A Novel Mucoadhesive Polymer Prepared by Template Polymerization of Acrylic Acid in the Presence of Poloxamer

MYUNG-KWAN CHUN,[1] CHONG-SU CHO,[2] HOO-KYUN CHOI[1]

[1] College of Pharmacy, Chosun University, 375 Seoseok-dong, Dong-gu, Kwangju 501-759, Korea

[2] School of Agricultural Biotechnology, Seoul National University, Suwon 441-744, Korea

Received 6 March 2000; accepted 4 April 2000

ABSTRACT: A new mucoadhesive polymer was prepared by template polymerization of acrylic acid using poloxamer as a template polymer. FTIR results showed that the interpolymer complex was formed by hydrogen bonding between the carboxyl group of poly(acrylic acid) (PAA) and the ether group of poloxamer. The extent of hydrogen bonding in the PAA/poloxamer interpolymer complex increased as the ratio of PAA/poloxamer decreased. The T_g of PAA/poloxamer interpolymer complexes was matched well with the T_g calculated by Gordon-Taylor's equation than that of their blends. This result suggests that the PAA and poloxamer in the interpolymer complexes are more compatible than their blends. The dissolution rate of PAA/poloxamer interpolymer complexes was much slower than that of their blends, and was dependent on the pH of the medium and the ratio of PAA/poloxamer. The adhesive bond strength of PAA/poloxamer interpolymer complexes to a plastic (polypropylene) plate was greater than their blends or a commercial product, Carbopol 971P NF. © 2000 John Wiley & Sons, Inc. J Appl Polym Sci 79: 1525–1530, 2001

Key words: mucoadhesive; template polymerization; adhesive bond strength; dissolution rate

INTRODUCTION

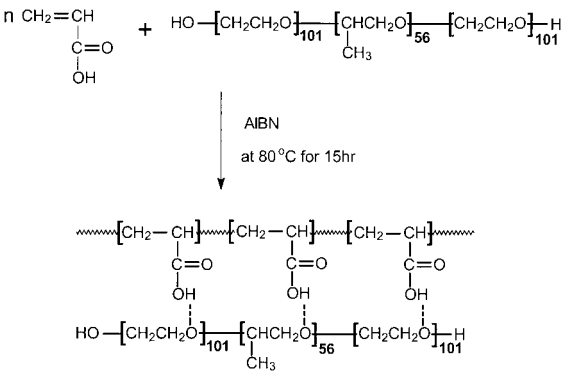
Many different kinds of polymers have been investigated for their potential use as a platform to deliver a drug in an efficient and a controlled manner, i.e., a drug delivery system. One of the many different methods used in those drug delivery systems is a transmucosal drug delivery system. A transmucosal drug delivery (TMD) system is applied on a mucous membrane and delivers a drug across the mucous membrane to achieve a local or systemic effect for an extended period of time. One of the major components of the system is a mucoadhesive polymer that serves as a matrix for a drug. Many researchers in polymer and pharmaceutical chemistry have developed and utilized various mucoadhesive polymers for TMD systems.[1–4] Among various synthetic and natural mucoadhesive polymers, poly(acrylic acid) (PAA) has been considered as one of the best mucoadhesive polymers based on its excellent mucoadhesive property. Despite the excellent mucoadhesive property of PAA, it has some drawbacks if used in a TMD system, such as high glass transition temperature (T_g) and high water solubility. The high

Correspondence to: H.-K. Choi.

Contract grant sponsor: Korean Ministry of Public Health and Welfare; contract grant number: HMP-97-E3-0018.

Contract grant sponsor: Brain Korea 21 Project.

Journal of Applied Polymer Science, Vol. 79, 1525–1530 (2001)



Scheme 1 Synthesis of the PAA/poloxamer interpolymer complex.

T_g of PAA may pose a problem in terms of flexibility at room temperature, which is required for optimal wetting and intimate contact with mucous membrane.[5] High water solubility of PAA critically limits its use as a TMD system, because it may dissolve before the desired duration for the delivery of the drug across the membrane.[6]

Many studies have been done to prepare copolymers or interpolymer complexes with PAA,[5,7–9] however, only a limited number of studies have been done to use a PAA interpolymer complex as a mucoadhesive polymer. Strong intermolecular forces, such as hydrogen bonding, connect the growing polymer chain and the template in the interpolymer complex,[6,9] and this may result in different physico-chemical characteristics. We have attempted to prepare PAA interpolymer complexes with a methoxy poly(ethylene glycol) and methoxy poly(ethylene glycol) macromer for application as a mucoadhesive polymer.[6,10] The complex formation was attributed to hydrogen bonding between the ether group of the methoxy poly(ethylene glycol) or methoxy poly(ethylene glycol) macromer and the carboxyl group of PAA. This study was conducted as a continuing effort to prepare a new mucoadhesive polymer using poloxamer as a template polymer. Similar hydrogen bonding is expected between the ether group of poloxamer and the carboxyl group of PAA.

The objectives of this work are to decrease the water solubility of PAA and to maintain or improve mucoadhesive property of PAA for its application in a TMD system. To decrease water solubility of PAA, interpolymer complexes between PAA and poloxamer with various ratios were prepared by polymerizing acrylic acid in the presence of poloxamer as a template without a crosslinking agent, as shown in Scheme 1. We expected that the protons of the carboxyl groups on PAA would form hydrogen bonding with the ether groups on the poloxamer chain. The resulting interpolymer complex will be more hydrophobic than the constituent polymers. The hydrophobic methyl groups on the poloxamer chain may further increase the hydrophobicity of the complex. The PAA/poloxamer interpolymer complexes were characterized in terms of their adhesive bond strength, thermal property, dissolution rate, and spectroscopic property.

EXPERIMENTAL

Materials

Poloxamer 407 was provided by BASF (Ludwigshafen, Germany). PAA (M_v: 450,000) was purchased from Aldrich Chemical Co. (Milwaukee, WI). Azobisisobutyronitrile (AIBN) and acrylic acid were purchased from Junsei Chemical Co. (Tokyo, Japan), and used after removing the inhibitor. All other chemicals were of reagent grade, and were used without further purification.

Template Polymerization

As shown in Scheme 1, the PAA/poloxamer interpolymer complex was synthesized by template polymerization of acrylic acid in the presence of poloxamer. To prepare the PAA/poloxamer interpolymer complexes, acrylic acid and poloxamer were dissolved in ethanol, and the solution was purged 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

Infrared absorption spectra of PAA/poloxamer interpolymer complexes were studied by an FTIR spectrophotometer (Magna-IR 550, Nicolet).

Thermal Analysis

Glass transition temperatures (T_gs) of PAA/poloxamer interpolymer complexes and their blends were measured by a differential scanning calorimeter (DSC-2010, TA Instrument) at a scan rate of 10°C/min.

Measurement of Dissolution Rate

Dissolution rates of the PAA/poloxamer interpolymer complexes and their blends were measured

as a function of time at 37°C in phosphate buffer solutions at various pHs. The specimens in disc form were solvent cast with a thickness of 0.4 mm and diameter of 8 mm. The disc was placed in 10 mL of phosphate buffer solutions at pH 2.0, pH 4.0, or pH 7.4, and it was shaken at 60 cycles/min. At predetermined time intervals the disc was taken out and dried at 120°C in a vacuum oven for 24 h to measure the weight. The dissolution degree was calculated by $[(W_p - W_s)/W_p) \times 100$, where W_s and W_p are dried weight of samples after the test and before the test, respectively.

Measurement of Adhesive Bond Strength

A motor-driven tension meter (AGS-5000D, Shimadzu) was used to measure the adhesive bond strength of the PAA/poloxamer interpolymer complexes and their blends to a plastic (polypropylene) plate. The specimens were cut as discs, with area of 1.32 cm^2, and the discs wetted with water and placed on the surface of a plastic plate. Contact continued with the plate 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 plastic plate was measured.

RESULTS AND DISCUSSION

The PAA/poloxamer interpolymer complexes were prepared by the template polymerization of acrylic acid in the presence of poloxamer using various monomer mol ratios of PAA to poloxamer (1/1, 4/1, 8/1, and 16/1). The monomer mol ratio was calculated by dividing the number of monomers in PAA by those in poloxamer. We have shown in the previous study that hydrogen bonding was formed in a PAA/methoxy poly(ethylene glycol) interpolymer complex. To test if we can observe the same phenomena in the PAA/poloxamer interpolymer complex, FTIR was used to observe a shift of the carbonyl stretching band of PAA resulting from hydrogen bonding. Figure 1 shows the effect of monomer mol ratios of PAA to poloxamer used to prepare interpolymer complexes on the carbonyl stretching band of PAA. The PAA itself shows the band at 1712 cm^{-1} due to the intramolecular hydrogen bonding between carboxyl groups of PAA. However, some of the intramolecular hydrogen bondings break, once PAA and poloxamer form interpolymer complex, because new hydrogen bonds will be formed between the carboxyl groups of PAA and the ether

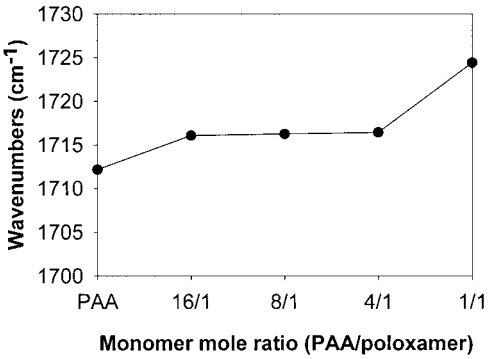


Figure 1 Effect of monomer mol ratio of the PAA/poloxamer interpolymer complexes on the carbonyl absorption band of PAA.

groups of poloxamer, as shown in Scheme 1. Therefore, once the interpolymer complex is formed, the carbonyl absorption band of PAA is expected to be shifted to a higher wave number.[11] As can be seen in Figure 1, the extent of the shift is minimal up to the monomer mol ratio of 4/1, and becomes significant at the ratio of 1/1. A large portion of carboxyl groups of PAA still form intramolecular hydrogen bonding up to the monomer mol ratio of 4/1, because more carboxyl groups of PAA are available than ether groups of poloxamer. At the monomer mol ratio of 1/1, every carboxyl group of PAA has an ether group of poloxamer available to form hydrogen bonding, and their interaction becomes significant, resulting in a large shift in carbonyl absorption band of PAA. The results suggest that PAA and poloxamer formed a complex through hydrogen bonding by template polymerization of acrylic acid in the presence of poloxamer.

Figure 2 shows the effect of the monomer mol ratio of the PAA/poloxamer on the T_g of the PAA/poloxamer interpolymer complexes and their blends. The T_g of the PAA/poloxamer interpolymer complexes decreased with a decrease in the monomer mol ratio of the PAA/poloxamer. Gordon-Taylor's equation provides a relationship between T_g and the composition of a random copolymer or a compatible polymer blend as follows.[12]

$$T_g = W_1 T_{g_1} + W_2 T_{g_2}$$

where T_{g_1} and T_{g_2} represent the T_g of the two corresponding components, and W_1 and W_2 refer to the weight fraction of the two corresponding components, respectively.

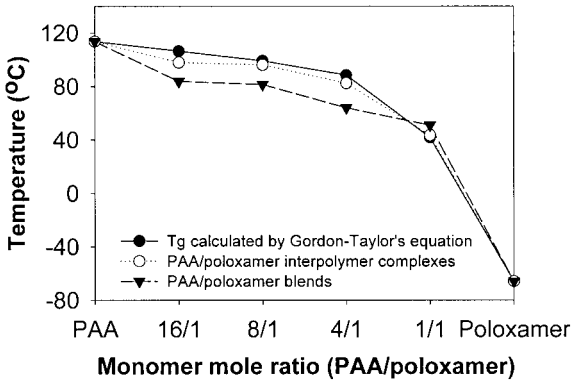


Figure 2 Effect of monomer mol ratio of the PAA/poloxamer interpolymer complexes and their blends on the glass transition temperature (T_g).

Gordon-Taylor's equation was used to compare calculated data with the T_g of complexes and blends. The T_gs of PAA/poloxamer interpolymer complexes matched well with the T_gs calculated by Gordon-Taylor's equation, while those of their blends showed some deviation from the calculated value as shown in Figure 2. These results suggest PAA and poloxamer in the interpolymer complexes were more compatible with each other than those in blends.

Figure 3 compares the dissolution degree of PAA/poloxamer interpolymer complexes and their blends with various monomer mol ratios after 4 h in phosphate buffer solutions at pH 2.0, pH 4.0, and pH 7.4. The dissolution degree of PAA/poloxamer interpolymer complexes was lower than that of their corresponding blends at all monomer mol ratios and at all pHs tested. This may due to stronger interaction between PAA and poloxamer in the interpolymer complex resulting from better compatibility of two components than in their blends. At pH 2.0 and pH 4.0, the dissolution degree of the PAA/poloxamer blend with the monomer mol ratio of 1/1 was similar to that of the PAA/poloxamer interpolymer complex with the same monomer mol ratio. A similar result was obtained from the measurement of T_g. The T_g of the PAA/poloxamer blend with the monomer mol ratio of 1/1 was similar to the T_g of the interpolymer complex with the same monomer mol ratio, as shown in Figure 2. The results suggest that the PAA/poloxamer blend with the monomer mol ratio of 1/1 may form hydrogen bonding more efficiently than the blends with other monomer mol ratios.

It was also observed that the dissolution rate of the PAA/poloxamer complex was slower than that

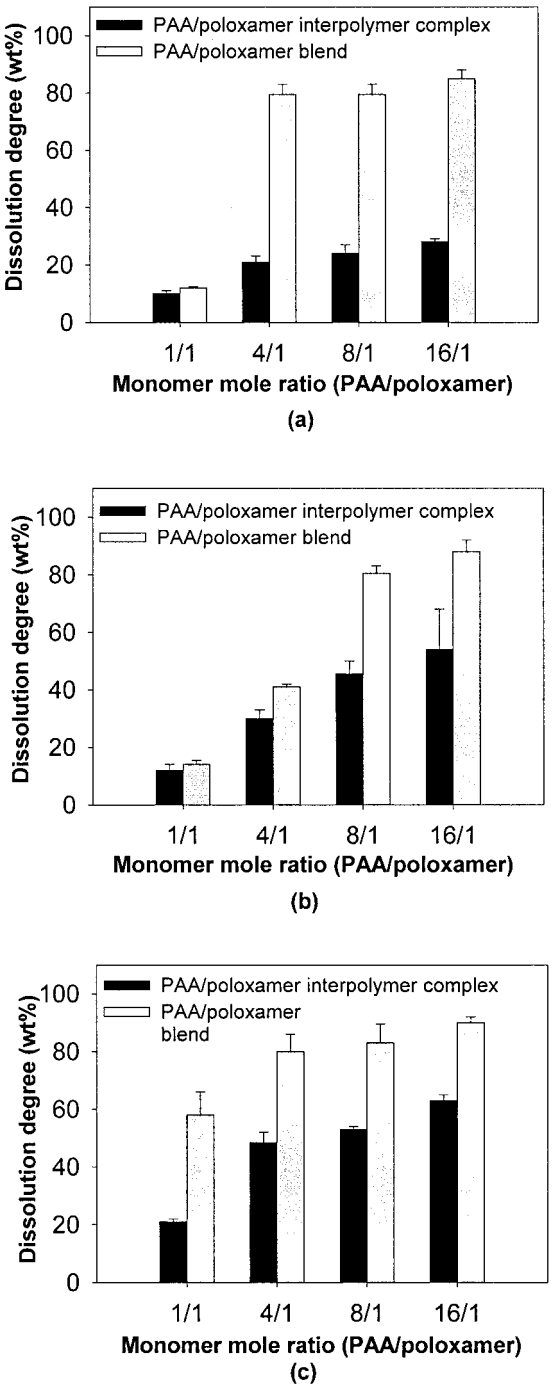


Figure 3 Comparison of the dissolution degree between PAA/poloxamer interpolymer complexes and their blends after 4 h in phosphate buffer solutions at pH 2.0 (a), pH 4.0 (b), and pH 7.4 (c).

of the PAA/PEG macromer complex reported previously. It has been reported in the literature that hydrophobic interaction contributed to the formation of the interpolymer complex.[13] In an inter-

macromolecular complex system, the resulting complex becomes more hydrophobic in nature due to the shielding of hydrophilic groups, such as the carboxyl group of PAA and the ether group of poloxamer. The hydrophobicity of the complex can further be increased by the presence of a nonpolar side group such as the methyl group of poloxamer. Therefore, shielding of hydrophilic groups and hydrophobic interaction within the complex contribute to the slower dissolution rate of the PAA/poloxamer interpolymer complex than their blend or the PAA/PEG macromer interpolymer complex reported previously.[10]

Figure 4 shows the effect of the pH of the medium on the dissolution rate of PAA/poloxamer interpolymer complexes with the monomer mol ratios of 1/1, 4/1, 8/1, and 16/1. The dissolution rate increased as the ratio of PAA in the interpolymer complex increased due to the hydrophilicity of PAA. As the pH of the medium increased, the dissolution rate increased. When the pH was lower than the pKa of PAA (4.75), the majority of the carboxyl groups of PAA were nonionized and the hydrogen bonding could be maintained, leading to a slower dissolution rate.

Table I shows the adhesive bond strength of the PAA/poloxamer interpolymer complexes and their blends to a plastic (polypropylene) plate against monomer mol ratios. The adhesive bond strength was measured by measuring the force required to break the contact between the PAA/poloxamer interpolymer complex and plastic plate. The results show that the adhesive bond strength of PAA/poloxamer interpolymer complexes was increased as the fraction of PAA in the complex increased. The adhesive bond strength of the complex was greater than their corresponding blends at all ratios and Carbopol 971P NF, a well-known commercial mucoadhesive polymer, which is PAA crosslinked with allylpentaerythritol.

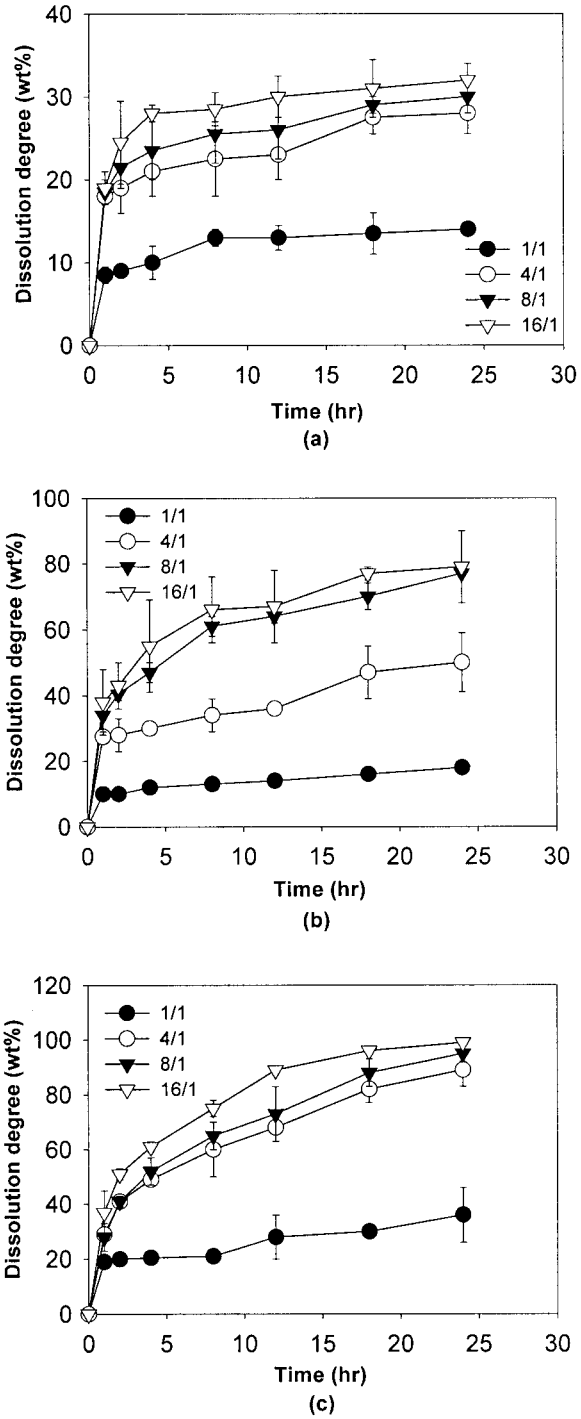


Figure 4 Effect of the pH of the medium and monomer mol ratio of PAA/poloxamer on the dissolution degree of PAA/poloxamer interpolymer complexes at pH 2.0 (a), pH 4.0 (b), and pH 7.4 (c).

CONCLUSIONS

The PAA/poloxamer interpolymer complex prepared by template polymerization of acrylic acid in the presence of poloxamer showed strong adhesive bond strength and a limited water solubility, which are essential requirements for developing a transmucosal drug delivery system. The interpolymer complexes were formed through hydrogen bonding, and was confirmed by FTIR. The carbonyl band of PAA in the interpolymer complexes was shifted to a higher wave number due to hydrogen bonding between PAA and poloxamer. The T_g in PAA/poloxamer interpolymer

Table I The Effect of Monomer Mol Ratio on Adhesive Bond Strength of PAA/Poloxamer Interpolymer Complexes and Their Blends to Plastic (Polypropylene) Plate

	Adhesive Bond Strength (Kgf)	
Monomer mol Ratio of PAA/Poloxamer	PAA/ Poloxamer Interpolymer Complexes (Av. ± SD)	PAA/Poloxamer Blends (Av. ± SD)
1/1	1.63 ± 0.19	0.36 ± 0.02
4/1	1.98 ± 0.09	1.52 ± 0.17
8/1	2.19 ± 0.25	1.86 ± 0.08
16/1	2.58 ± 0.35	2.05 ± 0.13
Carbopol 971P NF	1.27 ± 0.04	

$n = 10$.

complexes was decreased with a decrease in monomer mol ratio of PAA/poloxamer. PAA and poloxamer in the interpolymer complexes were more compatible with each other than those in the blends. The dissolution rate of PAA/poloxamer interpolymer complexes was slower than that of PAA/poloxamer blends due to hydrogen bonding and hydrophobic interaction, and dependent on the pH, monomer mol ratio of PAA/poloxamer. The adhesive bond strength of the interpolymer complexes was greater than that of their blends and commercial Carbopol 971P NF. It was concluded that the PAA/poloxamer interpolymer complex was a better mucoadhesive polymer to be used for the transmucosal drug delivery system than PAA/PEG or PAA/PEG macromer interpolymer complexs.

This research was supported in part by the fund provided by the Korean Ministry of Public Health and Welfare (HMP-97-E3-0018) and by the Brain Korea 21 Project.

REFERENCES

1. McQuinn, R. L.; Kvam, D. C.; Maser, M. J.; Miller, A. L.; Oliver, S. J Control Release 1995, 34, 243.
2. Nakamura, K.; Maitani, Y.; Lowman, A. M.; Takayama, K.; Peppas, N. A.; Nagai, T. J Control 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 Control Release 1998, 56, 75.
5. Shojaei, A. H.; Li, X. J Control Release 1997, 47, 151.
6. Choi, H.-K.; Kim, O.-J.; Chung, C.-K.; Cho, C.-S. J Appl Polym Sci 1999, 73, 2749.
7. De Vries, M. E.; Bodde, H. E.; Nascimento, A.; Busscher, J. H.; Junginger, H. E. STP Pharma 1989, 5, 847.
8. Kumar, V.; Yang, T.; Yang, Y. Int J Pharm 1999, 188, 221.
9. Staikos, G.; Bokias, G.; Karayanni, K. Polym Int 1996, 41, 345.
10. Chun, M.-K.; Choi, H.-K.; Cho, C.-S. J Appl Polym Sci, submitted.
11. Baranovsky, V. Y.; Kotlyarsky, I. V. Eur Polym J 1992, 28, 1427.
12. Gordon, M.; Taylor, J. S. J Appl Chem 1952, 2, 493.
13. Oyama, H. T.; Tang, W. T.; Frank, C. W. Macromolecules 1987, 20, 1839.