Characteristics of Poly(vinyl pyrrolidone)/Poly(acrylic acid) Interpolymer Complex Prepared by Template Polymerization of Acrylic Acid: Effect of Reaction Solvent and Molecular Weight of Template

Myung-Kwan Chun,[1] Chong-Su Cho,[2] Hoo-Kyun Choi[1]

[1]*College of Pharmacy, Chosun University, Gwangju 501-759, Korea*
[2]*School of Agricultural Biotechnology, Seoul National University, Seoul 151-742, Korea*

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ABSTRACT: Poly(vinyl pyrrolidone) (PVP)/poly(acrylic acid) (PAA) interpolymer complexes were prepared, in ethanol or dimethylformamide (DMF), by template polymerization of acrylic acid in the presence of PVP (MW: 42.5 or 1100 K) used as the template. FTIR analysis showed that the complexes were formed through hydrogen bonding between the carboxyl groups of the PAA and the carbonyl groups of the PVP. The glass-transition temperature (T_g) of the complex, prepared in ethanol, was higher than that of the component polymers, whereas the T_g of the complex, prepared in DMF, was located between that of the component polymers. The dissolution rate of the complex was affected by the molecular weight of the PVP and the reaction solvent. The release rate of ketoprofen from the complexes showed a pH dependency, and was slower at a lower pH. The ketoprofen release rate from the complex was controlled mainly by the dissolution rate of the complex above the pK_a of PAA (4.75) and by the diffusion rate below the pK_a. © 2004 Wiley Periodicals, Inc. J Appl Polym Sci 94: 2390–2394, 2004

Key words: drug delivery systems; glass transition; interpolymer complex; templates; water-soluble polymers

INTRODUCTION

Various interpolymer complexes have been examined for applications in the medical and pharmaceutical fields. Recently, interpolymer complex formation, between proton-accepting and proton-donating polymers, has been widely investigated because of the formation of cooperative hydrogen bonds and its unique properties in solution as well as in the solid state.[1–3] Several methods have been used to prepare various interpolymer complexes.[2–5] Template polymerization is a process of forming a polymer chain in the presence of a macromolecule (template). Complex formation between the polymer chain formed and the template has been generally attributed to hydrogen bonding, electrostatic forces, or covalent bonding.[6–10] The presence of such a template during polymerization is known to have kinetic and structural effects.[10] Therefore, a template can influence the molecular weight and microtacticity of the growing polymer chain as a result of the ordering effect of the pattern on the monomer molecules.

Jiang et al.[4] suggested that competition between polymer–polymer interactions and polymer–solvent interactions might be a decisive factor governing complexation in solution. This is because solvent molecules also participate in the hydrogen-bonding interactions with the component polymer, as either a donor or an acceptor.[11–16] Lau and Mi[17] reported on the physicochemical properties of a PAA/PVP complex, such as the thermal and spectroscopic properties. We previously reported on the effect of PVP and PAA mole ratios, in PVP/PAA interpolymer complexes prepared by template polymerization, on the drug release rate.[2] However, the effects of the reaction solvent, and the PVP molecular weight during template polymerization on the drug release rate from the PAA/PVP interpolymer complexes, have not been reported.

In this study, ethanol and DMF were selected as model reaction solvents because the complexes prepared in these solvents have different physicochemical properties.[11,12,15,16] The effect of the PVP molecular weight as a template on the drug release rate from the complex was also studied.

EXPERIMENTAL

Materials

PVP samples, with viscosity-average molecular weights (MW) of 42.5 and 1100K, were provided by

Correspondence to: H.-K. Choi (hgchoi@chosun.ac.kr).
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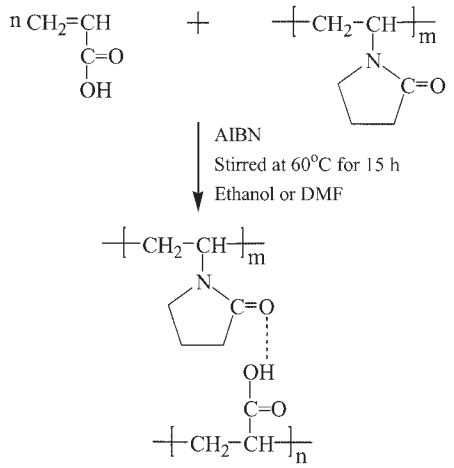


Figure 1 Synthesis of the PVP/PAA interpolymer complex.

BASF AG (Ludwigshafen, Germany). The 2,2′-azobisisobutyronitrile (AIBN) and acrylic acid were purchased from Junsei Chemical Co. (Tokyo, Japan) and the acrylic acid was used after removing the inhibitor. All other chemicals were of reagent grade and used without further purification.

Preparation of PVP/PAA interpolymer complexes

The PVP/PAA interpolymer complexes were prepared by the template polymerization of acrylic acid, in the presence of PVP, as a template, as shown in Figure 1. To prepare the complex, 12.14 g of acrylic acid and 18.72 g of PVP (MW: 42.5 or 1100K) were dissolved in 90 mL of either ethanol or DMF, and the solution was purged with nitrogen gas for 15–20 min to remove the oxygen. The polymerization was performed with 0.27 g of AIBN as an initiator at 60°C for 15 h. When ethanol was used as the reaction medium, the supernatant was removed and the resulting precipitate was dried at 80°C for 12 h and then in a vacuum oven at 80°C for 1 week. When DMF was used as a reaction medium, the reaction solution was poured into a silicone-coated mold and dried, at 80°C for 12 h then in a vacuum oven at 80°C, for 1 week.

FTIR spectra of PVP/PAA interpolymer complexes

The infrared absorption spectra of the PVP/PAA interpolymer complexes and PAA were examined using an FTIR spectrophotometer (IFS-85, Bruker, Darmstadt, Germany). To prepare an FTIR pellet, the sample was thoroughly mixed and ground with a large volume of KBr in an agate mortar. The mixture then was pressed into a pellet die (diameter of 13 mm), using a force of 10 tons.

Measurement of the glass-transition temperature of the complexes

Glass-transition temperatures (T_gs) of PVP/PAA interpolymer complexes were measured using a differential scanning calorimeter (DSC-2010, TA Instruments, New Castle, DE). To cure the samples, the DSC system was heated to over 200°C at a scan rate of 10°C/min, cooled to ambient temperature, then reheated at a scan rate of 10°C/min with a flow of nitrogen gas, to measure the T_g values of the PVP/PAA interpolymer complexes.

Viscosities of PVP/PAA interpolymer complexes

The inherent viscosities of the PVP and PVP/PAA interpolymer complexes were measured at 37°C using an Ubbelohde viscometer [Type 52501/0b, Schott Gerate GmbH (Mainz, Germany), acquired by Nova Analytics Corp. (Woburn, MA)] and a 0.1 g/dL aqueous solution.

Measurement of dissolution rate of the complexes

To prepare tablets, approximately 200 mg samples, of the PVP/PAA interpolymer complex powders, were pressed by a hydraulic press with a 13-mm die and flat-faced punches at a compression pressure of 20 kN/cm^2 with a dwell time of 60 s. The dissolution test of the PVP/PAA interpolymer complex was performed using a dissolution tester (DST 600A, Labfine Instruments, Seoul, Korea). A tablet made of the complex was placed in 500 mL of a dissolution medium and the dissolution rate of the tablet was measured as a function of time at 37°C in a pH 2.0 HCl solution and a pH 7.4 phosphate buffer solution (PBS). At predetermined time intervals, the tablet was removed and dried to measure its weight. The degree of dissolution was calculated by $[(W_p - W_s)/W_p] \times 100$, where W_s and W_p are the dried weight of the samples after the test and before the test, respectively.

Release rate of ketoprofen from the complexes

Each of the PVP/PAA interpolymer complexes was mixed with ketoprofen (5%, w/w) to prepare a tablet. The 200 mg tablet was prepared using a hydraulic press, with 13-mm die and flat-faced punch, at 20 kN/cm^2 with a dwell time of 60 s. The drug release test was carried out using a dissolution tester (DST 600A, Labfine Instruments). The tablet was placed in 500 mL of a release medium and stirred at 100 rpm at 37°C. The pH values of the release medium used were 2.0 and 7.4. Aliquots of the medium were withdrawn at predetermined time intervals and equivalent amounts of fresh medium were added. The amount of ketoprofen, released from a tablet, was determined by

filtering the collected sample through a 0.45-μm syringe filter, and analyzed by a UV spectrophotometer (UV-1601, Shimadzu, Kyoto, Japan) at 260 nm.

RESULTS AND DISCUSSION

FTIR study

The PVP/PAA interpolymer complexes were prepared in either ethanol or DMF, as a reaction solvent, by template polymerization. When ethanol was used as the reaction solvent, the resulting polymer complex precipitated in the reaction solvent. However, no precipitate was formed when DMF was used as the reaction solvent. It was also reported that no precipitation, between poly(4-hydroxyl styrene) and PVP, was formed in DMF.[15] The formation of the polymer complex, between PVP and PAA, was confirmed by the shift in the carbonyl absorption bands of PAA using FTIR. PAA itself shows a band at 1703 cm^{-1} attributed to intramolecular hydrogen bonding between the carboxyl groups of PAA. However, some of the intramolecular hydrogen bonds break when PAA and PVP form an interpolymer complex because new hydrogen bonds are formed between the carboxyl groups of PAA and the carbonyl groups of PVP. Accordingly, the carbonyl absorption band of PAA shifted to a higher wavenumber once an interpolymer complex had formed.[2] In both complexes, prepared in either ethanol and DMF, the carbonyl absorption band of PAA at 1703 cm^{-1} was shifted to a higher wavenumber over 1730 cm^{-1} as a result of hydrogen bonding between the carboxyl group of PAA and the carbonyl group of PVP in the complexes, as shown in Table I.

T_g values of the complexes

It is known that the T_g of the complex made by hydrogen bonding shows a significant deviation from the weight-average law or the Fox equation.[2,4,15] Although the divergence of T_g from the weight-average law does not always appear as a positive deviation, hydrogen bonding often increases the T_g because it restricts the motion of the polymer segments.[2,4,15] Figure 2 shows the T_g of the PVP/PAA complexes prepared in either ethanol or DMF. Both the complexes, prepared in either ethanol or DMF, showed a single T_g. The appearance of a single T_g for the complex indicates that its miscibility is fairly good.[17] In addition, it was observed that the T_g, of the complex prepared in DMF, was located between the T_g values of each constituent (PVP and PAA), whereas the T_g, of the complex prepared in ethanol, was higher than the T_g of both PVP and PAA. Wang et al.[15] also reported that mutual precipitates of PVP and poly(4-hydroxyl styrene) showed a higher T_g than the weight-average values. In contrast clear films, cast from dimethyl sulfoxide, have lower T_g values. Lau and Mi[17] reported that the T_g, of the precipitates formed by physically mixing PAA and PVP in ethanol, was higher than that of the two constituent polymers, whereas the T_g of the films, cast from 1-methyl-2-pyrrolidone, was between T_g values of the two constituent polymers. The fact that the T_g of the complex, prepared in ethanol, was higher than that of the complex prepared in DMF indicates that the motion of the polymer segments in the complex prepared in ethanol is more restricted than the complex prepared in DMF as a result of the stronger interaction.

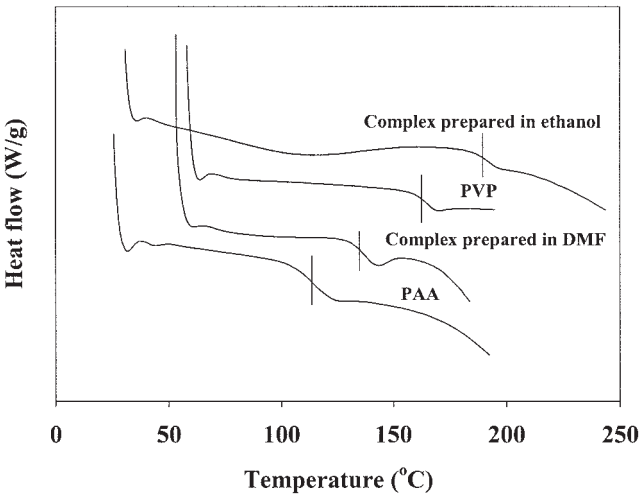


Figure 2 Effect of the nature of the reaction solvent on the glass-transition temperature (T_g) of the complex prepared in either ethanol or DMF.

TABLE I
Effect of the Complexation Between the PVP and PAA in the PVP/PAA Complex, Prepared in Either Ethanol or DMF, on the Carbonyl Absorption Band of PAA

Molecular weight of PVP	Carbonyl absorption band of PAA (cm^{-1})	
	Ethanol	DMF
42.5K	1732	1738
1100K	1736	1730
PAA	1703	

Viscosities of the complexes

The presence of a template during the template polymerization influences the molecular weight of the growing polymer chain.[10] The effects of the PVP molecular weight as a template and the solvent nature on the viscosities of the PVP/PAA complexes were investigated (Table II). When the same molecular weight of PVP was used as a template, the viscosity of the complexes prepared in ethanol was lower than that of the complexes prepared in DMF. The precipitation of the

TABLE II
Effect of the Molecular Weight of Template (PVP) and Solvent Nature on the Viscosity of PVP/PAA Interpolymer Complexes

Molecular weight of PVP	Inherent viscosity (g/dL)	
	Ethanol	DMF
42.5K	0.46	0.68
1100K	2.11	2.60
PVP (MW: 42.5K)	0.23	
PVP (MW: 1100K)	1.16	

complexes, prepared in ethanol, appeared to terminate the growth of the PAA chain at an earlier phase, whereas the PAA chain prepared in DMF continued to grow to a certain point.

Effect of the molecular weight of the template and solvent nature on the dissolution rate of the complexes

The effects of the molecular weight of PVP and reaction solvent on the dissolution rate of the PVP/PAA complexes at pH 2.0 and 7.4 are shown in Figure 3. When the pH was higher than the pK_a of PAA (4.75), the majority of the carboxyl groups of PAA were ionized and hydrogen bonding between the PAA and PVP could not be maintained, resulting in a rapid dissolution rate. For the complex to be dissolved, water must penetrate the polymer network and dissociate the hydrogen bonding between the PAA and PVP. Therefore, the extent of entanglement and the force of the hydrogen bonding affect the dissolution of the complex. It was previously reported that the interaction is weaker when the molecular weight of the complexing polymer is low.[1] This is illustrated by the observation that the complex, of low molecular weight PVP prepared in ethanol, had completely dissolved in about 40 min. Because of the weaker interaction and lower molecular weight of the complex prepared in ethanol, it dissolved faster than a similar complex prepared in DMF. In contrast, the complex prepared in ethanol dissolved slower than that prepared in DMF when a high molecular weight PVP was used. When a high molecular weight PVP was used to prepare the complex, the force of the interaction played a major role in determining the dissolution rate of the complex and it outweighed the effect of the molecular weight of the complex. Consequently, the dissolution rate of the complex prepared in ethanol was slower than that prepared in DMF.

When the pH was lower than the pK_a of PAA (4.75), the majority of the carboxyl groups in PAA are nonionized and hydrogen bonding between the PVP and PAA in the complex can be maintained, leading to a slower dissolution rate. At pH 2.0, the dissolution rate of the complex was extremely slow regardless of the reaction solvent. Initially, the dissolution rate was relatively fast and gradually decreased thereafter. The faster initial dissolution rate may partly be attributable to oligomers and other side products.

Release rate of ketoprofen from the complexes

Figure 4 shows the effect of the molecular weight of PVP and the reaction solvent on the release rate of ketoprofen from the complex at pH 2.0 and 7.4. The release rate, of ketoprofen from the complexes at pH 2.0, was significantly lower than that at pH 7.4. This coincides with the results obtained from the dissolution study. The ketoprofen release profile from the complex, prepared with the low molecular weight PVP at pH 7.4, almost overlaps the dissolution profile

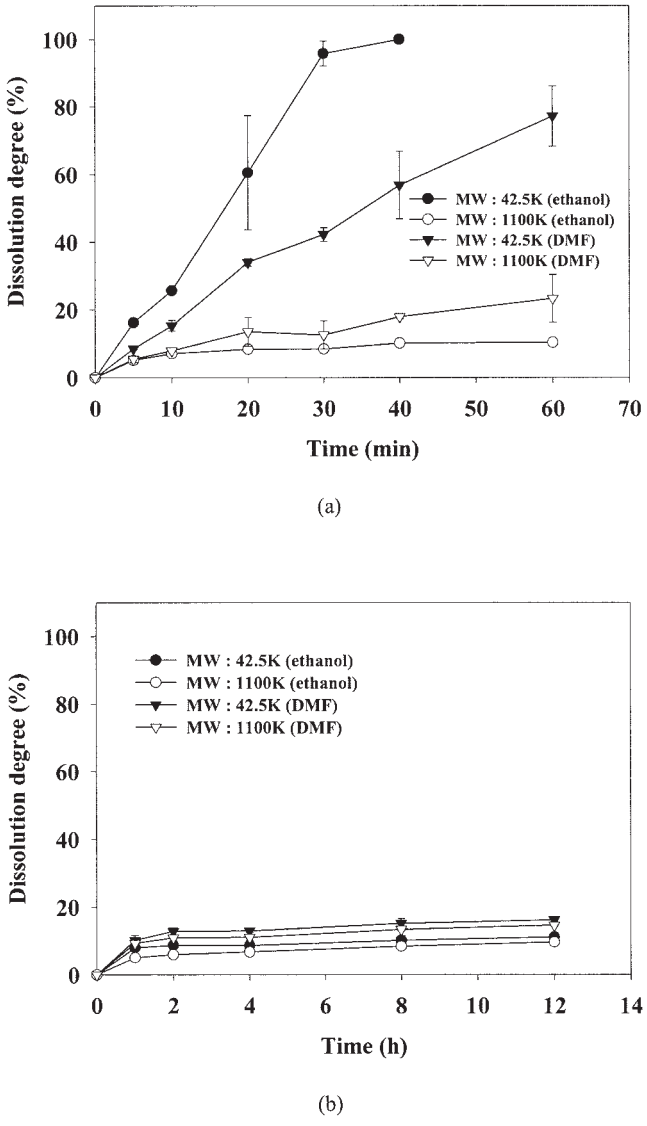
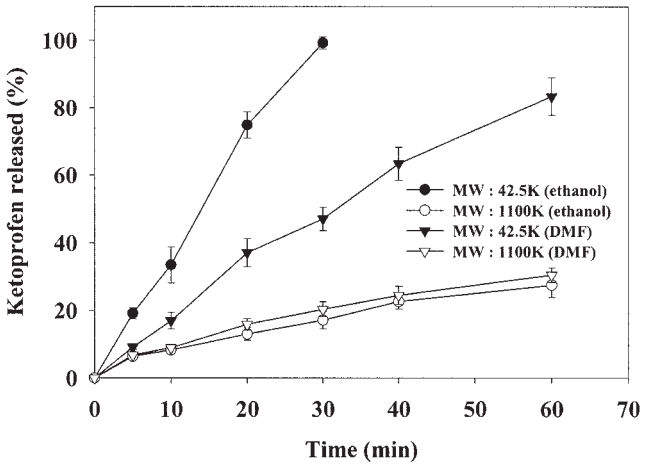
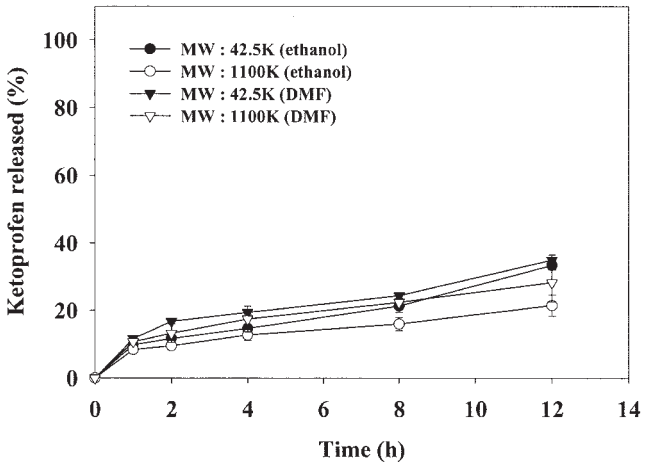


Figure 3 Effect of the molecular weight of PVP and the nature of the solvent on the dissolution rate of the complex prepared in either ethanol or DMF at pH 7.4 (a) and 2.0 (b).



(a)



(b)

Figure 4 Effect of the molecular weight of PVP and the nature of the solvent on the ketoprofen release rate from the complex prepared in either ethanol or DMF at pH 7.4 (a) and 2.0 (b).

of the complex. This indicates that the release of the drug was mainly attributed to the dissolution of the complex (dissolution controlled). The ketoprofen release profile from the complex, prepared with a high molecular weight PVP at pH 7.4, was slightly above the dissolution profile of the complex, indicating that the release of the drug might be attributable to both the dissolution of the complex and the diffusion of the drug. However, the drug release profile was well above the dissolution profile of the complex at pH 2.0. Although no significant dissolution of the complex was observed after 1 h, ketoprofen was continuously released from the complex, which suggests that the release of the drug occurred mainly as a result of drug diffusion across a slightly swollen complex matrix (diffusion controlled).

CONCLUSION

PVP/PAA interpolymer complexes were prepared by template polymerization of acrylic acid in the presence of PVP (MW: 42.5 or 1100K) as a template in either ethanol or DMF as a reaction solvent. The FTIR results showed that the interpolymer complexes were formed by hydrogen bonding between the carboxyl groups in PAA and the carbonyl groups in PVP. The molecular weight of the template (PVP), and the nature of the reaction solvent, control the dissolution rate of the complexes as well as the drug release rate from the complexes.

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