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

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ABSTRACT: A new mucoadhesive polymer was prepared by template polymerization of acrylic acid in the presence of poly(ethylene glycol) (PEG). FTIR results indicated that a polymer complex was formed between poly(acrylic acid) (PAA) and PEG through hydrogen bonding. The hydrogen bonding in the PAA/PEG polymer complex was stronger than that in the PAA/PEG blend, and became stronger as the molecular weight of PEG increased. Glass transition temperatures (T_g) of PAA in the PAA/PEG polymer complexes was shifted to a lower temperature than that of PAA in the PAA/PEG blend. However, they tended to become higher as the molecular weight of PEG increased. The dissolution rate of the PAA/PEG polymer complex was much slower than the PAA/PEG blend, and was dependent on pH and molecular weight of the PEG. The mucoadhesive force of the PAA/PEG polymer complexes was stronger than for the PAA/PEG blend or a commercial product, Carbopol 971P NF. © 1999 John Wiley & Sons, Inc. J Appl Polym Sci 73: 2749–2754, 1999

Key words: mucoadhesive; template polymerization; adhesive force; dissolution rate

INTRODUCTION

Recently, many researchers in the pharmaceutical field have shown increasing interest in the development of a transmucosal drug delivery (TMD) system. A TMD system, delivering a drug across the mucous membrane to achieve local or systemic effect for an extended period of time, consists of a drug, mucoadhesive polymer, and other excipients. Mucoadhesive polymer can adhere directly to the apical membrane of the epithelial cell or the mucosal epithelial tissue. Mucoadhesive polymers have been used to develop buccal,[1] nasal, ocular,[2] rectal, vaginal,[3] gastrointestinal[4] drug delivery, and surgical glue and wound healing. The TMD systems offer many advantages; [5] (a) prolonged delivery of drugs to improve patient compliance, (b) drug delivery can be localized, (c) by-pass of first-pass metabolism, (d) easy of accessibility, (e) ease of removal. Various synthetic and natural polymers have been investigated for their application in TMD systems as mucoadhesive polymers,[5–7] including poly(acrylic acid) (PAA), hydroxyalkyl cellulose, polymethacrylate, hyaluronic acid, chitosan, and collagen. Despite excellent mucoadhesive property of PAA,

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it has some drawbacks for TMD systems, such as a high glass transition temperature (T_g) and a high water solubility. A high T_g of PAA may pose problems in terms of flexibility at room temperature required for optimal wetting and intimate contact with the mucous membrane.[8] High water solubility of PAA critically limits its use as a TMD system to be applied in the buccal mucous membrane, because it may dissolve before the desired duration for the drug to permeate across the membrane.[9]

PAA, a proton donor, has also been a subject of many investigations in interpolymer complex formation with a proton acceptor, such as poly(ethylene glycol)(PEG) or poly(vinyl pyrrolidone) (PVP), through template polymerization.[10] The template polymerization is a process of forming a polymer chain in the presence of a macromolecule (template) that was introduced into the reaction system beforehand. The complex formation between the formed polymer chain and the template has been generally attributed to hydrogen bonding between the ether group of PEG and the carboxylic group of acrylic acid. The presence of such a template during the polymerization is known to have kinetic and structural effects. It influences the molecular weight and microtacticity of the growing polymer chain due to the ordering effect of the template on monomer molecules.[11] Various interpolymer complexes have been studied for their application in the medical and pharmaceutical area. A pH sensitive hydrogel was obtained from the interpolymer complex formation between methacrylic and polyethylene glycol monomethacrylate using tetraethylene glycol dimethacrylate as a crosslinking agent.[12] However, the mucoadhesive property of PAA may not be maintained when the complex is crosslinked. A mucoadhesive copolymer has been obtained by copolymerization acrylic acid and polyethylene glycol monomethylether with molecular weights of 200, 400, and 1000.[13]

The objectives of this study were to decrease the water solubility of PAA and to maintain or improve mucoadhesive property of PAA for its application in the TMD system. It has been well known that complex formation may result in the precipitation of polymers from solution and changes in network swelling due to increased hydrophobicity. To decrease water solubility of PAA, novel interpolymer complexes of PAA and methoxy PEG with various molecular weights and compositions were prepared by polymerizing acrylic acid in the presence of methoxy PEG without a crosslinking agent, and the products were characterized in terms of their adhesive force, thermal properties, dissolution rate, and spectroscopic properties.

EXPERIMENTAL

Material

Methoxy PEG, with molecular weights of 2000 and 5000, were purchased from Sigma Chemical Co. (St. Louis, MO). Methoxy PEG, with molecular weight of 10,000, was generously donated by Nippon Oil and Fat Co. Azoisobutyronitrile (AIBN) was purchased from Janssen of Reagent Chimia (Geel, Belgium). PAA was purchased from Aldrich Chemical Co. (Milwaukee, WI). Acrylic acid was purchased from Showa Chemicals Inc. (Tokyo, Japan), and used after removing the inhibitor. Methoxy PEG was purified by azeotropic distillation from a benzene solution. All other chemicals were of reagent grade and were used without further purification.

Template Polymerization

PAA/PEG polymer complexes were synthesized by template polymerization of acrylic acid in the presence of methoxy PEG. To prepare the PAA/PEG polymer complexes, acrylic acid and methoxy PEG were dissolved in ethanol and the solution was purged with nitrogen for 15–20 min. The polymerization was carried out with AIBN as an initiator at 80°C for 15 h. The prepared PAA/PEG polymer complexes were repeatedly washed with cold water to remove unreacted methoxy PEG and acrylic acid.

Thermal Analysis

Melting points (T_m) and glass transition temperatures (T_g) of PAA/PEG blend and PAA/PEG polymer complexes were measured by a differential scanning calorimeter (DSC-30, Mettler) at a scan rate of 10°C/min.

IR Spectroscopy Study

Infrared absorption spectra of PAA/PEG blend and PAA/PEG polymer complexes were studied by a FTIR spectrometer (Magna-IR550, Nicolet).

Measurement of Dissolution Rate

Dissolution rates of the PAA/PEG blend and the PAA/PEG polymer complex were measured as a

function of time at 37°C at various pHs. The samples were film cast with a dry thickness of 0.4 mm, and were cut as discs with a diameter of 0.8 cm. Each disc was placed in 10 mL of appropriate medium, and was shaken at 60 reciprocations/min. At predetermined time intervals the discs were taken out and dried for weight measurement. Dissolution rate was calculated by [Wp−Ws)/Wp] × 100, where Ws and Wp are dry weight after the test and dry weight of samples before the test, respectively.

Measurement of Adhesive Force

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

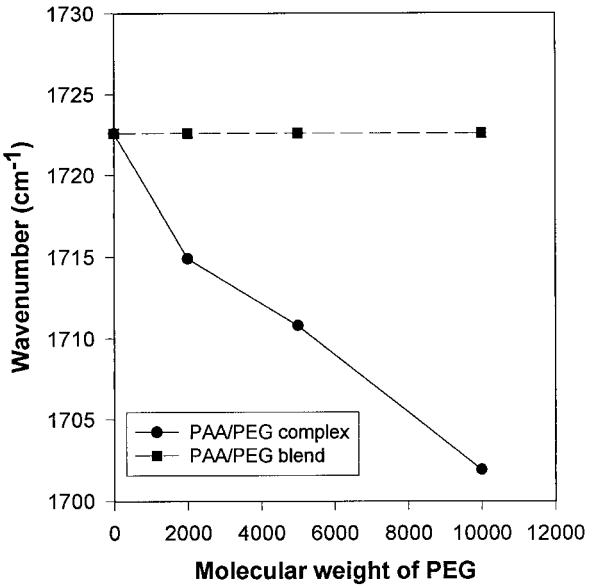

Figure 1 Effect of complex formation between poly(acrylic acid) (PAA) and methoxy poly(ethylene glycol) (PEG) and molecular weight of PEG on wave number of the carbonyl peak of PAA in the PAA/PEG polymer complex.

RESULTS AND DISCUSSION

The PAA/PEG polymer complexes were prepared by the template polymerization of acrylic acid in the presence of methoxy PEG with molecular weights of 2000, 5000, and 10,000, respectively. An FTIR study was conducted to investigate the complex formation between methoxy PEG and PAA through hydrogen bonding by observing the carbonyl stretching band for PAA. Figure 1 shows the wave numbers of the carbonyl peak for PAA in the PAA/PEG polymer complexes against the molecular weight of the methoxy PEG. The carbonyl absorption band for the PAA/PEG polymer complex was shifted to a lower wave number due to H-bonds between carboxylic acid groups of PAA and ether groups of methoxy PEG. The extent of the shift increased with an increase of the methoxy PEG molecular weight, indicating that the H-bond density increases with an increase of the methoxy PEG molecular weight in the PAA/PEG polymer complex due to an increased number of potential H-bond sites, i.e., ether groups, in higher molecular weight methoxy PEG.[14–16] However, the carbonyl absorption band for PAA in the PAA/PEG blend did not change significantly. The results suggest that PAA and PEG formed a complex through H-bonds by template polymerization of AA in the presence of methoxy PEG. It has been known that the template may influence the microtacticity of growing chains, and the tacticity of PAA seemed to be changed by template polymerization. The adsorption band at 1240 cm^{-1} for PAA in the PAA/PEG polymer complex suggests a syndiotactic-rich structure, whereas commercial PAA is known to have an atactic-rich structure. It has been reported in the literature that syndiotactic PAA can be characterized by a strong absorption at 1240 cm^{-1}, whereas isotactic PAA can be characterized by a band at 935 cm^{-1} and two bands at 1215 cm^{-1} and 1270 cm^{-1}. Atactic PAA also shows a band at 1250 cm^{-1} and a shoulder at 1300 cm^{-1}.[8,17] The IR spectrum for the PAA/PEG polymer complex clearly indicated a syndiotactic-rich structure (not shown in figure).

Figure 2 compares the glass transition temperature (T_g) for PAA in the PAA/PEG blend and the PAA/PEG polymer complexes against PEG molecular weight. T_g of PAA in the PAA/PEG polymer complexes was lower than that of PAA in the PAA/PEG blend. This may be due to the increased compatibility of PAA with PEG through the hydrogen bonding. The T_g of PAA in the PAA/PEG polymer complexes increases with an increase in

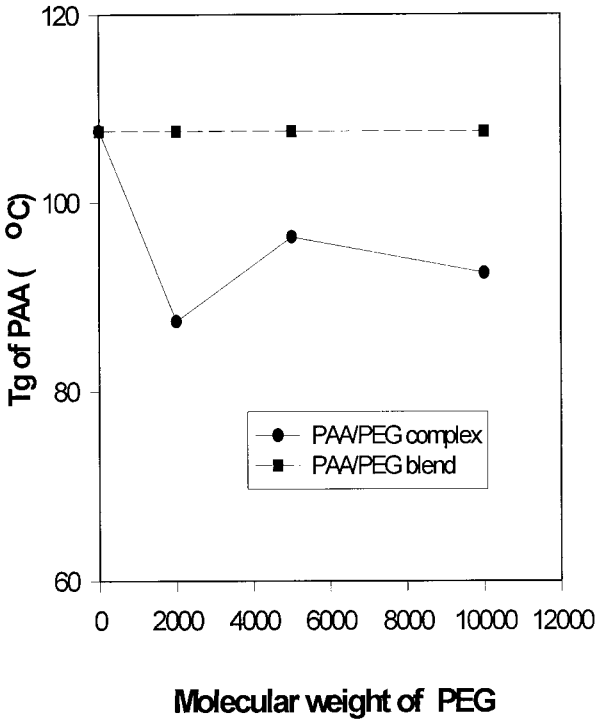

Figure 2 Effect of complex formation between PAA and methoxy PEG and molecular weight of PEG on the glass transition temperature of PAA in the PAA/PEG polymer complex.

PEG molecular weight, whereas those of PAA in PAA/PEG blends were not changed. These results indicate that the force of hydrogen bonding increased with an increase in PEG molecular weight, as was shown in the previous IR study results.[18] The T_gs of PEG in the PAA/PEG polymer complexes were not observed.

Figure 3 shows the degree of dissolution of the PAA/PEG blend and the PAA/PEG polymer complexes after 1 h in aqueous solutions at various pH values. The molecular weight of the methoxy PEG used for this study was 5000. The dissolution rate of the PAA/PEG polymer complex was fairly slow, and was similar to that of the PAA/PEG blend at pH 2. However, it was much slower than the dissolution rate of the PAA/PEG blend at pH 4.7 and 7.4. In both cases the dissolution rate became faster with an increase in pH. It can be speculated that the extent of hydrogen bonding between PAA and PEG in the polymer complex is different, depending on the pH of the medium, causing the difference in the dissolution rate. When the pH is lower than 4.7, the majority of the carboxyl groups of PAA is nonionized and available for formation of H-bonds. Consequently, it takes a longer time for the polymer complex to be dissolved in the medium due to stronger attractive forces. But, when the pH is higher than 4.7, the majority of the carboxyl groups of PAA are ionized and H-bonds cannot be formed, leading to a faster dissolution rate due to increased hydrophilicity.[19]

Figure 4 shows the effect of PEG molecular weight on the dissolution rate of the PAA/PEG complex at pH 7.4. When the molecular weights of PEG used to prepare the PAA/PEG complex were 2000 and 5000, they were completely dissolved within 2 h. On the contrary, only ca. 5% of the PAA/PEG polymer complex was dissolved after 2 h when the molecular weight of PEG used was 10,000. As the molecular weight of PEG is increased, the number of H-bonds within the polymer complex increases, resulting in stronger attractive force between a PEG and a PAA chain. Consequently, the aqueous solubility of the polymer complex decreases as the molecular weight of PEG is increased. The photographic comparison of dissolution degree of the PAA/PEG polymer complexes, in comparison with Carbopol 971P®, with time is shown in Figure 5. Carbopol 971P® is a well-known commercial mucoadhesive polymer that has been widely investigated in the area of mucoadhesion. They were compressed into discs

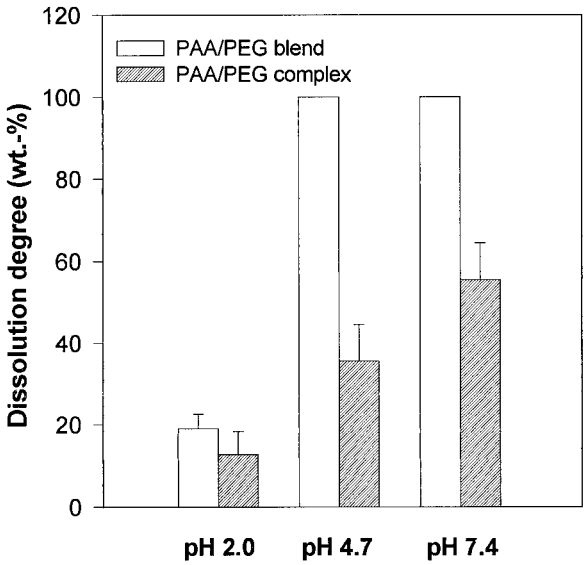

Figure 3 Comparison of the dissolution rate between the PAA/PEG blend and the PAA/PEG polymer complex at various pH values ($n = 3$). The dry weight of the polymer was measured 1 h after they were stored in aqueous solution at pH 2.0, 4.7, and 7.4. The molecular weight of the methoxy PEG used was 5000.

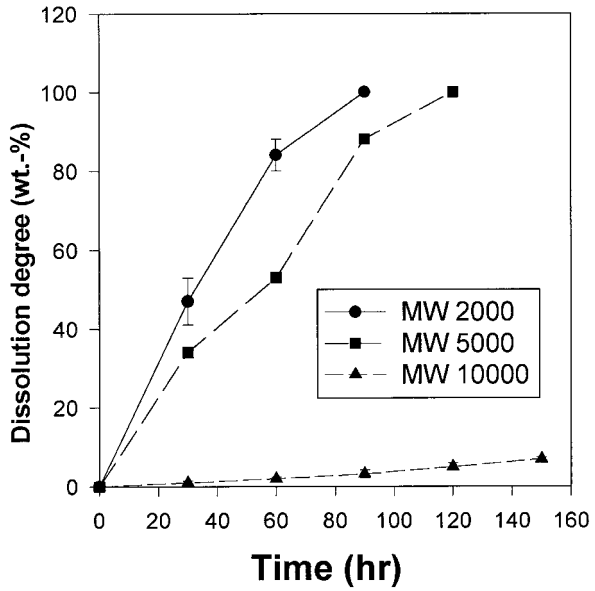

Figure 4 Effect of the molecular weight of methoxy PEG on the dissolution rate of the PAA/PEG polymer complex. The prepared polymer complexes were stored in phosphate buffer (pH = 7.4).

and attached onto a slide glass using acrylic adhesive. They were then immersed into aqueous solution and their pictures were taken at predetermined time intervals. As can be seen in the photograph, Carbopol 971P® swelled greatly within an hour and lost its shape after 4 h. However, the PAA/PEG complex almost maintained its original shape even after 8 h of immersion. Furthermore, while Carbopol 971P® did not have adequate adhesive force after 1 h, the complex showed adequate adhesive force even after 8 h.

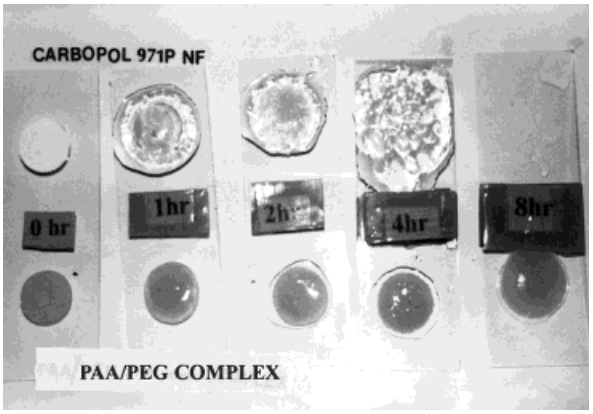

Figure 5 The photographic comparison of the dissolution rate of the PAA/PEG polymer complex with that of Carbopol 971P® in aqueous solution.

Table I The Adhesive Force of the PAA/PEG Polymer Blend and Complexes with Polypropylene Plate (n = 5)

Molecular Weight of PEG	Adhesive Force (kg_f) (Av. ± SD)
Carbopol 971P NF	1.29 ± 0.08
PAA/PEG blend[a] (14 : 1)	1.31 ± 0.26
350	1.83 ± 0.09
2000	1.84 ± 0.16
5000	1.97 ± 0.18
10,000	1.88 ± 0.05

[a] Molecular weight of PEG used was 5000.

Table I shows the effect of the molecular weight of methoxy PEG on the adhesive force of the PAA/PEG polymer complexes. The adhesive force was measured by measuring the force required to break the contact between the PAA/PEG polymer complex and the plastic plate. The results indicate that the adhesive force of the PAA/PEG complex is not dependent on the molecular weight of PEG in the PAA/PEG polymer complex. Interestingly, the PAA/PEG polymer complex prepared by template polymerization showed a greater force of adhesion than commercial Carbopol 971P®.

CONCLUSION

A novel PAA/PEG polymer complex prepared by template polymerization of acrylic acid in the presence of methoxy PEG showed strong adhesive force and limited aqueous solubility, which are essential requirements for developing a transmucosal drug delivery system. The polymer complex was formed by H-bonding. This was confirmed by IR and DSC. The carbonyl band of PAA in the complex was shifted to a lower wave number due to H-bonding between PAA and PEG. The syndiotactic-rich structure of PAA in the PAA/PEG polymer complex resulted from the template polymerization. The T_g in PAA was increased with an increase of the PEG molecular weight.

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