A Mucoadhesive Polymer Prepared by Template Polymerization of Acrylic Acid in the Presence of Poly(ethylene glycol) Macromer

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ABSTRACT: A new mucoadhesive polymer complex was prepared by the template polymerization of acrylic acid with poly(ethylene glycol) macromer (PEGM) as a template polymer. Fourier transform infrared results showed that the poly(acrylic acid) (PAA)/PEGM mucoadhesive polymer complex was formed by hydrogen bonding between the carboxyl groups of PAA and the ether groups of PEGM. The glass-transition temperature of the PAA/PEGM mucoadhesive polymer complexes was shifted to a lower temperature as the repeating unit ratio of PAA/PEGM in the complex decreased. The dissolution rate of the PAA/PEGM mucoadhesive polymer complex was much slower than that of the PAA/poly(ethylene glycol) (PEG) mucoadhesive polymer complex and was dependent on the pH and molecular weight of PEGM. The mucoadhesive force of the PAA/PEGM mucoadhesive polymer complexes was stronger than that of commercial Carbopol 971P NF and almost the same as that of the PAA/PEG mucoadhesive polymer complex. The PAA/PEGM interpolymer complex seemed to be a better mucoadhesive polymer matrix than the PAA/PEG interpolymer complex. © 2002 John Wiley & Sons, Inc. J Appl Polym Sci 83: 1904–1910, 2002

Key words: mucoadhesive; template polymerization; adhesive force; dissolution rate; glass transition; FTIR; drug delivery systems

INTRODUCTION

The applications of various polymers for developing a drug delivery system have been the subject of many creative studies in polymer and pharmaceutical chemistry. Drug delivery systems have been used for reducing side effects, enhancing therapeutic efficacy, and improving patient compliance. One drug delivery system that has attracted wide attention recently is the transmucosal drug delivery (TMD) system.[1–6] The TMD system, delivering a drug across a mucous membrane to achieve a local or systemic effect for an extended period of time, consists of a drug, a mucoadhesive polymer, and other excipients. The mucoadhesive polymer can adhere directly to the apical membrane of the epithelial cell or the mucosal epithelial tissue. Mucoadhesive polymers have been used for developing various kinds of TMD systems for buccal,[1] nasal,[2] ocular,[3] rectal,[4] vaginal,[5] and gastrointestinal[6] administration. A large number of new mucoadhesive polymers

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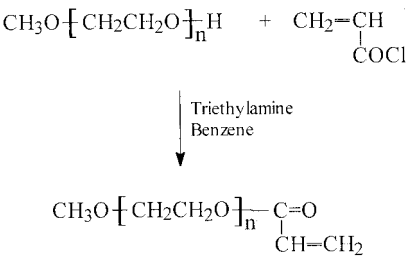
have been synthesized and characterized to improve mucoadhesive properties. Among various synthetic and natural mucoadhesive polymers, poly(acrylic acid) (PAA) has been considered one of the best mucoadhesive polymers because of its excellent mucoadhesive property. The drawbacks of PAA being used as a matrix polymer for TMD systems are its high glass-transition temperature (T_g) and high water solubility. The high T_g of PAA may pose problems in terms of the flexibility required for optimal wetting and intimate contact with mucous membrane.[7] The high water solubility of PAA critically limits its use as a TMD system because it may be dissolved before the desired duration for the delivery of the drug across the membrane.[8]

In our previous work, we reported the synthesis and physical properties of PAA/poly(ethylene glycol) (PEG) interpolymer complexes obtained by the template polymerization of acrylic acid in the presence of PEG.[9] The aqueous solubility was significantly reduced in comparison with that of PAA, and the mucoadhesive force was better than that of a commercial mucoadhesive polymer. However, PAA/PEG interpolymer complexes were dissolved within an hour at pH 7.4 when the molecular weight of PEG was under 5000. The objectives of this work were to further retard the dissolution rate of the complex and to investigate the effect of a template polymer on the final product. To retard the dissolution rate of the PAA/PEG interpolymer complex, we designed the PAA/poly(ethylene glycol) macromer (PEGM) mucoadhesive polymer complex. The complexes were characterized in terms of their adhesive force, thermal property, dissolution rate, and spectroscopic property.

EXPERIMENTAL

Materials

Methoxy PEGs with molecular weights of 2000 and 5000 were purchased from Sigma Chemical Co. (St. Louis, MO). Methoxy PEG with a molecular weight of 11,000 was kindly donated by Nippon Oil and Fat Co. Methoxy PEG was purified via azeotropic distillation from a benzene solution. Azobisisobutyronitrile (AIBN) and acrylic acid were purchased from Junsei Chemical Co. (Tokyo, Japan). Acrylic acid was used after removal of the inhibitor. All other chemicals were reagent-grade and were used without further purification.



Scheme 1 Synthesis of PEGM.

Synthesis of PEGM

The synthesis method of PEGM was previously reported.[10] As shown in Scheme 1, 20 g of purified methoxy PEG (molecular weight = 5000) was added to 150 mL of benzene and heated to 80°C. A total of 1.12 mL of triethylamine and 0.65 mL of acryloyl chloride were added and reacted at 80°C for 3 h. The reaction mixture was filtered to remove triethylamine hydrochloride, and then PEGM was obtained by the supernatant being dropped into *n*-hexane. The final product was dried at 40°C in a vacuum oven.

Template Polymerization

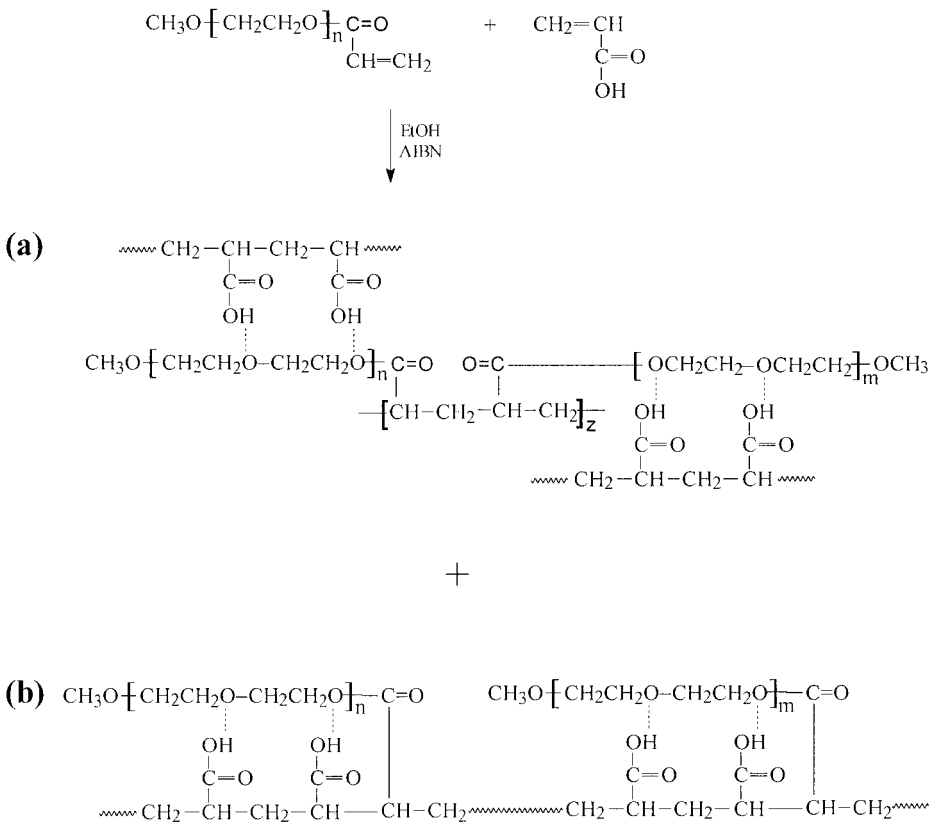
As shown in Scheme 2, the PAA/PEGM mucoadhesive polymer complex was synthesized by the template polymerization of acrylic acid in the presence of PEGM. To prepare the PAA/PEGM mucoadhesive polymer complexes, we dissolved acrylic acid and PEGM in ethanol, and we purged the solution with nitrogen gas for 15–20 min to remove oxygen. The polymerization was carried out with AIBN as an initiator at 80°C for 15 h.

IR Spectroscopy Study

IR absorption spectra of the PAA/PEGM mucoadhesive polymer complexes were studied with a Fourier transform infrared (FTIR) spectrophotometer (Nicolet Magna-IR 550).

Thermal Analysis

T_g's of the PAA/PEGM mucoadhesive polymer complexes were measured with a differential scanning calorimeter (DSC-2010, TA Instrument) at a scan rate of 10°C/min.



Scheme 2 Synthesis of the PAA/PEGM mucoadhesive polymer complex.

Measurement of the Dissolution Rate

Dissolution rates of the PAA/PEGM mucoadhesive polymer complexes and PAA/PEG interpolymer complexes were measured as a function of time at 37°C at various pHs. The specimens, as a disc type, were solvent-cast with a thickness of 0.4 mm and a diameter of 0.8 cm. The disc was placed in 10 mL of an appropriate medium and was shaken at 60 reciprocation/min. At predetermined time intervals, the disc was taken out and dried for measuring the weight. The dissolution degree was calculated by $[(W_p - W_s)/W_p] \times 100$, where W_s and W_p are the dried weights of samples after and before testing, respectively.

Measurement of the Adhesive Force

We used a motor-driven tension meter (Shimadzu AGS-5000D) to measure the adhesive force of the PAA/PEGM mucoadhesive polymer complexes and the PAA/PEG interpolymer complexes with a pig intestinal mucosa. The PAA/PEGM mucoadhesive polymer complexes were cut as a disc with an area of 1.32 cm^2, and the disc was wetted with water and placed on the surface of a pig intestinal mucosa. They were kept in contact with the pig intestinal mucosa under a force of 1.2 N/cm^2 for 3 min before the measurement. The peak force required to detach the disc from the pig intestinal mucosa was measured.

RESULTS AND DISCUSSION

The PAA/PEGM mucoadhesive polymer complexes were prepared by the template polymerization of acrylic acid in the presence of PEGM with molecular weights of 2000, 5000, and 11000. It was hypothesized that an interpolymer complex in the PAA/PEGM mucoadhesive polymer complex was formed by the template polymerization between the ether groups of PEGM and the carboxyl groups of PAA through hydrogen bonding. To prove the hypothesis, we used FTIR to check for a shift of the carbonyl stretching band of PAA as a result of hydrogen bonding. Figure 1 shows the effect of the repeating unit ratio of PAA to PEGM (molecular weight = 5000) on the carbonyl

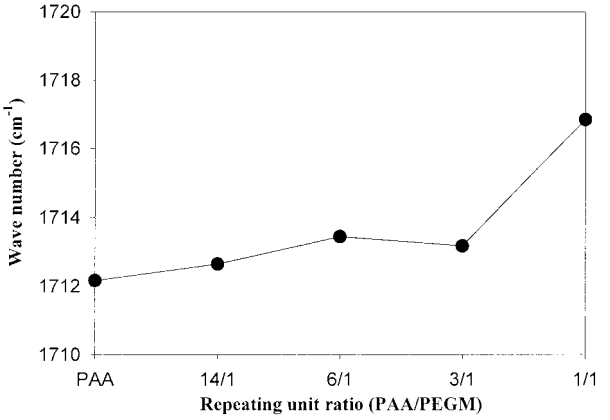


Figure 1 Effect of the repeating unit ratio of the PAA/PEGM mucoadhesive polymer complexes on the carbonyl absorption band of PAA.

stretching band of PAA in the PAA/PEGM mucoadhesive polymer complexes. The PAA itself shows a band at 1712 cm^{-1} due to intramolecular hydrogen bonding between carboxyl groups of PAA. However, some of the intramolecular hydrogen bonds were broken once PAA and PEGM formed the complex between carboxyl groups of PAA and ether groups of PEGM through hydrogen bonding, as shown in Scheme 2(a). Therefore, if the complex in the PAA/PEGM mucoadhesive polymer complex was formed, the carbonyl absorption band of PAA was shifted to a higher wave number.[11,12] As shown in Figure 1, the extent of the shift was minimal up to the repeating unit ratio of 3/1 and became significant at the repeating unit ratio of 1/1. It is thought that a large portion of carboxyl groups of PAA still form intramolecular hydrogen bonding up to the repeating unit ratio of 3/1 because more carboxyl groups of PAA were available than ether groups of PEGM. At the repeating unit ratio of 1/1, most carboxyl groups of PAA formed hydrogen bonding with ether groups of PEGM, and their interaction became significant, resulting in a large shift in the carbonyl absorption band of PAA. The results suggested that PAA and PEGM formed a complex through hydrogen bonding by the template polymerization of acrylic acid in the presence of PEGM.

Figure 2 shows the effect of the repeating unit ratio of PAA/PEGM on T_g of the PAA/PEGM mucoadhesive polymer complexes. The results showed that T_g of PAA in the complexes decreased with a decrease in the repeating unit ratio of PAA/PEGM. The PAA/PEGM mucoadhesive polymer complex prepared in this study seemed to be a mixture of the PEGM/PAA interpolymer complex [Scheme 2(a)] and its copolymer [Scheme 2(b)], as shown in Scheme 2; the presence of the copolymer led to the decrease in T_g, and T_g of the pure interpolymer complex appeared to be masked. However, the separation of the copolymer in the mixture of the PAA/PEG interpolymer complex and the copolymer failed with general methods, such as gel permeation chromatography and NMR.

Figure 3 shows the dissolution rate of the PAA/PEGM mucoadhesive polymer complexes with repeating unit ratios of 3/1, 6/1, and 14/1 at various pHs. The complex with the repeating unit ratio of 14/1 was completely dissolved within 8 h at pH 7.4. Approximately 65% of the complex with the repeating unit ratio of 6/1 was dissolved within 8 h. When the repeating unit ratio was 3/1, the dissolution degree was only about 42% after 24 h. Figure 3(b) shows that the dissolution degree of the complex was significantly reduced at pH 4.0. The complexes with repeating unit ratios of 14/1, 6/1, and 3/1 were dissolved by almost 100, 43, and 23% after 12 h, respectively. At pH 2.0 [Fig. 3(c)], the complexes with repeating unit ratios of 14/1, 6/1, and 3/1 were dissolved by 38, 24, and 20% after 24 h, respectively. The dissolution rate of the PAA/PEGM mucoadhesive polymer complexes seemed to vary with the complexation density between carboxyl groups of PAA and ether groups of PEGM, which masked hydrophilic groups such as carboxyl groups of PAA and ether groups of PEGM. The complex with the lower repeating unit ratio seemed to have a higher degree of complexation because more PEGM was available to form hydrogen bonding and thus dis-

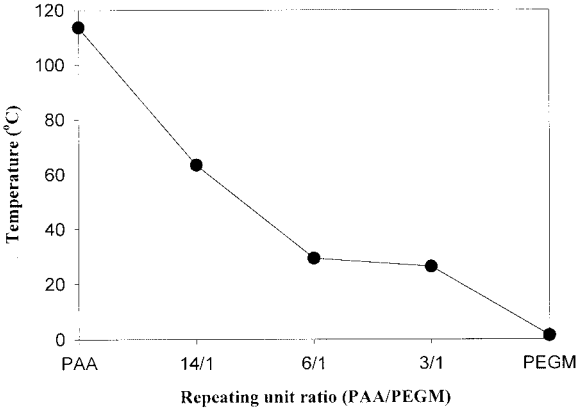
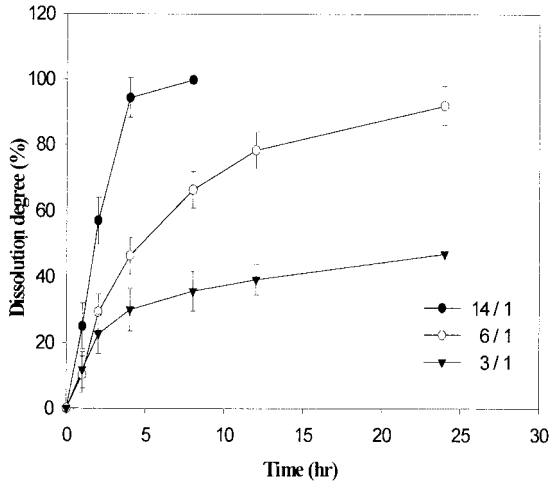
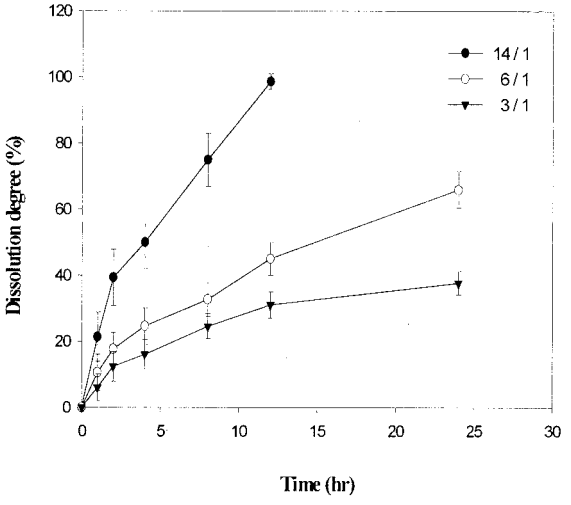


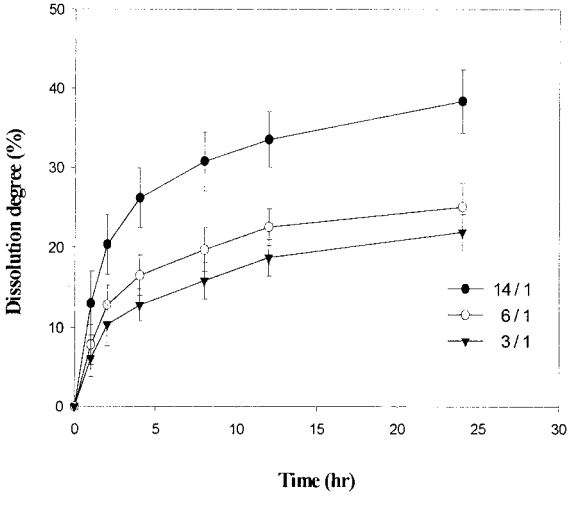
Figure 2 Effect of the repeating unit ratio of the PAA/PEGM mucoadhesive polymer complexes on T_g.



(a)



(b)



(c)

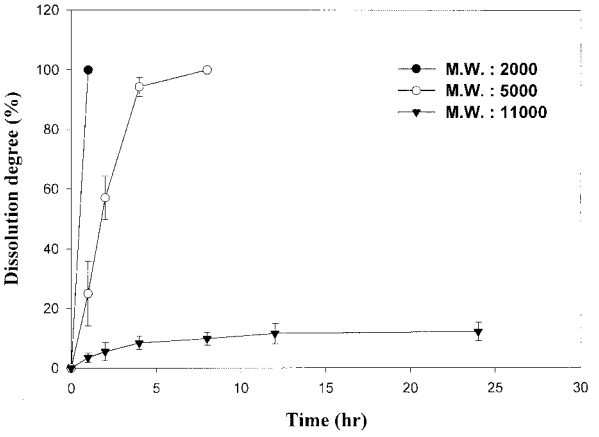


Figure 4 Effect of the PEGM molecular weight on the dissolution rate of the PAA/PEGM mucoadhesive polymer complexes with a repeating unit ratio of 14/1 at pH 7.4. Data are presented as the mean plus or minus the standard error of the mean ($n = 3$).

solved more slowly than the complexes with the higher repeating unit ratio. It was also shown that the dissolution rate of the complexes increased as the pH of the dissolution medium increased. It was thought that when the pH was much higher than the pK_a value of PAA (4.75), the number of dissociated carboxyl groups in the complex increased and hydrogen bonding between the carboxyl groups of PAA and the ether groups of PEGM could not be formed, leading to faster dissolution rates of the complexes.[9] In general, a decrease in T_g for the polymer should result in an increase in the solubility. However, we obtained the opposite results. It is thought that the decrease in T_g of the polymer is attributable to the presence of the copolymer, whereas the decrease in the dissolution of the polymer is attributable to the hydrophobic interaction of the vinyl groups and high polymerization rate of PEGM, an indication of the opposite direction of T_g and the dissolution of the polymer.

Figure 4 shows the effect of the PEGM molecular weight on the dissolution rate of the PAA/PEGM mucoadhesive polymer complex with the repeating unit ratio of 14/1 at pH 7.4. For the PEGM molecular weights of 2000 and 5000, they

Figure 3 Effect of the repeating unit ratio of PAA/PEGM on the dissolution degree of the PAA/PEGM mucoadhesive polymer complexes at (a) pH 7.4, (b) pH 4.0, and (c) pH 2.0. Data are presented as the mean plus or minus the standard error of the mean ($n = 3$).

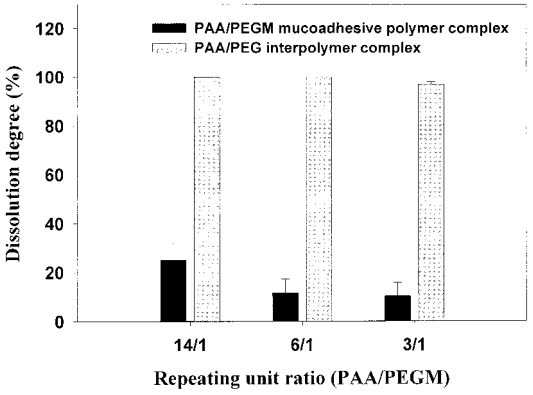


Figure 5 Comparison of the dissolution degree between the PAA/PEGM mucoadhesive polymer complexes and the PAA/PEG interpolymer complexes at pH 7.4 after 1 h in the dissolution medium. Data are presented as the mean plus or minus the standard error of the mean ($n = 3$).

were completely dissolved within 1 and 8 h, respectively. When the molecular weight of PEGM was 11000, only about 10% of the complex was dissolved after 24 h. As the molecular weight of PEGM increased, the molecular weight of the PAA/PEGM complex should increase, resulting in increased hydrophobicity and decreased aqueous solubility. Also, it is thought that the degree of polymerization of the acrylate increased as the molecular weight of PEGM increased because the critical micelle concentration of the vinyl groups in the micellar structure decreased with an increase in the molecular weight of PEGM.

Figure 5 compares the dissolution degree of the PAA/PEGM mucoadhesive polymer complexes and the PAA/PEG interpolymer complexes with various repeating unit ratios at pH 7.4 after 1 h. The dissolution degree of the PAA/PEGM mucoadhesive polymer complexes was lower than that of the PAA/PEG interpolymer complexes at all repeating unit ratios. It is suggested that PEGM has a PEG central domain and a polymerizable acrylic end group. When the complex is formed through the template polymerization of acrylic acid in the presence of PEGM, PEGM is also polymerized because of polymerizable end groups. Thus, the PAA/PEGM mucoadhesive polymer complex is composed of the PAA/PEGM interpolymer complex and its copolymer, as shown in Scheme 2. Because the PAA/PEGM copolymer can form intramolecular hydrogen bonding between carboxyl groups of PAA and ether groups of PEGM, as shown in Scheme 2(b), its hydrophobicity is greater than that of the PAA/PEG interpolymer complex, resulting in lower aqueous solubility. Also, it is thought that more stoichiometrical interpolymer complexes between the carboxyl groups of PAA and ether groups of PEGM occurred because of the incorporation of the acrylate moiety into the PEG chain because the PEG endcapped with hydrophobic polymerizable units formed micellar structures in water or organic solvents, indicating of a strong hydrophobic association of vinyl groups.[13] This micellar structure led to an increased rate of the propagation reaction and a decrease in the termination rate in a free-radical polymerization,[13] suggesting a high polymerization rate of PEGM. This resulted in a decreased dissolution rate of the polymer compared with that of the PAA/PEG interpolymer complexes and a large shift in the carbonyl absorption band of PAA at the repeating unit ratio of 1/1. Therefore, the comparison of the molecular weights of PEG and PEGM after the polymerization of PEGM is not significant but is meaningful before its polymerization. Also, there was no differences in solubility between PEG and PEGM at the same molecular weight before polymerization.

Table I compares the adhesive forces of the PAA/PEGM mucoadhesive polymer complexes and PAA/PEG interpolymer complexes with pig intestinal mucosa against repeating unit ratios. We measured the adhesive force by measuring the force required to break the contact between the complex and pig intestinal mucosa. The results indicated that the adhesive force for the PAA/PEGM mucoadhesive polymer complexes decreased with an increase of PEGM in the complex and was stronger than commercial Carbopol 971P NF. Because the main mechanism of mucoadhesiveness for the PAA/PEGM complex is hydrogen bonding and chain entanglement between the carboxyl groups of PAA free from forming hydrogen bonding with the ether groups of PEGM and mucin mucopolysaccharide, the more carboxyl groups of PAA there are free from forming hydrogen bonding with the ether groups of PEGM, the better the mucoadhesiveness is that can be expected. Thus, the adhesive force of the PAA/PEGM mucoadhesive polymer complexes decreased with an increased ratio of PEGM in the complex.

CONCLUSIONS

The PAA/PEGM mucoadhesive polymer complex prepared by the template polymerization of

Table I Effect of Repeating Unit Ratio on the Adhesive Force of the PAA/PEG Interpolymer Complexes and the PAA/PEGM Mucoadhesive Polymer Complexes with Pig Intestinal Mucosa

	Adhesive Force (Kg_f)[b]	
Repeating Unit Ratio (PAA/PEGM[a])	PAA/PEGM Mucoadhesive Polymer Complexes ($M \pm SD$)	PAA/PEG Interpolymer Complexes ($M = SD$)
14/1	1.62 ± 0.14	1.69 ± 0.10
6/1	1.57 ± 0.12	1.57 ± 0.09
3/1	0.80 ± 0.20	0.80 ± 0.17
Carbopol 971P NF	1.26 ± 0.04	

$n = 5$.
[a] The molecular weight of PEGM used was 5000.
[b] 1 $Kg_f = 9.8\ N$.

acrylic acid in the presence of PEGM showed strong adhesive force and limited solubility in water, essential requirements for the mucoadhesive polymer to be used in TMD systems. The complex was formed through hydrogen bonding, which was confirmed by FTIR. The carbonyl band of PAA in the complex was shifted to a higher wave number because of hydrogen bonding between PAA and PEGM. T_g of PAA in the PAA/PEGM mucoadhesive polymer complexes decreased with a decrease in the repeating unit ratio of PAA/PEGM. The dissolution rate of the PAA/PEGM mucoadhesive polymer complexes was slower than that of the PAA/PEG interpolymer complexes. It is concluded that the PAA/PEGM mucoadhesive polymer complex is a better mucoadhesive polymer than the PAA/PEG interpolymer complex for developing TMD systems.

REFERENCES

1. McQuinn, R. L.; Kvam, D. C.; Maser, M. J.; Miller, A. L.; Oliver, S. J Controlled Release 1995, 34, 243.
2. Nakamura, K.; Maitani, Y.; Lowman, A. M.; Takayama, K.; Peppas, N. A.; Nagai, T. J Controlled Release 1999, 61, 329.
3. Davies, N. M.; Farr, S. J.; Hadgraft, J.; Kellaway, I. W. Pharm Res 1991, 8, 1039.
4. Miyazaki, S.; Suisha, F.; Kawasaki, N.; Shirakawa, M.; Yamatoya, K.; Attwood, D. J Controlled Release 1998, 56, 75.
5. Gürsoy, A.; Sohtorik, I.; Uyanik, N.; Peppas, N. A. S T P Pharm 1989, 5, 886.
6. Lehr, C.; Bouwstra, J. A.; Tukker, J. J.; Junginger, H. E. J Controlled Release 1990, 13, 51.
7. Shojaei, A. H.; Li, X. J Controlled Release 1997, 47, 151.
8. Ian, G. N.; Frederick, C. S. Biomaterials 1995, 16, 617.
9. Choi, H. K.; Kim, O. J.; Chung, C. K.; Cho, C. S. J Appl Polym Sci 1999, 73, 2749.
10. Cho, C. S.; Ha, J. H.; Han, S. Y.; Kim, S. H.; Kwon, J. K.; Sung, Y. K. J Appl Polym Sci 1996, 60, 161.
11. Baranovsky, V. Yu.; Kotlyarsky, I. V.; Etlis, V. S.; Kabanov, V. A. Eur Polym J 1992, 28, 1428.
12. Chun, M. K.; Cho, C. S.; Choi, H. K. J Appl Polym Sci 2001, 79, 1525.
13. Sawhney, A. S.; Pathak, C. P.; Hubbel, J. A. Macromolecules 1993, 26, 581.