Thermosensitive Interpenetrating Polymer Networks Composed of Poly(acrylamide-co-dimethylacrylamide) and Poly(acrylic acid)

Jeongil Byun and Young Moo Lee

Department of Industrial Chemistry, Hanyang University, Seoul 133-791, Korea

Chong-Su Cho*

Department of Polymer Engineering, Chonnam National University, Kwangju 500-757, Korea

Yong-Kiel Sung

Department of Chemistry, Dongguk University, Seoul 100-715, Korea

Received August 1, 1994

ABSTRACT: The swelling behavior of interpenetrating polymer networks (IPNs) composed of poly (acrylamide-co-dimethylacrylamide-co-butylmethacrylate) [p(AAm-co-DMAAm-co-BMA)] and poly(acrylic acid) (PAAc) in water was studied and indomethacin release from the IPNs gels was performed. The IPNs were synthesized by a sequential IPN method in which crosslinked PAAc chains were formed inside of p(AAm-co-DMAAm-co-BMA) networks as initial gels. Positive swelling changes were obtained with changes in temperature for IPNs gels containing higher AAm and AAc contents. The positive temperature dependence was attributed to the formation and dissociation of hydrogen-bond complexes between AAm and AAc with changes in temperature. Stepwise changes in swelling behavior of the IPN-0.8 gels was observed as a function of the temperature. Indomethacin release from the IPN-0.8 at 53 °C was larger than that measured at 37 °C.

Introduction

Hydrogel of stimuli sensitive polymers have promising potentials as intelligent materials which show structural and physical changes to external signals. Environmental stimuli factors include temperature,1–2 pH,3–7 electric field,8–9 light,10 ion or certain chemical species.11 Among these, thermally sensitive polymers receive much attention because body temperature may increase when people get an illness.

Much of the fundamental swelling behaviors of the hydrogels has been investigated since Tanaka et al. suggested the swelling theory with respect to the change in temperature.12 The hydrogel could be described as that containing either a negative or positive temperature-sensitive system.

In a negative temperature-sensitive system, a phase transition or a gel shrinking occurs at a certain temperature that is called a lower critical solution temperature (LCST). Poly(N-isopropyl acrylamide) (PNIPAAm) hydrogel is a well-known negative temperature sensitive polymer showing LCST at 30–32 °C.13 Many attempts have been made to
change LCSTs of the polymers in the aqueous system through a variation in polymer-water interaction and polymer-polymer interaction.\textsuperscript{14}

In a positive temperature sensitive system, a phase transition occurs at a temperature which is called an upper critical solution temperature (UCST). Al-Alaw et al.\textsuperscript{15} first reported on the positive temperature dependent polymer gels showing UCST based on IPNs from poly(acrylamide) (PAAm) and poly(acrylic acid) (PAAc). It has been used for drug delivery system. This phenomenon is closely related to the polymer-polymer complex between PAAm and PAAc through hydrogen bonding. Recently, Jung et al. reported positive swelling behavior of IPNs composed of poly(N-vinylpyrrolidone-co-butyl methacrylate) and PAAc.\textsuperscript{16}

In this study, we wish to report on the swelling behavior of IPNs composed of poly(acrylamide-co-dimethylacrylamide-co-butyl methacrylate)[p(AAm-co-DMAAm-co-BMA)] and PAAc and the release of indomethacin as a model drug from the IPNs gels. The new positive temperature dependent polymer gels are expected by an incorporation of polydimethylacrylamide(PDMAAm) in the complex between polyacrylamide(PAAm) and poly(acrylic acid) (PAAc).

**Experimental**

**Materials.** Acrylamide(AAm), dimethylacrylamide(DMAAm), butylmethacrylate(BMA), acrylic acid (AAc), dimethyl sulfoxide(DMSO) and ammonium persulfate(AP) were purchased from Junsei Chemicals Co. Methylenebisacrylamide(MBAAm) and N,N-azobisisobutyronitrile(AIBN) were purchased from Tokyo Chemical Industry Co.(TCI). Indomethacin was purchase from Aldrich Chem. Co. AAm was purified by recrystallization. AAc, DMAAm, BMA and DMSO were distilled under reduced pressure before use.

**Synthesis of P(AAm-co-DMAAm-co-BMA) and PAAc IPNs.** The IPNs were prepared by a sequential method of IPNs synthesis. First initial gel was synthesized and then swollen in another monomer solution which contains a crosslinker and an initiator. The swollen gel was heated to form IPNs. P(AAm-co-DMAAm-co-BMA) gels and PAAc gels were synthesized as initial gels and secondary gels, respectively.

The feed compositions of initial gels are listed in Table I. AAm, DMAAm, BMA, MBAAm and AIBN were dissolved in a certain amount of DMSO. The solutions were bubbled with dry nitrogen gas for 10 mins and injected between two glass plates separated by a silicone rubber spacer measuring 1mm in thickness. The solutions were heated at 80°C for 30 hours. After cooling to room temperature, the initial gels obtained were separated from the glass plates. At first the initial gels were immersed in DMSO at room temperature for five days to remove any unreacted monomers. The gels were further soaked in 75/25 and 50/50 DMSO/distilled water (BMA: 30 wt% in initial gel, [DMAAm + AAm]/[AAc] = 1).

### Table I. The Feed Composition of Initial Gels

<table>
<thead>
<tr>
<th>Sample</th>
<th>DMAAm (g)</th>
<th>AAm (g)</th>
<th>BMA (g)</th>
<th>MBAAm (g)</th>
<th>AIBN (g)</th>
<th>DMSO (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INI(DMAAm-AAm)-0</td>
<td>2.8</td>
<td>0</td>
<td>1.2</td>
<td>0.0283</td>
<td>0.04</td>
<td>16</td>
</tr>
<tr>
<td>INI(DMAAm-AAm)-20</td>
<td>2.24</td>
<td>0.56</td>
<td>1.2</td>
<td>0.03</td>
<td>0.04</td>
<td>16</td>
</tr>
<tr>
<td>INI(DMAAm-AAm)-40</td>
<td>1.68</td>
<td>1.12</td>
<td>1.2</td>
<td>0.0317</td>
<td>0.04</td>
<td>16</td>
</tr>
<tr>
<td>INI(DMAAm-AAm)-60</td>
<td>1.12</td>
<td>1.68</td>
<td>1.2</td>
<td>0.0334</td>
<td>0.04</td>
<td>16</td>
</tr>
<tr>
<td>INI(DMAAm-AAm)-80</td>
<td>0.56</td>
<td>2.24</td>
<td>1.2</td>
<td>0.0352</td>
<td>0.04</td>
<td>16</td>
</tr>
<tr>
<td>INI(DMAAm-AAm)-100</td>
<td>0</td>
<td>2.8</td>
<td>1.2</td>
<td>0.0369</td>
<td>0.04</td>
<td>16</td>
</tr>
</tbody>
</table>

### Table II. Feed Composition of IPNs Gels

<table>
<thead>
<tr>
<th>Sample</th>
<th>AAc (mol/100 g)</th>
<th>AAc (g)</th>
<th>MBAAm (g)</th>
<th>AP (g)</th>
<th>water (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPN-0</td>
<td>1.069×10⁻¹</td>
<td>7.704</td>
<td>0.084</td>
<td>0.2</td>
<td>92.296</td>
</tr>
<tr>
<td>IPN-20</td>
<td>1.067×10⁻¹</td>
<td>7.688</td>
<td>0.084</td>
<td>0.2</td>
<td>92.312</td>
</tr>
<tr>
<td>IPN-40</td>
<td>1.238×10⁻¹</td>
<td>8.924</td>
<td>0.096</td>
<td>0.2</td>
<td>91.067</td>
</tr>
<tr>
<td>IPN-60</td>
<td>1.397×10⁻¹</td>
<td>10.068</td>
<td>0.108</td>
<td>0.2</td>
<td>89.932</td>
</tr>
<tr>
<td>IPN-80</td>
<td>1.420×10⁻¹</td>
<td>10.263</td>
<td>0.108</td>
<td>0.2</td>
<td>89.764</td>
</tr>
<tr>
<td>IPN-100</td>
<td>1.984×10⁻¹</td>
<td>14.296</td>
<td>0.152</td>
<td>0.2</td>
<td>85.704</td>
</tr>
</tbody>
</table>
water (V/V) solution for three days each, followed by the final soaking in 100% distilled water for a week. The initial gels were dried at room temperature for a day and then at 80 °C under reduced pressure for three days. Feed compositions of initial gel are listed in Table II. Each initial gel was immersed in AAc aqueous solution with concentration of AAc monomer(C_AAc) adjusted to that of AAm and DMAAm (AAm+DMAAm) in each initial gel containing MBAAm(0.5 mol%) and AP(2 g/L) and then further swollen for 24 h at 5 °C. These initial gels swollen in the AAc aqueous solutions were heated at 50 °C for 3 days to synthesize PAAc gels interpenetrated within the initial gels. After the synthesis, IPNs were soaked in distilled water for a week to remove any unreacted monomers.

Swelling Measurement. After an immersion in 20cc water at a desired temperature, the IPNs (1.5×1.5 cm²) were removed from water and tapped with filter paper to remove any excess water remaining on the sample surfaces. The polymer samples were weighed at a fixed temperature until hydrated membrane reached a constant weight. After equilibration at a certain temperature, samples were reequilibrated at a higher temperature. The weight ratio, \( W_w/W_p \), was used to evaluate the swelling ratio, where \( W_w \) and \( W_p \) are the weight of absorbed water and dry polymer, respectively.

Indomethacin Release. Indomethacin release experiments were conducted in one ml phosphate buffered saline (pH=7.4) in a shaking water-bath at 10 °C and 60 °C, respectively. The concentration of the samples were determined by UV spectrophotometer (Shimadzu Model UV-2101PC) at 266 nm.

Results and Discussion

Temperature dependence of equilibrium swelling of poly(DMAAm-co-BMA) gels is shown in Figure 1. Samples are designated as INI(DM)-X, where X represents the wt% of BMA in the copolymer. Gels showed a negative swelling behavior with increasing temperature. The slope of swelling vs. temperature curve slightly decreased as BMA content increased attributed to the hydrophobicity of BMA. DMAAm homopolymer showed a negative swelling behavior and LCST. This result may be regarded that heat of dilution of PAAm in water is exothermic whereas those of N-substituted polymers are exothermic. PAAm residues require separation of the amide dipoles for hydration. The N,N-dimethyl substituted structure in PDMAAm does not promote dipole interaction or intramolecular complexation and the two terminal methyl groups maintain only minimal mobility.17,18

In general PAAc is known to increase the swelling degree with temperature. Therefore, poly(DA-
MMm-co-BMA) gels were used for preparing IPNs with PAAc. Figure 2 illustrates the temperature dependence of equilibrium swelling degree of poly(DMAAm-co-BMA)/PAAc IPNs. Samples are designated as IPN(DM-X), where X represents the wt% of BMA in the copolymer. However, the effect of PAAc in IPNs systems was not seen as was expected and the swelling degree did not increase with temperature. The reason might be that the hydrogen bonding between poly(DMAAm-co-BMA) and PAAc was not disturbed much with increasing temperature owing to the powerful hydrogen bond acceptor of the dimethylamido group. However, the swelling ratios of these gels at low temperatures are much lower than those of their respective initial gels due to the formation of hydrogen bonding in DMAAm-AAc complex at low temperatures.

AAm was incorporated into poly(DMAAm-co-BMA) gels because of the appearance of the negative swelling changes with increasing temperature. Poly(AAm-co-DMAAm-co-BMA) was anticipated to show positive swelling changes with increasing temperature after an introduction of AAm in the poly(DMAAm-co-BMA). Figure 3 represents the temperature dependence of swelling in poly(AAm-co-DMAAm-co-BMA) crosslinked gels. AAm content was varied and the BMA content was fixed to 30 wt% to the total monomer content. Samples are designated as INI-X, where X represents ([AAm] \times 100)/[(AAm+DMAAm)]. The swelling degree of the gels containing AAm was not much changed in comparison with the previous gels. The slope of the swelling vs. temperature curve, however, decreased as the AAm content increased. This is attributed to the fact that the relative amount of dimethylamido group content decreases as AAm content increases. This was due to the weak positive therosensitivity of PAAm in swelling.

Figure 4 illustrates the temperature dependence of swelling of poly(AAm-co-DMAAm-co-BMA)/PAAc (BMA = 30 wt%, [(AAm+DMAAm)]/[AAc] = 1). Sample designation is the same as in INI-X. These gels containing 80 and 100 wt% AAm show positive swelling changes with increasing temperature whereas the IPNs gels containing less than 80 wt% AAm exhibit negative swelling changes although the slope of the swelling vs. temperature curve is smaller than that of their respective initial gels. For the IPNs gels containing less than 80 wt% AAm, dissociation of DMAAm and AAc complex units may not occur as the temperature is increased owing to the powerful hydrogen bond acceptor of DMAAm. For IPNs containing 80 and 100 wt% AAm, some AAm-AAc complex units start to dissociate by breaking hydrogen bonds when the temperature is increased. Therefore, the interaction between AAc and water increases and the swelling
degree increases. Also, LCST to UCST may have occurred.

AAc content was varied using INI-60 (BMA: 30 wt%, [AAm]/[AAm + DMAAm] = 0.6) to prepare various IPNs. Figure 5 represents the temperature dependence of swelling of these IPNs. The number after IPN represents [AAc]/([AAm + DMAAm] + [AAc]) in mole fraction. Depending upon the AAc contents, these IPNs showed a temperature of minimum swelling degree indicating a transition from LCST to UCST. For the IPN-0.2, transition from LCST to UCST was a marked observation. Only a small amount of AAc may have participated in the hydrogen bonding so that the swelling degree was large. However, at an elevated temperature, the interaction between the polymer chain and water was reduced to decrease the swelling degree. At a much higher temperature, their interaction between the chain and water may play a role again, resulting in an increase of the swelling because of the presence of AAc. The transition temperature from LCST to UCST depends on the content of AAc in IPNs. As the AAc content increased, the transition temperature was lowered. A possible reason for this is that only a certain amount of AAc may participate in the hydrogen bonding and the rest of the AAc may swell to lower the UCST.

Figure 6 shows a stepwise swelling behavior of IPN-0.8 measured at pH 7. The temperature was changed from 10 °C to 60 °C for every two hours. The swelling degree of IPN-0.8 is high at 60 °C while it is low at 10 °C and this trend is reversible by changing the temperature. The total swelling ratio increased as time goes on. This is attributed from the fact that the hydrogen bonding may have broken during the experiment. However, the swelling behavior showed similar patterns.

The release of indomethacin through IPN-0.8 was measured as a function of temperature and shown in figure 7. A marked difference in the indomethacin release amount was observed between 37 °C
and 53 °C. The release of indomethacin from the IPN-0.8 at 53 °C is larger than that at 37 °C because of positive swelling changes of IPNs gels with increasing temperature. From the above results, it may be expected that drug release from the IPNs gels can be controlled by an on-off system.

Conclusions

The swelling behavior of interpenetrating polymer networks composed of poly(acrylamide-co-di-methylacrylamide) and poly(acrylic acid) showed positive changes in swelling as temperature increased for IPNs gels containing higher AAm and AAc contents. The positive temperature dependence was attributed to the formation and dissociation of the hydrogen bond between AAm and AAc. A stepwise swelling experiment using IPN-0.8 showed that a reversible change in swelling ratio as temperature changed from 10 to 60 °C for every two hours. Results on indomethacin release from IPN-0.8 showed that the release amount measured at 53 °C was larger than that at 37 °C and the release pattern was reversible with temperature changes.

Acknowledgement. This work was supported by Korea Science and Engineering Foundation under the grant 92-23-00-02.

References