BA copolymer films from a stainless-steel plate increased gradually up to 1.3 kgf/in. with the St content. This is attributed to an increase in cohesion force of the film by the introduction of the St component. Cohesive failures occurred in peeling at an St content of less than 20 mol %. Furthermore, the ball tack exhibited a maximum at an St content of 10 mol %. On the other hand, in the GEMA–BA copolymer films, the small amount of GEMA (5 mol %) led to a sharp increase in the peel strength from 0.076 kgf/in. (the peel strength of the PBA film) to 2.0 kgf/in. Over 10 mol %, however, the peel strength decreased drastically. The maximum peel strength of the GEMA–BA copolymer film is higher than that of the St–BA copolymer film. As can be seen from the results of the ball tack, the GEMA–BA copolymer film exhibited the best tackiness at a GEMA content of 5 mol %. Interfacial peeling between the pressure-sensitive adhesive and the adherend was clearly observed with the GEMA–BA copolymer films, in contrast to cohesive failures with the PBA and St–BA copolymer films. A pressure-sensitive adhesive is composed of a soft segment whose glass transition temperature ($T_g$) is low and a hard segment whose $T_g$ is high, and the balance in the content of their segments must be controlled for the

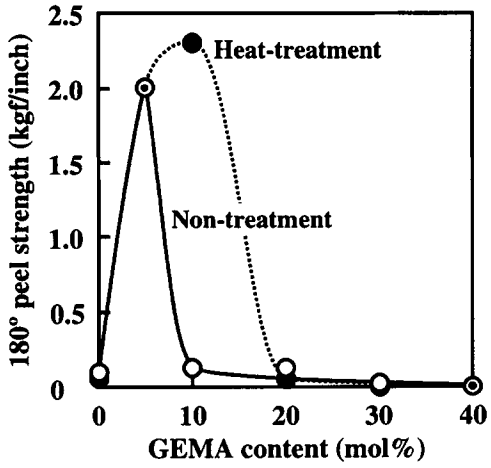



**Figure 4** Effects of GEMA content on 180° peel strength in GEMA–BA copolymer (○) before and (●) after heat-treatment (100°C, 1 h).

development of a pressure-sensitive adhesive with strong adhesion force, cohesion force, and tackiness. The GEMA and BA components play roles in the hard segment and soft segment, respectively. Since the introduction of 5 mol % GEMA leads to an optimum balance, the film shows both very high peel strength and high ball tack. These results indicate that the cohesion force of the film can be improved, without lowering the wettability for the adherend, by the introduction of a small amount of the GEMA component which has a strong cohesion force. The drop of the peel strength at more than 10 mol % is attributed to a drastic decrease in wettability accompanied by a rising $T_g$, although the cohesion force of the pressure-sensitive adhesive becomes strong. We tried, therefore, to improve the wettability of the film by a heat treatment.

Figure 4 shows 180° peel strength after the GEMA–BA copolymer cast on the PET film was stuck on a stainless-steel plate (adherend) and then treated at 100°C for 1 h. The heat treatment did not influence the peel strength at a GEMA content less than 5 mol % or more than 20 mol %. However, the peel strength at 10 mol % increased notably from about 0.1 kgf/in. to about 2.3 kgf/in. and was higher than at 5 mol %. The increase in the peel strength by the heat treatment is due to the improvement of wettability of the GEMA–BA copolymer for the adherend by the heat treatment at a temperature above $T_g$. Moreover, the GEMA–BA copolymer film at 10 mol % has a stronger cohesion force than that at 5 mol %, because the former contains a larger amount of the GEMA component with its strong cohesion force than does the latter. Therefore, the strong cohesion force of the GEMA component and good wettability by the heat treatment cause the excellent pressure-sensitive adhesive properties.

The effect of the GEMA content on holding power of the GEMA–BA copolymer film before and after the heat treatment at 100°C for 1 h is shown in Figure 5. Before the heat treatment, the holding power increased up to about 500 min with increasing GEMA content to 20 mol % and then decreased drastically at more than 30 mol %. As the cohesion force is an important factor related to shear strength in a pressure-sensitive adhesive, the holding power corresponds to the cohesion force of the pressure-sensitive adhesive. Therefore, the increase of the holding power with the GEMA content also arises from the strong cohesion force of the GEMA component. However, since the wettability of the GEMA–BA copolymer film for the adherend drops drastically at more than 30 mol %, due to increasing $T_g$ of the copolymer film, the holding power falls. On the other hand, the heat treatment improved the holding power notably. This is because the heat treatment improves wettability and the contact area between the GEMA–BA copolymer film and the adherend increases.

These results led us to the conclusion that the GEMA–BA copolymer film with GEMA content of 5 mol % is a useful pressure-sensitive adhesive. In using the GEMA–BA copolymer as a pressure-sensitive adhesive in a transdermal therapeutic system, it must adhere to the adherend under such severe conditions as high humidity.

Figure 6 shows 180° peel strength of the GEMA–BA and St–BA copolymer films under high humidity. After the film was stuck on a stainless-steel plate,

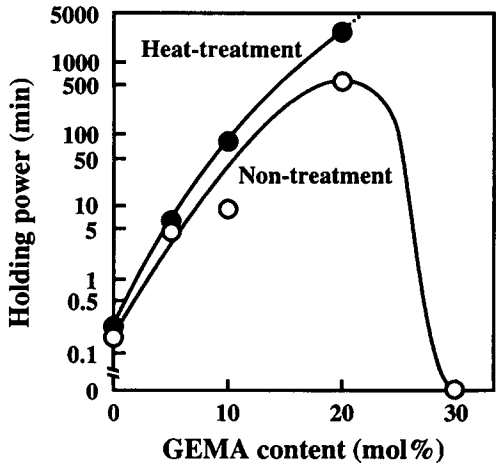



**Figure 5** Holding power of GEMA–BA copolymer (○) before and (●) after heat-treatment (100°C, 1 h).

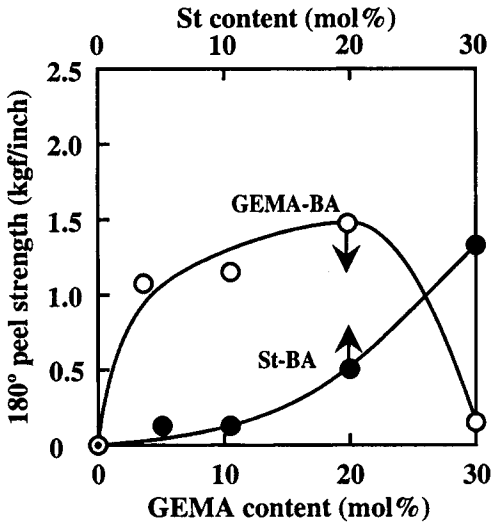



**Figure 6** 180° peel strength of (○) GEMA–BA and (●) St–BA copolymer films, stuck on the stainless-steel plates and kept under relative humidity of 98% at 30°C for 50 h.

and then kept under relative humidity of 98% at 30°C for 50 h, the peel strength was measured. The GEMA–BA copolymer film has a much higher peel strength than that of the St–BA copolymer film under high humidity. Furthermore, the peel strength of the GEMA–BA copolymer film under high humidity is found to be very high, even for GEMA contents of 10 and 20 mol %, which differs from results under dry conditions. This is attributed to both the high cohesion force of the GEMA component and the improvement of wettability by a drop in $T_g$ under high humidity. It is expected that the GEMA–BA copolymer has a high potential as a pressure-sensitive adhesive in a transdermal therapeutic system.

## Surface Characteristics of GEMA–BA Copolymer

Figure 7 shows the relationship between the GEMA content and the surface free energy, its dispersion force component, and its polar force component for the GEMA–BA copolymer films. The surface free energy increased gradually from 35 to 53 erg/cm$^2$ with increase in the GEMA content. The dispersion force component of the surface free energy decreased slightly and the polar force component increased gradually with the introduction of GEMA. Therefore, the increase in the surface free energy is attributed to an increase in its polar force component. Consequently, the larger the amount of GEMA in the GEMA–BA copolymer, the more hydrophilic the copolymer surface becomes.

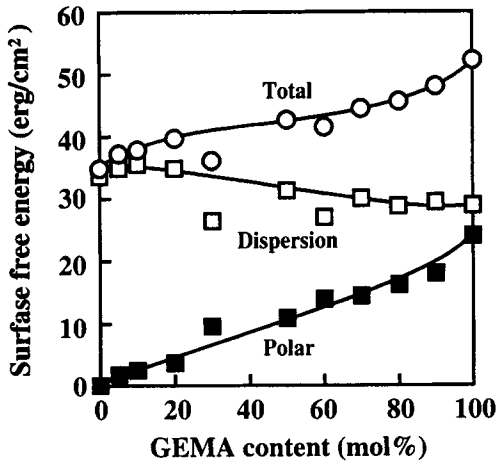



**Figure 7** Effects of GEMA content on the surface free energy of GEMA–BA copolymer film: (○) surface free energy; (□) dispersion force component; (■) polar force component.

We also determined the interfacial free energy between the GEMA–BA copolymer films and water in order to investigate the stability of the copolymer surface in water. The result is shown in Figure 8. The interfacial free energy was also divided into its dispersion force component and its polar force component, in the same way as for surface free energy. PBA homopolymer film has so high an interfacial free energy (about 100 erg/cm$^2$) that the film surface must be unstable in water. The increase in the GEMA content gave rise to a sharp decrease in the interfacial free energy between the GEMA–BA copolymer film and water. At a GEMA content of more

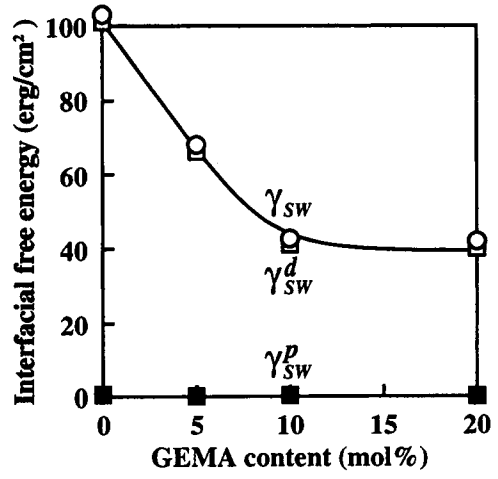



**Figure 8** Effects of GEMA content on the interfacial free energy of GEMA–BA copolymer film in water: (○) interfacial free energy; (□) dispersion force component; (■) polar force component.

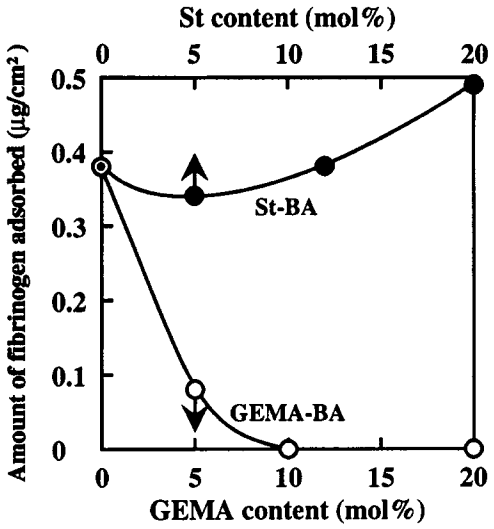



**Figure 9** Effects of GEMA or St content on the amount of fibrinogen adsorbed on the (○) GEMA–BA and (●) St–BA copolymer films.

than 10 mol %, ultimately, the interfacial free energy of the copolymer film reached about 40 erg/cm$^2$. Its polar force component of zero implies that the polarity of the copolymer is close to that of water. These results mean that the surface of the GEMA–BA copolymer film is very hydrophilic and is energetically stable in water, i.e., the introduction of GEMA leads to considerable stabilization of the GEMA–BA copolymer surface in water.

In a previous article,[23] protein adsorption onto the copolymer with pendant monosaccharide was investigated. We found that the introduction of the GEMA component suppresses protein adsorption onto the copolymer film. Protein adsorption onto the GEMA–BA copolymer that has a very stable surface in water attracts our attention from the viewpoint of its application to the medical field. The effects of the GEMA content on the amount of fibrinogen adsorbed onto the GEMA–BA and St–BA copolymer films are shown in Figure 9. Fibrinogen was adsorbed onto the St–BA copolymer films at a high level, and there is a tendency for the amount of adsorbed fibrinogen to increase with increase in the St content. Since the St component is more hydrophobic than is the BA component, the introduction of the former makes the copolymer surface more hydrophobic. Protein adsorption is known to take place on the basis of hydrophobic interaction, hydrogen bonding, electrostatic interaction, etc.[31–33] Therefore, the hydrophobic interaction between the St–BA copolymer film and fibrinogen must become strong with an increase in the St content, because the film becomes more hydrophobic. This is probably the main reason why the St–BA copolymer films have a large amount of adsorbed fibrinogen. On the other hand, the amount of fibrinogen adsorbed onto the GEMA–BA copolymer films decreased steeply with increasing GEMA content and was zero at a GEMA content of more than 10 mol %. The amount of adsorbed fibrinogen corresponds to the interfacial free energy between the GEMA–BA copolymer films and water. Thus, the GEMA–BA copolymer has high potential as a useful biomaterial, since the biocompatibility can be combined with pressure-sensitive adhesive properties in the GEMA–BA copolymer.

## Release of Vitamin $B_{12}$ from the GEMA–BA Copolymer

Figure 10 shows the release profiles of vitamin $B_{12}$ from the GEMA–BA copolymer films in 0.1*M* phosphate buffer (pH 7.4) at 37°C. Vitamin $B_{12}$ was immediately released from the GEMA–BA copolymer films at GEMA contents of 20 and 30 mol %. However, the release of vitamin $B_{12}$ from the films at 5 and 10 mol % was very slow and the release rate was constant for a long time. The GEMA–BA copolymer films at 20 and 30 mol % are so hydrophilic that the films swell considerably in water. Diffusivity of vitamin $B_{12}$ in the films at 5 and 10 mol % is lower than for 20 and 30 mol %, due to limited swelling of the films. This is the reason why vitamin $B_{12}$ is slowly released from the GEMA–BA film at GEMA contents of 5 and 10 mol %.

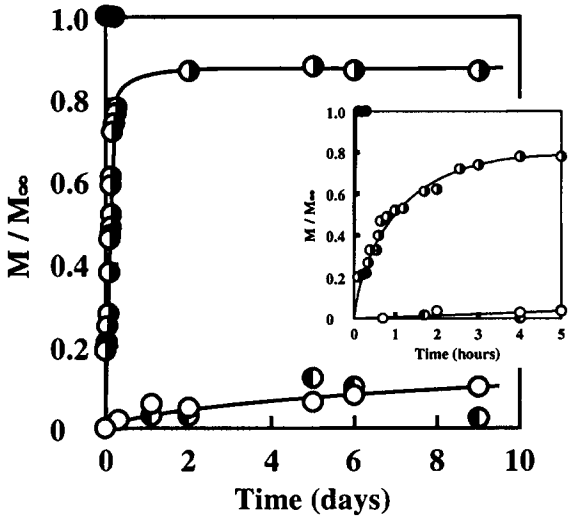



**Figure 10** Vitamin $B_{12}$ release from GEMA–BA copolymer films into 0.1*M* phosphate buffer (pH 7.4) at 37°C. GEMA content: (○) 5 mol %; (◐) 10 mol %; (◑) 20 mol %; (●) 30 mol %.

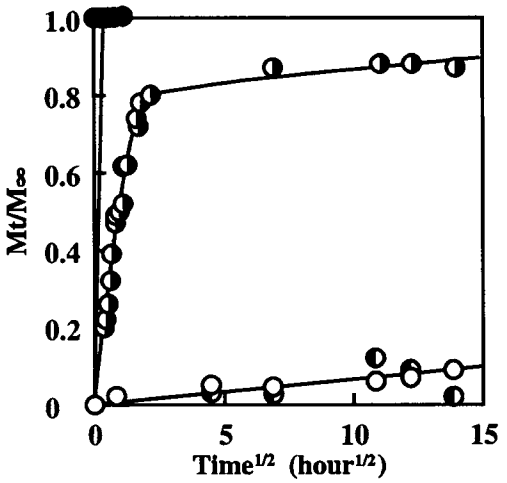



**Figure 11** Vitamin $B_{12}$ release profiles from GEMA–BA copolymer film as a function of square root of time. GEMA content: (○) 5 mol %; (◐) 10 mol %; (◑) 20 mol %; (●) 30 mol %.

In general, if diffusion of a drug is governed by Fick's law at steady state,[4–7] the correlation between time and the amount of released drug is given by the following equation:

$$\frac{M_t}{M_\alpha} = kt^{1/2} \tag{8}$$

where $k$ is the diffusion coefficient, and $Mt$, the amount of released drug at time $t$.

Figure 11 shows the release profiles of vitamin $B_{12}$ from the GEMA–BA copolymer films as a function of the square root of time. The amount of released vitamin $B_{12}$ from the films was proportional to the square root. This means that the release of vitamin $B_{12}$ is governed by Fick's law. For the GEMA–BA copolymer films at 5 and 10 mol %, especially, a slow release of vitamin $B_{12}$ is realized for a long time. Therefore, since the GEMA–BA copolymer film at the GEMA content of 5 mol % has excellent pressure-sensitive adhesive properties and can release the drug slowly, it has high potential for use in a transdermal therapeutic system.

## CONCLUSIONS

Pressure-sensitive adhesive copolymers with pendant monosaccharides were synthesized by the copolymerization of glycosyloxyethyl methacrylate (GEMA) and butyl acrylate (BA). Surface characteristics and pressure-sensitive adhesive properties of their films were studied. The GEMA–BA copolymer film with GEMA content of 5 mol % is an excellent pressure-sensitive adhesive and exhibits adequate adhesive properties even under a relative humidity of 98%. The surface of the film becomes hydrophilic with an increase in the GEMA content. A very small amount of fibrinogen was adsorbed onto the film at GEMA contents of more than 10 mol %. The release profiles of vitamin $B_{12}$ from the copolymer films were examined as a model of drug release in a transdermal therapeutic system. The release rate of vitamin $B_{12}$ could be controlled by the GEMA content and the copolymer film at 5 mol % released vitamin $B_{12}$ most slowly for a long time.

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