Novel Mucoadhesive Polymer Prepared by Template Polymerization of Acrylic Acid in the Presence of Silk Sericin

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ABSTRACT: A novel mucoadhesive polymer was prepared by template polymerization of acrylic acid in the presence of sericin for a transmucosal drug-delivery (TMD) system. FTIR results indicated that a polymer complex was formed between poly(acrylic acid) (PAA) and sericin through hydrogen bonding. The glass transition temperatures (T_g's) of sericin and PAA in the PAA/sericin polymer complex were inner-shifted compared with the T_g's of sericin and PAA themselves. This may be due to the increased miscibility of PAA with sericin through hydrogen bonding. The dissolution rate of the PAA/sericin interpolymer complex was dependent on the pH. The mucoadhesive force of the PAA/sericin polymer complex was similar to that of a commercial product, Carbopol 971P NF. © 2001 John Wiley & Sons, Inc. J Appl Polym Sci 80: 274–280, 2001

Key words: mucoadhesive; template polymerization; poly(acrylic acid); silk sericin; adhesive force

INTRODUCTION

In recent years, there has been much interest in the development of transmucosal drug delivery (TMD) for drug administration.[1] These dosage forms can be administered by different routes (e.g., ocular, buccal, nasal, rectal, vaginal), either for topical therapy or for systemic TMD. In particular, the buccal route appears to offer several advantages, such as rapid onset of action, high blood levels, avoidance of the first-pass effect, and exposure of the drug to the gastrointestinal tract compared with other routes.[2] The mucoadhesive buccal formulations include ointments, creams, solutions, microparticles, bandages, and tablets. Bioadhesive tablets appear to be attractive because the preparations can be readily attached to the buccal cavity, retained for a longer period of time, and removed at any time.[3] Various synthetic and natural polymers have been investigated for their application in a TMD system as mucoadhesive polymers, including poly(acrylic acid) (PAA),[4] hydroxyalkyl cellulose,[5] poly(methyl methacrylate),[6] hyaluronic acid,[7] chitosan,[7] and collagen.[8] Despite the excellent mucoadhesive property of PAA, it has some drawbacks to be

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used in a TMD system, such as a high glass transition temperature (T_g) and high water solubility. The high T_g of PAA may pose a problem in terms of the flexibility at room temperature required for optimal wetting and intimate contact with the mucous membrane.[9] The high water solubility of PAA critically limits its use as a TMD system to be applied to the buccal mucous membrane, since it may be dissolved before the desired duration for the drug to permeate across the membrane.[10]

In a previous study,[11] a novel mucoadhesive polymer was prepared by template polymerization of acrylic acid (AA) in the presence of poly(ethylene glycol) (PEG). It was found that a polymer complex was formed between PAA and PEG through hydrogen bonding. Also, the mucoadhesive force of the PAA/PEG polymer complexes was stronger than that of the PAA/PEG blend or a commercial product, Carbopol 971P NF.

In this study, we report another mucoadhesive polymer prepared by template polymerization of AA in the presence of silk sericin as the matrix. Sericin is a component of silk protein and water-soluble glue which bonds fibers together.[12,13] It contains mainly glycine, serine, and aspartic acid. Among them, serine, having an aliphatic alcohol moiety, occupied 33 mol % of sericin.[12] It may be expected that the complex formation between the prepared polymer chains and the template can be attributed to hydrogen bonding between the hydroxyl group of serine and the carboxylic group of PAA. Also, the obtained PAA/sericin complex will decrease the water solubility of PAA and improve the mucoadhesive property of PAA for its application in a TMD system due to the adhesive property of sericin.[13] Template polymerization of AA in the presence of sericin was performed against various pH's and compositions of sericin to AA without a crosslinking agent and the products were characterized in terms of their spectroscopic property, thermal property, dissolution degree, and adhesive force.

EXPERIMENTAL

Materials

AA was purchased from the Aldrich Chemical Co. (Milwaukee, WI) and used after removing the inhibitor. Silk sericin was obtained after treatment of a raw cocoon at 120°C for 1 h. PAA (M_v ~45,000) and ammonium persulfate (APS) as an initiator were purchased from the Aldrich Chemical Co. All other chemicals were of pure reagent grade and were used as received.

Template Polymerization of AA in the Presence of Sericin

PAA/sericin polymer complexes were synthesized by template polymerization of AA in the presence of sericin. A sericin aqueous solution was added to the AA solution and then the pH was adjusted to pH 3 and 5. The above-mixed solution was purged with nitrogen for 15–20 min. The polymerization was carried out with APS as an initiator at 80°C for 2 h. The prepared PAA/sericin polymer complexes were repeatedly washed with acetone to remove unreacted monomer. The residual solvent and water in the samples were vacuum-dried for 24 h.

Thermal Analysis

The glass transition temperature (T_g) of the PAA/sericin polymer complexes, PAA, and silk sericin were measured by differential scanning calorimetry (DSC; DSC 2910, TA Instruments, USA) at a scan rate of 10°C/min and by a dielectric thermal analyzer (DETA; DETA MARK IV, Rheometric Scientific Inc, UK) at a scan rate of 4°C/min and 100 Hz.

FTIR Spectroscopy Measurement

FTIR absorption spectra of the PAA/sericin polymer complexes, PAA, and sericin were measured by FTIR (M series, Midac Corp., USA) .

Measurement of Dissolution Degree

The dissolution degree of the PAA/sericin polymer complex was measured as a function of time at 37°C at various pH's. The discs were prepared by direct compression of a 100-mg PAA/sericin polymer complex powder using a KBr pellet mold with 7000 kg pressure for 1 min (diameter: 1.3 cm; thickness: 1 mm). The disc was placed in 5 mL of an appropriate medium. At predetermined time intervals, the disc was taken out and dried for weight measurement. The dissolution degree was calculated by $[(Wp - Ws)/Wp] \times 100$, where Ws and Wp are the dry weight of the samples after the test and before the test, respectively.[14]

Measurement of Adhesive Force

A tensile tester (Rheometric Scientific Inc, UK) was used to measure the adhesive force of the

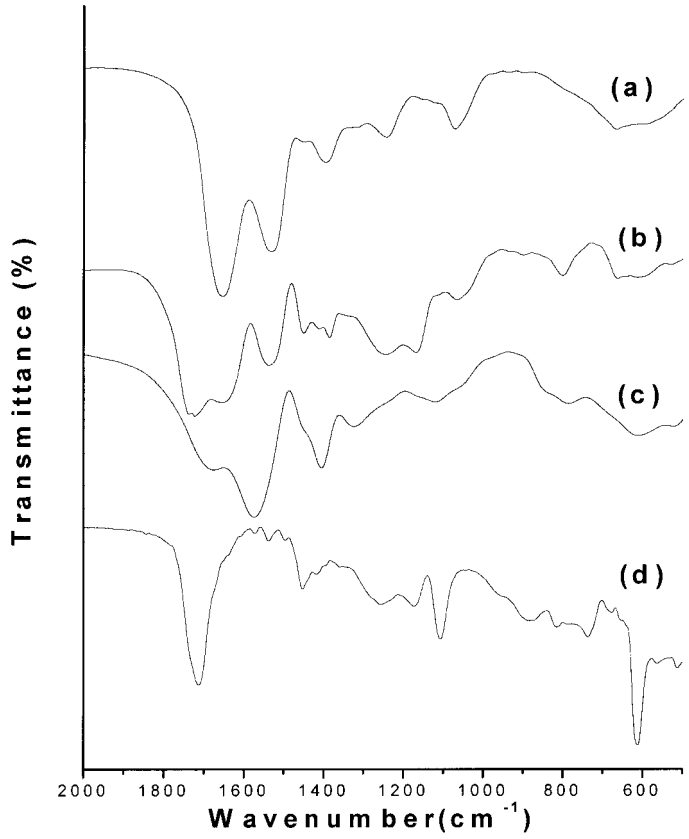

Figure 1 FTIR spectra of (a) sericin, (b) PAA/sericin (1:10) polymer complex prepared at pH 3, (c) PAA/sericin (1:10) polymer complex prepared at pH 5, and (d) PAA.

PAA/sericin polymer complexes with a plastic (polypropylene) plate. The interpolymer disc was prewetted with water and placed on the surface of the plastic plate. It was kept in contact with the plate under the force of a fingertip for 2 min before the measurement. The peak force required to detach the disc from the plastic plate was measured.

RESULTS AND DISCUSSION

The PAA/sericin polymer complexes were prepared by template polymerization of AA in the presence of sericin. An FTIR study was conducted to investigate the complex formation between PAA and sericin through hydrogen bonding by observing the carbonyl stretching band of PAA. Figure 1 shows the FTIR spectra of PAA, the PAA/sericin polymer complex, and sericin. The amide I and amide II of sericin itself are located at 1662 and 1538 cm^{-1} (refs. 13, 15, and 16) [Fig. 1(a)], respectively. Also, the carbonyl absorption band of the PAA itself appeared at 1715 cm^{-1} [Fig. 1(d)]. On the other hand, the carbonyl absorption band of PAA for the PAA/sericin polymer complex prepared at pH 3 was split into 1718 and 1733 cm^{-1} [Fig. 1(b)]. The former was assigned to PAA itself and the latter was shifted to a higher wavenumber due to hydrogen bonding between the carboxylic groups of PAA and the hydroxyl groups of sericin. The results suggest that the polymer–polymer complex between PAA and sericin was formed through hydrogen bonding by template polymerization of AA in the presence of sericin. In the spectrum of the PAA/sericin system prepared at pH 5 above the pK_a value of PAA, a strong band at 1576 cm^{-1} was observed due to the asymmetrical stretching of COO^- groups of PAA[17] [Fig. 1(c)], indicating no hydrogen bonding between them. Also, it was reported that template polymerization may influence the microtacticity of a growing chain. The adsorption band of the PAA at 1242 cm^{-1} for the PAA/sericin polymer complex prepared at pH 3 suggested a syndiotactic-rich structure of PAA, while the adsorption

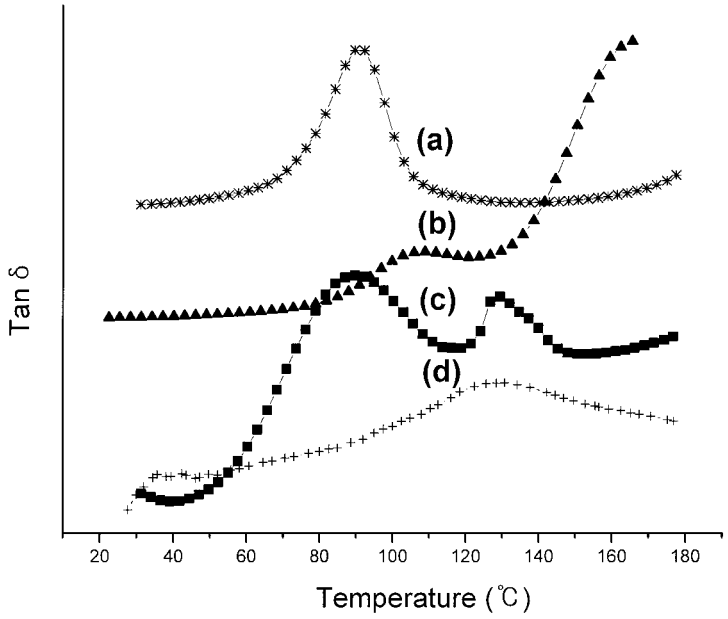

Figure 2 Dielectric thermogram of (a) sericin, (b) PAA/sericin (1:10) polymer complex prepared at pH 3, (c) PAA/sericin (1:10) polymer complex prepared at pH 5, and (d) PAA.

band at 1257 cm^{-1} [Fig. 1(d)] for commercial PAA itself is known to be an atactic-rich structure.[9]

The T_g's of sericin and PAA in the polymer complex measured by DSC were not distinct (data not shown). Therefore, we used DETA to measure the T_g. In DETA, it is generally reported that the temperature at the maximum value in tan δ corresponds to the glass–rubber transition. Figure 2(a) shows plots of tan δ versus temperature for sericin. The primary transition of sericin itself appeared around 90°C in tan δ. This peak corresponds to the α relaxation of sericin.[13] The α relaxation of PAA itself, assigned to the glass–rubber transition, was observed at 129°C, as shown in Figure 2(d).[18] But the α relaxation of sericin in the polymer complex was shifted to a higher temperature compared with sericin itself, whereas the α relaxation of PAA in the polymer complex was shifted to a lower temperature compared with PAA itself, as shown in Figure 2(b). The results suggested that the interaction between sericin and PAA was compatible. However, the PAA/sericin system prepared at pH 5 was observed with two peaks, indicating no H bonds.

Figure 3 shows the effect of pH during template polymerization on the dissolution rate of the PAA/sericin complex at pH 7.4 PBS (0.1*M*). The pH of the AA monomer was adjusted by a 0.1*M* NaOH aqueous solution. The PAA/sericin complex of 65 wt % prepared at pH 3 (below the pK_a value of PAA) was dissolved after 8 h, while 90 wt % of the PAA/sericin complex prepared at pH 5 (above the pK_a value of PAA) was dissolved. When the pH is below the pK_a value of PAA, hydrogen bonding between the carboxylic group of PAA and the hydroxyl one of sericin occurred, resulting in a stronger attractive force between sericin and PAA chains. Consequently, the water solubility of the polymer complex decreases below the pK_a value of PAA.

Figure 4 shows the degree of dissolution of the PAA/sericin blend and the PAA/sericin polymer complex prepared at pH 3 after 4 h at various pH values. The dissolution rate of the PAA/sericin complex was fairly slow and was similar to that of the PAA/sericin blend at pH 2. However, it was much slower than was the dissolution rate of the PAA/sericin blend at pH 4.8 and 7.4. In both cases, the dissolution rate of the PAA/sericin complex became faster with an increase of the pH. It might be supposed that the extent of hydrogen bonding between PAA and sericin in the interpolymer complexes depends on the pH of the medium, causing a difference in the dissolution degree.[14] When the pH is lower than 4.8, the majority of the carboxyl groups of PAA is nonionized and available for formation of H bonds with sericin. Consequently, it takes a longer time for the

polymer complex to be dissolved in the medium due to a stronger attractive force. But when the pH is higher than 4.8, 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]

The photographic comparison of the dissolution degree of the PAA/sericin polymer complex in comparison with Carbopol 971P NF with time is shown in Figure 5. Carbopol 971P NF is a well-known commercial mucoadhesive polymer which has been widely used in the investigation of mucoadhesives. They were compressed into a disc and attached onto a slide glass using water. They were immersed into an aqueous solution and their pictures were taken at predetermined time intervals. As can be seen in the photographs, Carbopol 971P NF swelled greatly and lost its shape after 4 h. However, the PAA/sericin complex almost maintained its original shape even after 8 h of immersion. Furthermore, while Carbopol 971P NF did not have an adequate adhesive force after 4 h, the complex showed an adequate adhesive force even after 8 h.

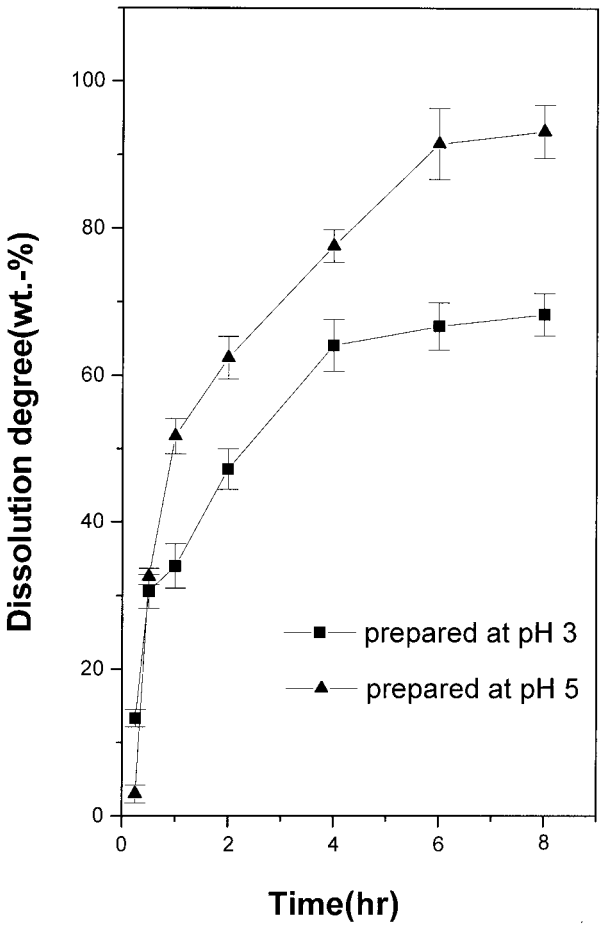

Figure 3 Dissolution degree at pH 7.4 PBS: (a) PAA/sericin (1:10) polymer complex prepared at pH 5; (b) PAA/sericin (1:10) polymer complex prepared at pH 3.

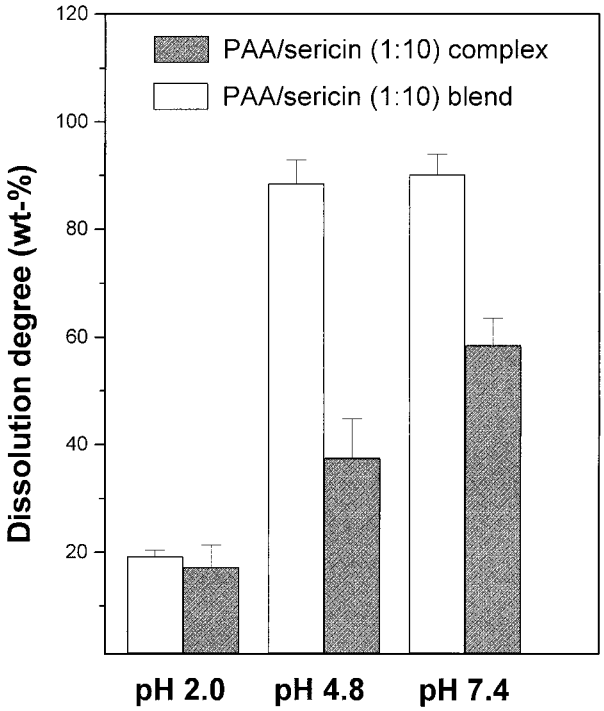

Figure 4 Comparison of dissolution rate between PAA/sericin (1:10) blend and PAA/sericin (1:10) polymer complex at various pH values after 4 h at 37°C (n = 3).

Table I shows the adhesive force of the PAA/sericin polymer complexes, the PAA/sericin polymer blend, and Carbopol 971P NF. The adhesive force was obtained by measuring the force required to break the contact between the PAA/sericin polymer complex and the plastic plate. The polymer complex prepared at below the pK_a value had a higher adhesive force than that prepared above the pK_a value. At pH 5 above the pK_a value, some of the carboxyl groups of PAA are ionized and then the adhesive force reduced. It was inferred that the carboxyl groups of PAA are related to the adhesive force. The mucoadhesive force of the PAA/sericin polymer complex was similar to that of Carbopol 971P NF, a well-known commercial mucoadhesive polymer.

CONCLUSIONS

A novel mucoadhesive polymer prepared by template polymerization of AA in the presence of seri-

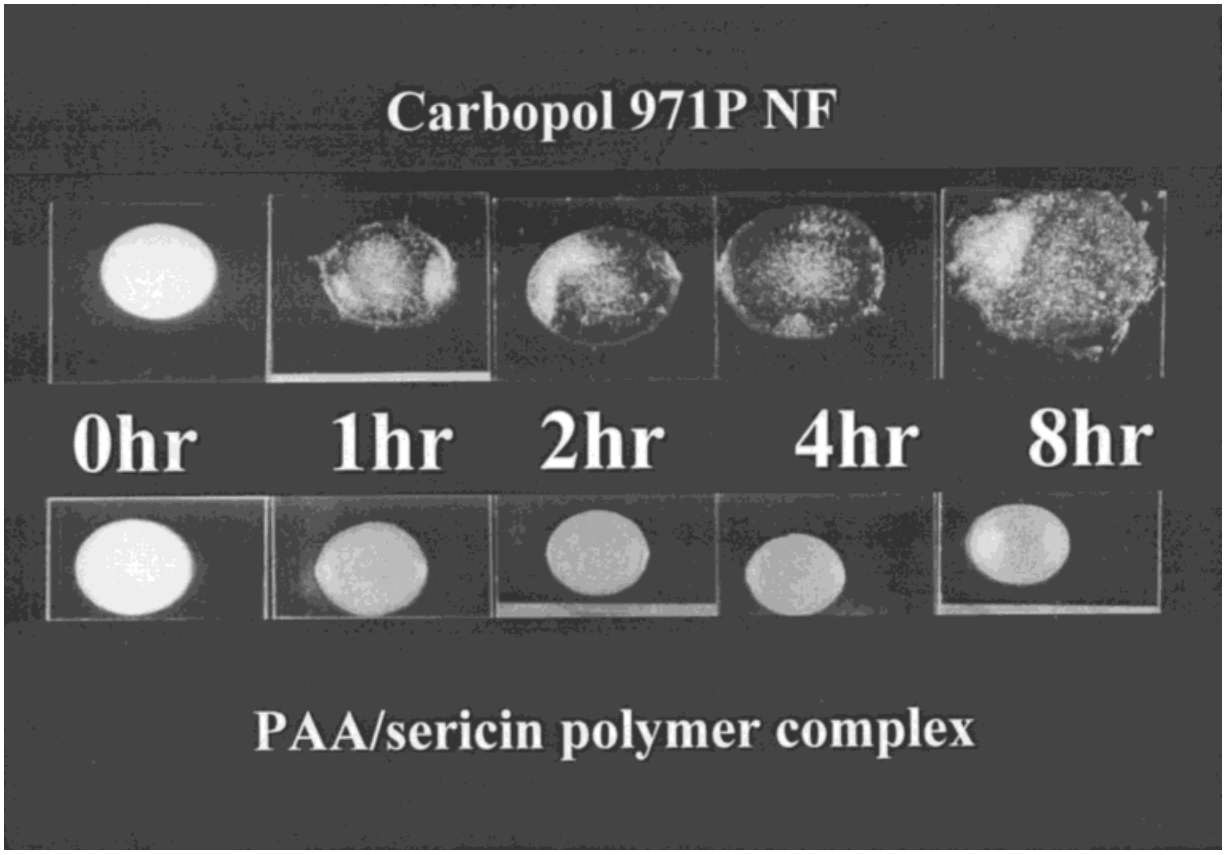

Figure 5 Photographic comparison of dissolution rate of PAA/sericin (1:10) polymer complex with that of Carbopol 971P NF in aqueous solution.

cin showed a strong adhesive force and limited aqueous solubility, which are essential requirements for developing a TMD system. The polymer complex was formed through H bonds. It was confirmed by FTIR and DETA. The carbonyl band of PAA in the complex was shifted to a higher wavenumber due to H-bonding between PAA and sericin. The T_g's of sericin and PAA in the PAA/sericin polymer complexes were inner-shifted compared with the T_g's of sericin and PAA themselves. The mucoadhesive force of the PAA/sericin polymer complex was similar to that of Carbopol 971P NF.

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

Polymer	Adhesive Force (N) Av ± SD
Carbopol 971P NF	16.9 ± 2.9
PAA/sericin (1:10) complex prepared at pH 3	15.3 ± 3.2
PAA/sericin (1:10) complex prepared at pH 5	12.0 ± 1.9
PAA/sericin (1:10) blend	6.3 ± 2.3
Sericin	4.1 ± 2.0

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