A Mucoadhesive Polymer Prepared by Template Polymerization of Acrylic Acid in the Presence of Poly(vinyl Alcohol) for Mucosal Drug Delivery

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ABSTRACT: The interpolymer complexes composed of PVA and PAA were prepared by template polymerization of acrylic acid in the presence of PVA with different molecular weights and degrees of saponification. The carbonyl absorption band of the PAA in the PAA/PVA interpolymer complexes was shifted to a lower wavenumber due to H-bonding between the carboxyl group of PAA and the hydroxyl group of PVA. The swelling ratio and the degree of dissolution of the PVA/PAA interpolymer complexes were dependent on the pH of the medium, the molecular weight, and the degree of saponification of the PVA. The release rate of a model drug, lidocaine, from the complexes decreased with increasing degree of saponification of the PVA due to the lower swelling degree of the complex. The adhesive force of the PVA/PAA interpolymer complexes with a plastic plate (poly propylene) was stronger than that of the commercial Carbopol 971P. © 2004 Wiley Periodicals, Inc. J Appl Polym Sci 94: 327–331, 2004

Key words: adhesion; drug delivery systems; templates; poly(acrylic acid); poly(vinyl alcohol)

INTRODUCTION

The phenomena of interpolymer interactions have been the focus of intensive fundamental and applied research[1] because they may possess unique properties that are different from those of the individual components. There is a great potential in utilizing these interpolymer complexes in many pharmaceutical preparations, particularly in controlled release drug delivery systems.[2,3] In recent years, drug delivery systems using mucoadhesive drug carriers have gained increasing importance, since they can adhere to the mucosal surfaces of the eye,[4,5] buccal cavity,[6] gastrointestinal tract,[7,8] nasal cavity,[9] and vagina,[10–12] and thereby increase the therapeutic efficacy. Typical polymers that have been used as mucoadhesive carriers include poly(acrylic acid) (PAA), poly(methacrylic acid), carboxylmethyl cellulose, hydroxypropyl methyl cellulose, and sodium alginate.[13,14] Of these, PAA and its lightly crosslinked commercial forms, such as Polycarbophil® and Carbopol®, exhibit the strongest mucoadhesion. Although PAA and lightly crosslinked forms of PAA have been used most extensively in mucoadhesive drug delivery, their water solubility limits their uses as a mucoadhesive drug carrier, because they might be dissolved before the drug is delivered across the membrane.[15] In previous studies, several mucoadhesive polymers were prepared by the template polymerization of acrylic acid (AA) in the presence of a template to solve the above-mentioned drawbacks.[16–19] The results showed that mucoadhesive force of the PAA/template interpolymer complexes was superior to that of commercial mucoadhesive polymers.

In this study, poly(vinyl alcohol) (PVA) was selected as a template for template polymerization of AA because the different molecular weights and degree of saponification of the PVA would affect the physicochemical properties of the interpolymer complex. In addition, the PVA has both a proton donating group and a proton accepting group for hydrogen bonding. To characterize the new PVA/PAA interpolymer complex, its spectroscopic properties, dissolution properties, adhesive forces, and release rates of lidocaine HCl, as a model drug, were evaluated.

EXPERIMENTAL

Materials

The PVA and potassium persulfate (KPS) were purchased from Aldrich Chemical Co. (Milwaukee, WI). The AA was purchased from Junsei Chemical Co. (Tokyo, Japan) and was used after removing the in-

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TABLE I
Properties of the PVA Used

	Degree of saponification (%)	Mw (g/mol)
PVA1	87–89	13,000–23,000
PVA2	87–89	31,000–50,000
PVA3	87–89	85,000–146,000
PVA4	98–99	31,000–50,000

hibitor. All other chemicals were of reagent grade, and were used without further purification. Table I shows the properties of the PVA used.

Methods

Synthesis of PAA/PVA interpolymer complexes

The PAA/PVA polymer complexes were synthesized by template polymerization of AA in the presence of PVA. To prepare the PAA/PVA polymer complexes, 15 mL of an AA aqueous solution (6.7%) was mixed with 15 mL of the PVA aqueous solution (4.1%). The monomer molar ratio of PVA to PAA used to prepare the complex was 1/1. This solution was purged with nitrogen gas for 15 ~ 20 min to remove the dissolved oxygen. The polymerization was carried out with KPS (60 mM), as an initiator, at 60°C for 2 h.

Fourier transform infrared (FT-IR) spectra of PVA/PAA interpolymer complexes

The IR absorption spectra of the PVA/PAA polymer complexes were obtained using an FT-IR spectrophotometer (FT-IR, 410, Jasco, Tokyo, Japan).

Measurements of swelling ratio and dissolution rate of polymer complexes

The swelling ratio and dissolution rates of the PVA/PAA polymer complexes were measured using a dissolution tester (DST 600A, LABFINE Ltd., Seoul, Korea) at pH 2.0 and pH 7.4. The swelling ratio and dissolution rates of the PVA/PAA interpolymer complexes were determined by placing PVA/PAA films in 500 mL of a dissolution medium, and were measured as a function of time at 37°C. At the predetermined time intervals, a sample film was removed and vacuum-dried for 24 h to determine its weight. The swelling ratio of the PVA/PAA interpolymer complexes was calculated using $[(W_s - W_d)/W_d]$, where W_s and W_d represent the weight of the swollen and dry films, respectively. The dissolution degree was calculated using $[(W_b - W_a)/W_b \times 100]$, where W_b and W_a are the dried weights of the samples before testing and after testing, respectively.

Measurement of adhesive force

An auto peeling tester (C. K. Trading Co., Seoul, Korea) was used to measure the adhesive force of the PVA/PAA interpolymer complexes to a plastic (polypropylene) plate. The specimens were cut as films with an area of 2.25 cm^2. They were wet with a pH 7.4 phosphate buffer solution for 1 min at room temperature. After excessive water on the surface of the complex films was removed, it was placed on the surface of a plastic plate. Contact of the complex film with the plate continued under a force of 2.4×10^{-3} N/cm^2 for 1 min before the measurements. The peak force required to detach the film from the plastic plate was measured.

Release of lidocaine HCl from the complexes

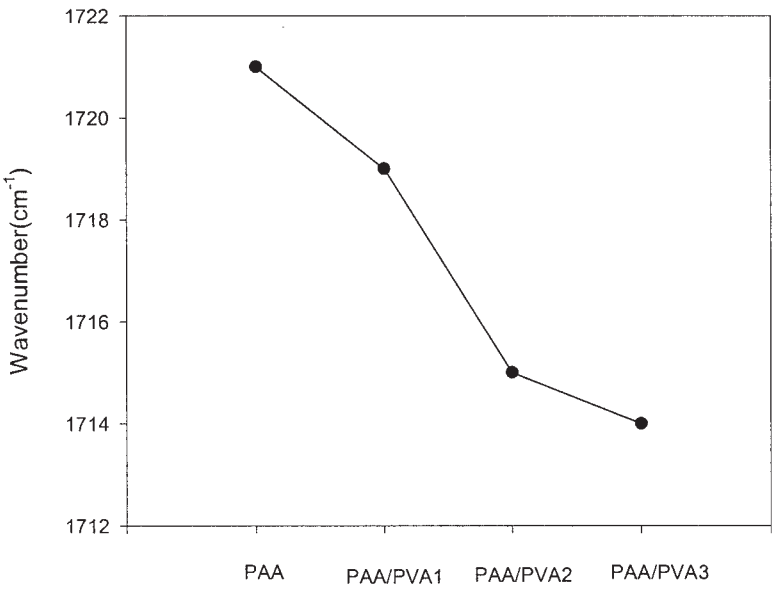
The drug release test was performed using a dissolution tester (DST 600A, LABFINE, Ltd., Seoul, Korea). The PVA/PAA interpolymer complex films containing lidocaine HCl were placed in 500 mL of a release medium and stirred at 100 rpm at 37°C. The pH value of the release medium used was 7.4. Aliquots of the medium were withdrawn at predetermined time intervals, and equivalent amounts of fresh medium were then added.

High performance liquid chromatography (HPLC) assay

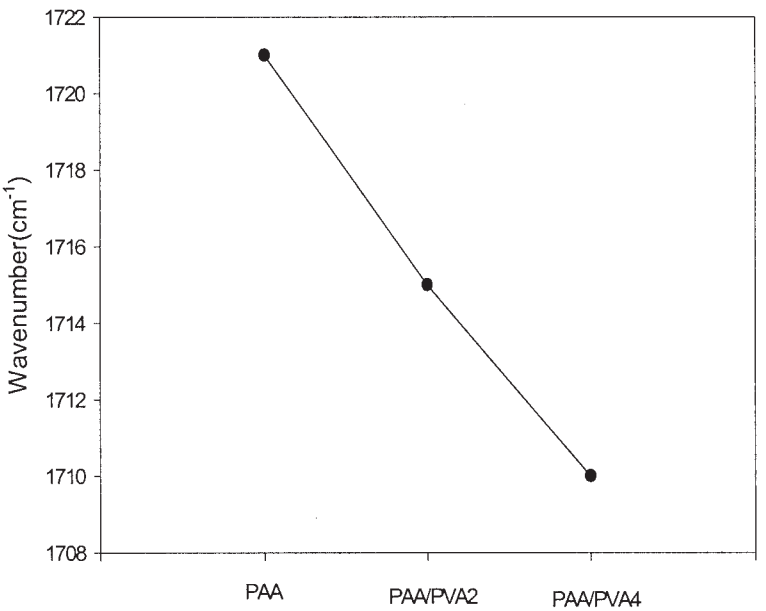
To determine the amount of lidocaine HCl released from the PVA/PAA interpolymer complex film, the samples collected from the drug release test were analyzed by HPLC (Shimadzu Scientific Instruments, MD, USA), consisting of a UV detector (SPD-10A; wavelength, 220 nm), a pump (LC-10AD), and an automatic injector (SIL-10A). A Nova-Pak® C18 (Waters, Ireland) column was used, and the column temperature was maintained at 30°C. The mobile phase consisted of methanol-water-phosphoric acid (60 : 40 : 0.1).

RESULTS AND DISCUSSION

The interpolymer complexes composed of PVA and PAA were prepared by template polymerization of AA in the presence of PVA with different molecular weights and degrees of saponification. An FT-IR study was conducted to investigate the complex formation between the carboxyl group of PAA and the hydroxyl group of PVA via hydrogen bonding by checking the carbonyl absorption band of PAA. Figure 1 shows the wavenumber of the PAA carbonyl peak in the PAA/PVA polymer complexes against the molecular weight of PVA and the degrees of saponification of PVA. The carbonyl absorption band of the PAA in the PAA/PVA interpolymer complexes was shifted to a lower wavenumber due to H-bonding between the carboxyl group of PAA and the



(a)



(b)

Figure 1 Effect of the molecular weight of PVA (a) and the degree of saponification of PVA (b) on the PAA carbonyl absorption band in the PAA/PVA interpolymer complexes.

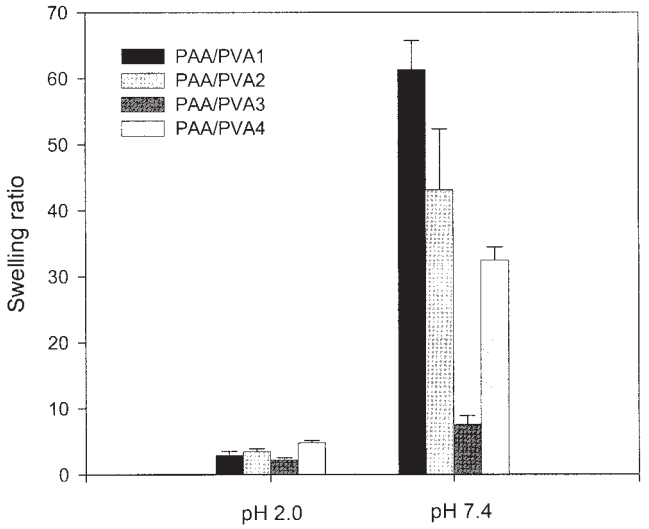


Figure 2 Effect of the molecular weight of the PVA and the degree of saponification of the PVA on the swelling ratio of the PAA/PVA interpolymer complexes at pH 2.0 and pH 7.4 after 1h.

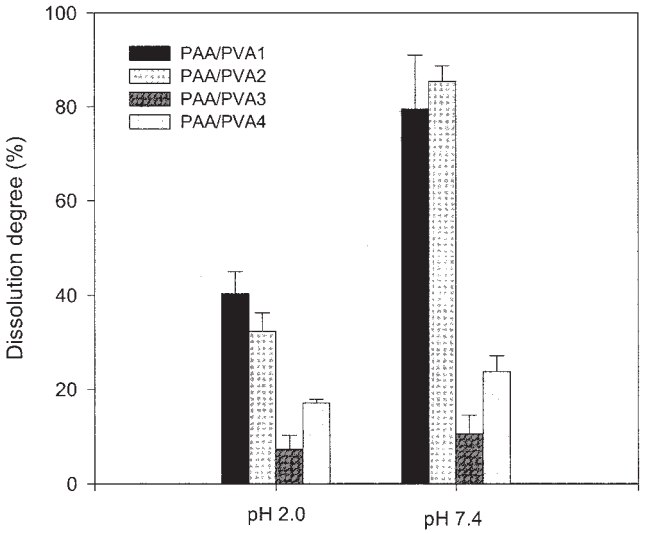


Figure 3 Effect of the molecular weight of the PVA and the extent of PVA hydrolysis on the dissolution degree of the PAA/PVA interpolymer complexes at pH 2.0 and pH 7.4 after 1h.

hydroxyl group of PVA. As is shown in Figure 1, the PAA itself has a carbonyl absorption band at 1721 cm^{-1}, due to intramolecular hydrogen bonding between the carboxyl groups of PAA. However, some of the intramolecular hydrogen bonds break when PAA and PVA form an interpolymer complex due to new hydrogen bonds that formed between the carboxyl groups of PAA and the hydroxyl groups of PVA. Therefore, once an interpolymer complex has formed, the carbonyl absorption band of PAA is shifted to a lower wavenumber. These results suggest that PAA and PVA formed a complex via hydrogen bonding by the template polymerization of AA in the presence of PVA. The extent of the shift in the PAA carbonyl absorption band increased with increasing molecular weight of the PVA and the degree of PVA saponification, indicating that the H-bond density of the complex increases with the degree of saponification of PVA in the PAA/PVA polymer complex as a result of the increased number of potential H-bond sites of PVA.

Figure 2 shows the swelling ratio of the PVA/PAA interpolymer complexes as a function of the molecular weight and the degree of saponification of the PVA at pHs 2.0 and 7.4. As the molecular weight and the degree of saponification of the PVA increased, the swelling ratio of the PVA/PAA interpolymer complexes decreased. These results coincided with the shift in the carbonyl absorption band in the FT-IR study. The PAA/PVA3 swelling ratio was much lower than that of the other PVA/PAA interpolymer complexes tested. This may be due to a stronger interaction between PAA and PVA in the interpolymer complexes with increasing molecular weight of PVA. In the case of PVA with a lower molecular weight, the interaction with PAA was much weaker and there was adequate space for water molecular to permeate, leading to a faster dissolution rate. However, there were minimal differences in the swelling ratio of the PVA/PAA interpolymer complexes at pH 2.0. In addition, the swelling ratio of the PVA/PAA interpolymer complexes at pH 2.0 was lower than that at pH 7.4. When the pH was lower than the pK_a of the PAA (4.75), the majority of the carboxyl groups of PAA were nonionized and the hydrogen bonds between the PAA and PVA in the complex could be maintained, leading to a slower dissolution rate. This then required a longer time for the interpolymer complex to be dissolved in the medium due to the stronger attractive forces. In contrast, when the pH is higher than the pK_a of PAA, the majority of the carboxyl groups of the PAA are ionized and the hydrogen bonds cannot be maintained, which leads to a higher dissolution rate. To confirm this, the dissolution degree of the PVA/PAA interpolymer complexes with the different molecular weight of the PVA and the degree of saponification of the PVA were compared at pHs 2.0 and 7.4 (Fig. 3). As

TABLE II
Comparison of the Adhesive Force of PAA/PVA Interpolymer Complexes with that of Carbopol 971P to the Plastic (Polypropylene) Plate (N = 5)

PAA/PVA	Adhesive bond strength (N/cm^2) (mean ± SD)
PAA/PVA1	7.44 ± 0.81
PAA/PVA2	3.83 ± 0.40
PAA/PVA3	0.11 ± 0.01
PAA/PVA4	2.40 ± 0.60
Carbopol 971P	1.71 ± 0.46

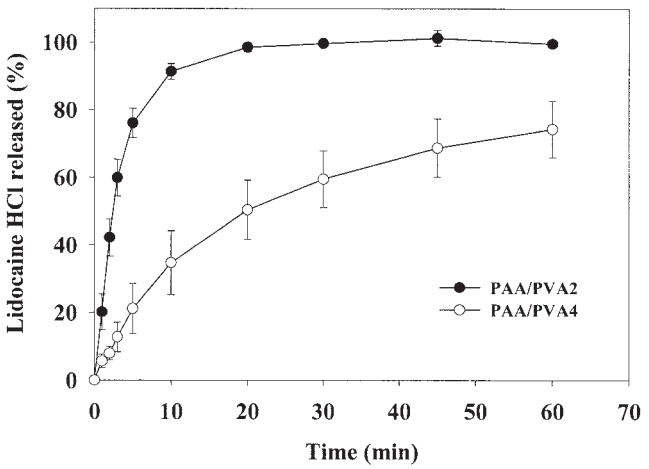


Figure 4 The release rate of lidocaine from the PAA/PVA interpolymer complexes according to degree of saponification of the PVA at pH 7.4.

shown in Figure 3, the dissolution degree of the complexes at pH 2.0 was lower than that of the complexes at pH 7.4. In addition, the degree of dissolution of the complexes had the same tendency with the swelling ratio of the complexes.

Table II shows the effect of the molecular weight and degree of saponification of PVA on the adhesive force of the PVA/PAA interpolymer complexes. The adhesive force was measured by measuring the force required to break the contact between the PVA/PAA interpolymer complex and the plastic plate. The results suggest that the adhesive force of the PVA/PAA mucoadhesive polymer complex with a plastic plate (poly propylene) was stronger than that of commercial Carbopol 971P, and the adhesive force of the PAA/PVA complex is dependent on the molecular weight as well as the degree of saponification of the PVA in the PVA/PAA interpolymer complexes. The adhesive force for the PAA/PVA mucoadhesive polymer complexes decreased with increasing molecular weight and degree of saponification of the PVA due to the increased hydrogen bonding between the PVA and PAA.

Figure 4 shows the lidocaine release rate from the PAA/PVA interpolymer complexes according to the degree of saponification of the PVA at pH 7.4. The lidocaine release rate from the complexes decreased with increasing degree of saponification of the PVA due to the lower swelling degree of the complex. The rigidity of the complex might also have increased due to stronger hydrogen bond in the case of PAA/PVA4. Only minimal differences in the lidocaine release rate were observed among the different PVA molecular weights.

CONCLUSION

The PVA/PAA interpolymer complexes were prepared by the template polymerization of AA in the presence of PVA. The interpolymer complex was formed by H-bonding, which was confirmed by FT-IR. The prepared complex exhibited appropriate mucoadhesive force, and the release rate of a drug from the complex could be controlled by the molecular weight and the degree of saponification of the template polymer. It can be concluded that the PVA/PAA interpolymer complexes are a suitable carrier for mucosal drug delivery systems. Further studies are required to investigate mucoadhesive performance of the PVA/PAA interpolymer complex *in vivo*.

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REFERENCES

1. Shojaei, A. H. J Pharm Pharm Sci 1998, 1, 15.
2. Gupta, A.; Garg, S.; Khar, R. K. Drug Dev Ind Pharm 1994, 20, 315.
3. Anlar, S.; Capan, Y.; Guven, O.; Gogus, A.; Dalkara, T.; Hincal, A. A. Pharm Res 1994, 11, 231.
4. Bourlais, C. L.; Acar, L.; Zia, H.; Sado, P. A.; Needham, T.; Leverge, R. Prog Retin Eye Res 1998, 17, 33.
5. Aiache, J. M.; el Meski, S.; Beyssac, E.; Serpin, G. J Biomater Appl 1997, 11, 329.
6. Bodde, H. E.; de Vries, M. E.; Junginger, H. E. J Control Release 1990, 13, 225.
7. Florence, A. T.; Jani, P. U. Drug Saf 1994, 10, 233.
8. Hwang, S. J.; Park, H.; Park, K. Crit Rev Ther Drug Carrier Syst 1998, 15, 243.
9. Junginger, H. E. Pharm Ind 1991, 53, 1056.
10. Han, K.; Park, J. S.; Chung, Y. B.; Jeong, J. J.; Park, H. B.; Robinson, J. R. Arch Pharm Res 1995, 18, 325.
11. Brannon-Peppas, L. Adv Drug Deliv Rev 1993, 11, 169.
12. Ghelardi, E.; Tavanti, A.; Lupetti, A.; Celandroni, F.; Boldrini, E.; Campa, M.; Sensei, S. Antimicrob Agents Chemother 1998, 42, 2434.
13. Ahuja, A.; Khar, R. K.; Ali, J. Drug Dev Ind Pharm 1997, 23, 489.
14. Yang, X.; Robinson, J. R. In Biorelated Polymers and Gels: Controlled Release Applications in Biomedical Engineering; Okano, T., Ed.; Academic Press: London, 1998; p. 135.
15. Needleman, I. G.; Smales, F. C. Biomaterials 1995, 16, 617.
16. Choi, H.-K.; Kim, O.-J.; Chung, C.-K.; Cho, C.-S. J Appl Polym Sci 1999, 73, 2749.
17. Chun, M.-K.; Cho, C.-S.; Choi, H.-K. J Appl Polym Sci 2001, 79, 1525.
18. Shojaei, A. H.; Li, X. J Control Release 1997, 47, 151.
19. Staikos, G.; Bodias, G.; Karayanni, K. Polym Int 1996, 41, 345.