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pH- and Temperature-Sensitive Bifunctional Hydrogels of *N*-Isopropylacrylamide and Sulfadimethoxine Monomer

Jin Woo Lee and Doo Sung Lee*

Center for Advanced Functional Polymers, Department of Polymer Science and Engineering, Sungkyunkwan University, Suwon, Kyungki 440-746, Korea

Sung Wan Kim

Department of Pharmaceutics and Pharmaceutical Chemistry, University of Utah, Salt Lake City, Utah 84112, USA

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Abstract: pH- and temperature-sensitive bifunctional hydrogels composed of *N*-isopropylacrylamide (NiPAAm) and a sulfadimethoxine monomer (SDM) derived from sulfadimethoxine were prepared. These hydrogels exhibit simultaneous pH- and temperature-induced volume-phase transitions. The pH-induced volume-phase transition behavior is produced by the ionization/deionization of SDM and is very sharp. In the high pH region, the ionization of SDM induces swelling of the hydrogels. In the low pH region, the deionization of SDM induces deswelling of the hydrogels. The temperature-induced volume-phase transition behavior of the bifunctional hydrogels exhibits negative thermosensitivity because of the NiPAAm component. The hydrogels swell even at low pH as the temperature decreases. The hydrogels swell at low temperature and high pH, and deswell at high temperature and low pH. The volume of the hydrogels depends on the balance of the swelling and deswelling produced by the two competing stimuli, pH and temperature.

Keywords: pH/temperature-sensitive bifunctional hydrogel, swell-deswell, *N*-isopropylacrylamide, sulfadimethoxine.

Introduction

Hydrogels sensitive to pH[1,2] and temperature[3] have been extensively studied because of their engineering applications as well as their biomedical applications (e.g., in artificial organs and drug delivery systems). The poly(*N*-isopropylacrylamide)(PiPAAm) hydrogel is typical of gels that exhibit volume phase transitions with changes in temperature. Hydrogels based on *N*-isopropylacrylamide and its copolymers have been used to develop temperature-modulated drug release systems.[4,5]

At the same time, hydrogels with pH-sensitivity have been found to be particularly useful in the delivery of drugs or peptides to specific sites by special ways. Conventional pH-sensitive polymers are mostly based on monomers containing ionizable groups of a weak acid (e.g., carboxylic acid) or a weak base (e.g., an amino group).[6,7]

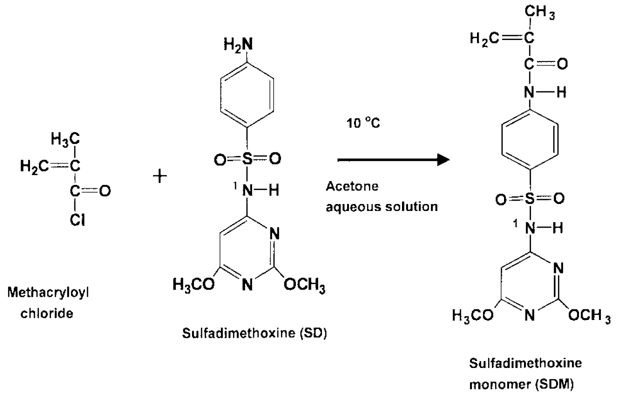
Bae has described the volume phase transition behavior of a hydrogel containing sulfadimethoxine monomer and explained this behavior in terms of the pH-dependent ionization/deionization of the sulfonamide group and reversible side group crystallization (physical cross-linking).[8] This side group crystallization was found to be primarily responsible for the sharp volumetric transition. This crystallization is also influenced by temperature-induced chain flexibility and related with hydrogen bonding amount between un-ionized sulfonamide groups. Up to 70 °C, this gel shows some positive thermosensitivity, thought to be induced by hydrogen bonding changes, even though the main component of this hydrogel, *N*,*N*-dimethylacrylamide, has some negative thermosensitivity.

The aim of the present study is to develop a new kind of hydrogel that responds simultaneously to pH and temperature. This new hydrogel incorporates two kinds of monomer, *N*-isopropylacrylamide (NiPAAm) and a sulfadimethoxine monomer (SDM). The pH- and temperature-dependent swelling behaviors in buffer solution of hydrogels of NiPAAm and SDM in varying proportions are investigated here in detail.

*e-mail : dslee@skku.ac.kr

Materials and Methods

Sulfadimethoxine monomer (SDM) was synthesized from



Scheme I

sulfadimethoxine (SD) and methacryloyl chloride as shown in Scheme I. The detailed steps were described before.[8] ^{1}H NMR measurements were performed on a Varian Unity Inova 500 instrument (500 MHz) to determine the molecular structure of SDM. The purity of the synthesized SDM was greater than 99%.

Hydrogels were synthesized by radical polymerization of SDM and *N*-isopropylacrylamide (NiPAAm). The two monomers NiPAAm and SDM, AIBN (0.2 mol% with respect to the total number of moles of monomer), and methylene-*bis*-acrylamide (MBAAm) were dissolved in DMSO (50% w/v with respect to total solute). The sample preparation method is same as described before.[8]

The dried disks (10 mm diameter) were immersed and equilibrated in buffer solutions of various pHs and temperatures for 3 days. Each sample was then removed from its respective buffer solution, wiped with a towel to remove excess liquid from the surface of the disk, and weighed directly. The swelling ratio was calculated using $(W_s - W_d)/W_d$, where W_s and W_d are the weights of the swollen gel and the dried gel respectively.

Results and Discussion

Characterization of the Hydrogels. The crosslinked hydrogels were prepared with varying the NiPAAm/SDM ratio, as shown in Table I. The resulting hydrogels are denoted here by SDM-0 to SDM-30 according to their SDM mole percentage.

The IR spectra of the hydrogels exhibit characteristic sulfonyl peaks (O=S=O) of SDM appear at 1330 and 1160 cm^{-1}. The intensities of the sulfonyl peaks increase with increasing feed ratio of SDM: SDM-5 < SDM-10 < SDM-15 < SDM-30.

pH-Dependent Equilibrium Swelling. Data for the pH-dependent equilibrium swelling of the series of hydrogels (SDM-0 to SDM-30) at 37 °C are shown in Figure 1. SDM-0 exhibits no swelling over the entire pH range because of NiPAAm's lower critical solution temperature (LCST), 32 °C, as discussed previously.[4,5] The poly(*N*-isopropylacrylamide) hydrogel is typical of such gels because of its negative temperature-sensitivity.

The pH-dependent swelling of hydrogels SDM-5 to SDM-30 is mainly due to the ionization of SDM. Hydrogels SDM-5 to SDM-30 do not exhibit swelling behavior at low pH (from pH 4 to 8) because of the LCST of NiPAAm and because of the interactions between sulfonamide groups in

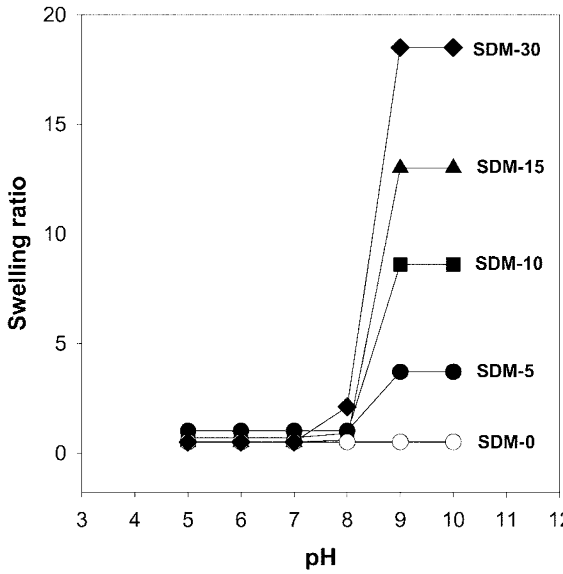


Figure 1. pH-Dependent equilibrium swelling behavior of hydrogels at 37 °C.

Table I. Hydrogels Prepared

Sample Code \ Monomers	Feed Ratio of Monomers		Crosslinking Agent
	NiPAAm	SDM	MBAAm(mol% to monomers)
SDM-0	100 mol %	0 mol %	1.5 mol %
SDM-5	95 mol %	5 mol %	1.5 mol %
SDM-10	90 mol %	10 mol %	1.5 mol %
SDM-15	85 mol %	15 mol %	1.5 mol %
SDM-30	70 mol %	30 mol %	1.5 mol %

the networks. In contrast, their swelling levels at higher pH (pH > 8) are remarkably elevated. This is because the H atoms of ¹N (sulfonamide) release their protons at high pH because of the strong electronegativity of the oxygen atoms of the sulfonyl groups. Thus the charge density and the mobile counter-ion content in the network increase,[9] the internal osmotic pressure increases, and the swelling ratio increases. Accordingly, the swelling ratios of the hydrogels increase at high pH (pH > 8) as their SDM content increases: SDM-5 < SDM-10 < SDM-15 < SDM-30.

Bae reported that the pH-dependent solubility of SDM has a very sharp transition around pH 7.2 for hydrogels with high proportions of SDM (30-40 mol%).[8] The crystallization of side group SDM is primarily responsible for this sharp transition, which is also influenced by temperature-induced chain flexibility and is associated with hydrogen bonding between un-ionized sulfonamide groups. In this study, the pH-dependent volume transitions are very sharp, even for low proportions of SDM. But, this transition shifted from pH 7.2 to 8 due to the deswelling power of NiPAAm component.

Figure 2 shows the pH-dependent equilibrium swelling behavior of hydrogels SDM-0 to SDM-15 at 10 °C. SDM-0 has a pH-independent swelling ratio of 11 at this temperature. In contrast to the behavior shown in Figure 1, hydrogels SDM-0 to SDM-15 exhibit intermediate volumetric behavior resulting from competition between the swelling and deswelling induced by the pH- and temperature-sensitive components of the hydrogels. At low pH, the hydrogels deswell because of the hydrophobic interactions between deionized sulfonamide groups. However, as the SDM content decreases the hydrogels swell even at low pH: SDM-15 < SDM-10 < SDM-5 < SDM-0 (see Figure 2). This swelling occurs because of NiPAAm's tendency to swell at 10 °C (i.e., below its LCST). At high pH, the swelling ratio of the hydrogels increases because of the increased swelling of their ionized SDM components. Note that, as shown in Figure 2, the swelling ratio of hydrogel SDM-5 does not increase above the swelling ratio of SDM-0, whereas the swelling ratios of SDM-10 and SDM-15 do exceed the SDM-0 swelling ratio at high pH.

At low temperature, the pH-dependent volume transitions for the low levels of SDM hydrogel shift to low pH and are not sharp due to swelling of the NiPAAm component. However, a sharp transition appears above 15 mol% SDM (SDM-15). Generally, these values are higher than those of Figure 1 due to the swelling of NiPAAm at 10 °C.

Temperature-Dependent Equilibrium Swelling. Figure 1 shows that at 37 °C all the hydrogels (SDM-0 to SDM-30) exhibit little change in their swelling ratios with a change in the pH from 4 to 8. However, at 10 °C they swell even at low pH. From these results, pH 8 was selected as the optimal pH for verification of the temperature-dependent equilibrium swelling of the hydrogels (Figure 3). SDM-0

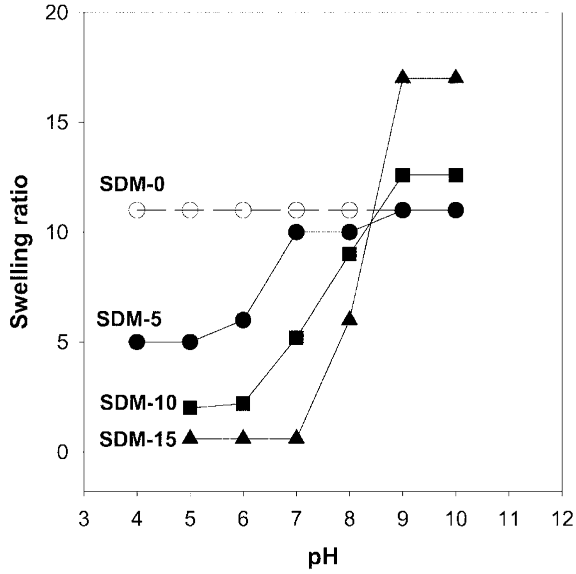


Figure 2. pH-Dependent equilibrium swelling behavior of hydrogels at 10 °C.

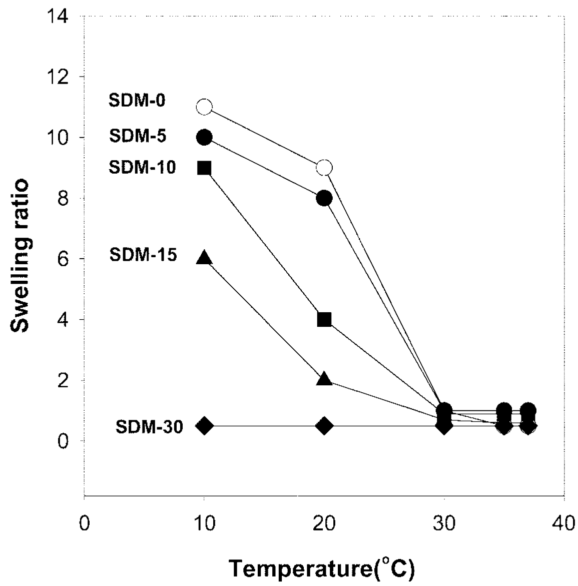


Figure 3. Temperature-dependent equilibrium swelling behavior of hydrogels at pH 8.

shows the typical negative thermosensitivity of NiPAAm hydrogels that has been observed in many previous studies.

As the SDM content increases, the equilibrium swelling ratios of the hydrogels gradually decrease: SDM-0 > SDM-5 > SDM-10 > SDM-15 > SDM-30. As the SDM content increases, the hydrophobic interactions between deionized SDM molecules in the hydrogels become stronger, and consequently the hydrogels swell less. Finally, the swelling ratio of SDM-30 does not vary with temperature even at 10 °C due to the very strong hydrophobic interactions between SDM molecules in hydrogels.[9,10]

pH- and Temperature-Dependent Equilibrium Swelling. To better understand the swelling behavior and associated interactions within the hydrogels, the effects of temperature on the pH-dependent equilibrium swelling of the hydrogels are compared in Figure 4. Figure 4 shows the pH-dependent equilibrium swelling behaviors at 10 and 37 ºC for hydrogels SDM-0 to SDM-15. At these temperatures, SDM-0 is not affected by changes in pH and shows only temperature-dependent swelling behavior (Figure 4(a)). SDM-5 exhibits pH- and temperature-dependent equilibrium swelling behavior (Figure 4(b)). In the low pH region at 10 ºC, the swelling ratio of SDM-5 is lower than that of SDM-0. At high pH region, that value at both of 10 and 37 ºC are shifted upward a little due to the ionization of SDM from the swelling ratio of NiPAAm (SDM-0).

At high SDM content (SDM-15), the swelling ratio curve at 10 ºC moved closely to the curve at 37 ºC remarkably in both of low and high pH region. This is because the hydrophobic interactions between sulfonamide groups strengthen as the SDM content increases.

Figures 5(a) and (b) show the three-dimensional swelling behaviors of SDM-5 and SDM-10 as functions of pH and temperature. These diagrams illustrate the negative thermo-sensitivity and positive pH-sensitivity of these two hydrogels, which swell in regions of low temperature and high pH. We conclude that the preparation of hydrogels that simultaneously respond to both pH and temperature requires the use of an appropriate composition of NiPAAm and SDM.

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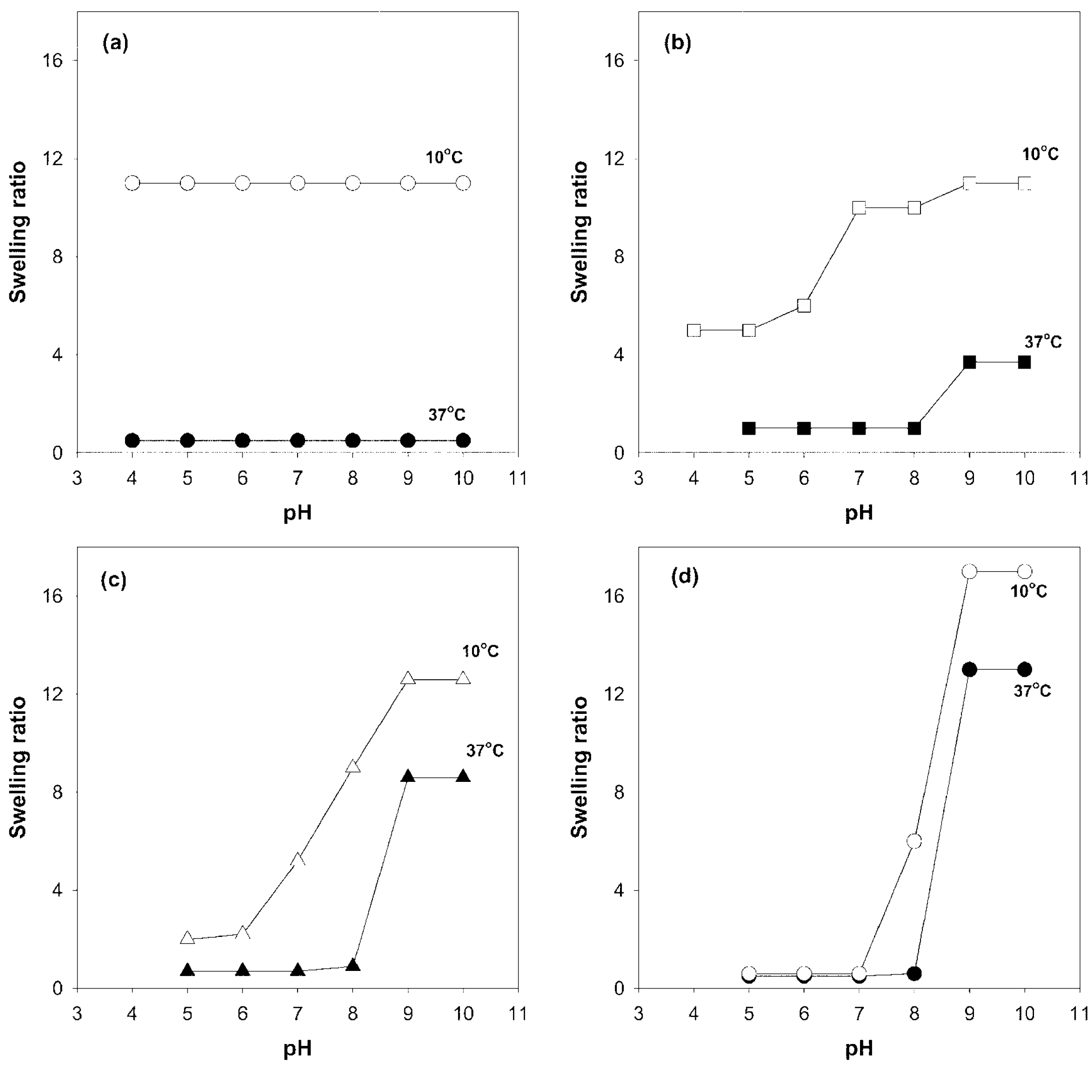

Figure 4. pH-dependent equilibrium swelling behavior at 10 and 37 ºC of (a) SDM-0, (b) SDM-5, (c) SDM-10, and (d) SDM-15.

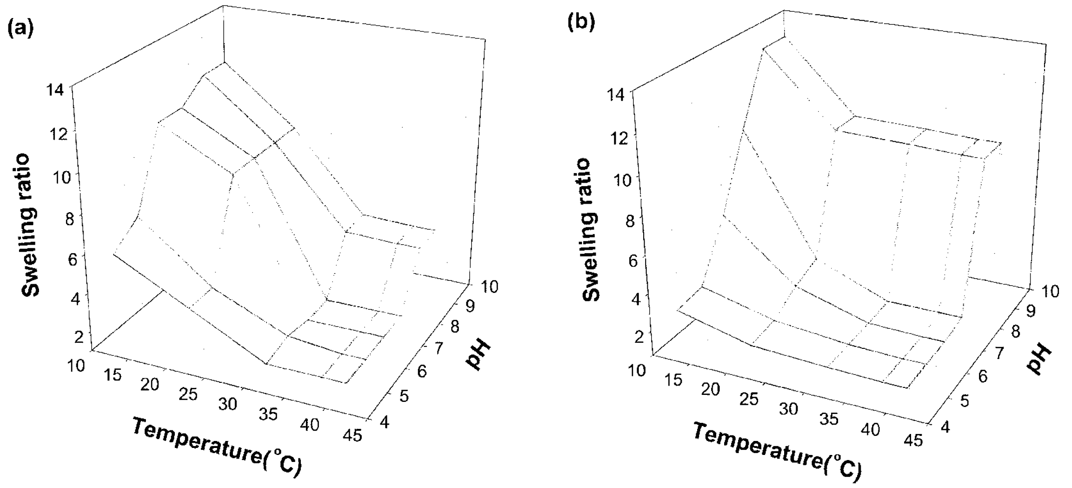

Figure 5. Three-dimensional diagram of the equilibrium swelling as a function of pH and temperature of (a) SDM-5 and (b) SDM-10.

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