# Amphiphilic Thermosensitive N-Isopropylacrylamide Terpolymer Hydrogels Prepared by Micellar Polymerization in Aqueous Media

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ABSTRACT: New amphiphilic terpolymer hydrogels containing a thermosensitive N-isopropylacryalmide component, a hydrophilic comonomer (sodium acrylate), and hydrophobic alkylated comonomers (N-alkylacrylamides) of various lengths were fabricated using a micellar polymerization technique in aqueous media. These gels exhibit compositionally dependent swelling as a function of both pH and temperature, demonstrating large, rapid discontinuous collapse in aqueous media between 30 and 40 °C. Surfactant release from these gels can be modulated by gel composition, demonstrating extended release over several weeks in some cases. The influence of hydrophobic chains in these networks is manifested in their robust mechanical properties, significant alteration of swelling, and influence on release of entrapped moieties.

## Introduction

Perhaps the most significant advance in water-soluble polymers during the past 2 decades has been their modification with hydrophobic moieties. Numerous achievements in polymeric surfactants or water-soluble polymers with a moderate content of hydrophobic groups that significantly lower the surface tension of water have been widely reported. These polymers play a very important role in an array of current interfacial technologies, including flotation, flocculation, wetting, biomedical, and pharmaceutical applications.

Unfortunately, very few polymers described to this point relate to cross-linked networks that contain surfactant-type hydrophobes. Covalent and ionically cross-linked networks of water-soluble polymers, commonly referred as hydrogels in their swollen state, are well known for their successful biomedical applications, such as soft contact lenses, wound management, and controlled drug delivery. Recently, hydrophobically modified hydrogels or so-called amphiphilic networks which exhibit hydrophilic/hydrophobic heterophase structure in aqueous media have received attention on account of their potentially important and fundamentally interesting properties.[1-3] Their unique morphological features greatly influence their properties compared to conventional hydrogels. In particular, heterophasic gel structure should provide versatile controlled delivery features for hydrophilic, hydrophobic, and amphiphilic agents, enhanced biocompatibility due to hydrophobic/hydrophilic balance, and improved mechanical strength.

The object of this paper is to describe new amphiphilic networks based on poly[(N-isopropylacrylamide)-co-(sodium acrylate)-co-(N-n-alkylacrylamide)] (PNiPAAm-co-SA-co-RAAm) hydrogel systems. PNiPAAm has been well characterized[4] in terms of its lower critical solution temperature in solution, as well as its dramatic, reversible aqueous swelling/deswelling behavior in cross-linked networks (hydrogels). A tailored, delicate balance between hydrophilic and hydrophobic components in PNiPAAm hydrogels provides novel thermosensitive swelling behavior in aqueous solution. Incorporation of a hydrophilic ionic comonomer (e.g., sodium acrylate, SA) into PNiPAAm hydrogels radically changes gel swelling behavior in aqueous media.[5-9] Copolymerization of hydrophobic N-n-alkylacrylamide into "neutral" PNiPAAm networks together with a hydrophilic comonomer (e.g., SA) should also strongly affect gel swelling behavior as well as other physicochemical properties including mechanical strength and solute diffusivity.

Nevertheless, little work has been reported for amphiphilic hydrogel synthesis due primarily to synthetic difficulties in dispersing and linking incompatible hydrophilic and hydrophobic polymers together in a gel. One such system based on poly(N,N-dimethylacrylamide)-1-polyisobutylene networks [poly(DMAAm-co-PIB)] has been synthesized for its potential biomedical and pharmaceutical applications.[2] The networks were prepared by radical copolymerization of methacrylate-telechelic PIB macromonomers (MA-PAB-MA, also serves as cross-linker) with DMAAm in THF. THF is a common solvent for both PIB and DMAAm, thereby allowing for a homogeneous reaction mixture.

This same polymerization method (i.e., free-radical initiation of organic solution)[10-16] and other methods including redox initiation in aqueous media,[17-22] ionic polymerization,[23-25] and radiation initiation[26,27] have been used to produce cross-linked PNiPAAm gels and their copolymers. However, for synthesizing amphiphilic poly(NiPAAm-co-SA-co-N-n-alkylacrylamide) networks no common solvent system is known which facilitates a homogeneous reaction mixture. Preparation of PNiPAAm gels in particular and hydrogels in general directly in aqueous media with redox initiation has a number of advantages. Thus, the synthesis of the amphiphilic terpolymer hydrogel networks under such conditions remains an extremely difficult and challenging, yet compelling, area of research.

In this paper a novel micellar copolymerization technique, adapted from a similar technique developed for linear poly(acrylamide-co-N-n-alkylacrylamide) synthesis,[28] has been used to synthesize amphiphilic terpolymer networks using low-temperature redox initiation in aqueous media. In this system, hydrophobic comonomer (N-n-alkylacrylamide, RAAm) was stabilized in aqueous dispersions by the surfactants sodium dodecyl sulfate (SDS) or 4-lauryl ether (Brij 30), forming mixed micelles of this monomer, coexisting in aqueous solutions with NiPAAm, SA, and either methylenebis(acrylamide) (MBAAm) or N,N'-bis(acryloyl)cystamine (BAC) as cross-linkers. The reaction scheme is illustrated in Figure 1. A

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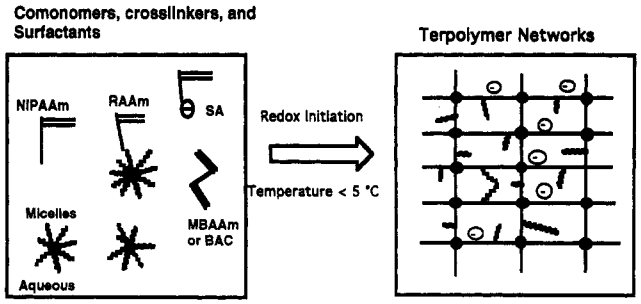


**Figure 1.** Schematic diagram of micellar copolymerization of poly(NiPAAm-*co*-SA-*co*-*N*-*n*-alkylacrylamide) networks in aqueous media, with MBAAm or BAC as cross-linker, SDS or Brij 30 as surfactant stabilizer, and AP/TEMED as redox initiator.

common redox initiation system (ammonium peroxydisulfate and *N,N,N′,N′*-tetramethylethylenediamine) is used to initiate the polymerization reaction and gel network formation at low temperature directly in aqueous media. The comonomer properties, specifically their stability in the reaction system, are significantly dependent on the type and amount of the amphiphile used as well as the mixing conditions (i.e., temperature, pH, and stirring).

The micellar copolymerization technique has many unique advantages in preparing amphiphilic polymeric networks for controlled release applications:

1. It is a more efficient incorporation of hydrophobic components into a mainly hydrophilic framework when compared to conventional approaches.
2. Aqueous phase polymerization can be performed in the presence of either water-soluble or micellar-stabilized (insoluble) proteins, polypeptides, drugs, or other species at low temperature.
3. Stability and bioactivity of certain entrapped proteins or peptides can be enhanced by this mild, encapsulating approach.
4. It contains extended release kinetics due to a "depot effect" from hydrophobic domains within the gel.

## Experimental Section

**Materials.** All solvents used were reagent grade. *N*-Isopropylacrylamide (NiPAAm; Eastman Kodak) was recrystallized twice from benzene/hexane (4:6). Sodium acrylate (SA; Pfaltz & Bauer) was used as received. Methylenebis(acrylamide) (MBAAm; Aldrich) was recrystallized from ethanol. Acryloyl chloride (Aldrich) was distilled under $N_2$ before use. Cystamine dihydrochloride (Sigma), *n*-alkylamine (*n*-octyl-, *n*-decyl-, *n*-dodecyl-, *n*-tetradecyl-, and *n*-octadecylamine; Aldrich) were used without further purification. *N*-*n*-Butylacrylamide (Polysciences), tetramethylethylenediamine (TEMED; Aldrich), ammonium persulfate (AP; Aldrich), sodium dodecyl sulfate (SDS; Sigma), and 4-lauryl ether (Brij 30; Sigma) were used as received without further purification. All buffer salts and solutes were reagent-grade compounds. Water for buffers, gel swelling, and release measurements was first reverse-osmosis filtered (deionized) and then Millipore filtered to yield purified water having 18 MΩ/cm resistivity.

**Synthesis. *N*-*n*-Alkylacrylamide.** The classical route to prepare the N-substituted acrylamide family is from the reaction of acryloyl chloride with its respective amine at low temperature. The reaction equation is

$$CH_2{=}CR_1C(O)Cl + R_2NHR_3 \rightarrow CH_2{=}CR_1C(O)NHR_2R_3$$

where $R_1$ = H or Me, $R_2$ and $R_3$ = H, alkyl, or aralkyl. Detailed descriptions of the chemistry and procedures for this reaction can be found in the original literature.[29-31] We prepared *N*-*n*-octyl-, *N*-*n*-decyl-, *N*-*n*-dodecyl-, *N*-*n*-tetradecyl-, and *N*-*n*-octadecylacrylamide by the same reaction scheme above according to the following procedure.

*n*-Alkylamine (20 mmol) and triethylamine (21 mmol) were dissolved in 50 mL of tetrahydrofuran (THF). This solution was cooled in an acetone/ice bath, and 20 mL of a THF solution containing acryloyl chloride (20 mmol) was slowly added with constant stirring over 30 min. The reaction temperature was monitored and not permitted to exceed 0 °C. The reaction vessel was removed from the acetone/ice bath after addition of the acryloyl chloride and permitted to equilibrate to room temperature for 30 min. An inhibitor, hydroquinone (5 mg), was added to the reaction mixture prior to filtration through a medium-pore sintered-glass filter. Tetraethylamine hydrochloride byproduct was discarded, and the filtrate was washed with 0.1 N HCl, brine, and saturated $H_2O$/$NaHCO_3$/NaCl and dried with $MgSO_4$. After evaporating the solvent, the product was allow to recrystallize from petroleum ether at 5 °C. The overall recovery was greater than 40%. The characterization results are listed in Table 1.

***N,N′*-Bis(acryloyl)cystamine (BAC).** BAC was synthesized from the reaction of acryloyl chloride (1 mol equiv) with cystamine (2 mol equiv) by either the same procedure above or a heterogeneous phase reaction. The general procedure for the heterogeneous phase reaction follows.

Cystamine dihydrochloride (10 mmol) was dissolved in a mixture of 15 mL of 3.5 M NaOH and 10 mL of chloroform. This solution was heated to 50 °C, and 5 mL of chloroform containing 20 mmol of acryloyl chloride was added dropwise with constant stirring over 15 min while the reaction temperature was maintained near 50 °C. After separating the phases while still warm, the aqueous phase was discarded. The remaining organic phase was cooled to room temperature and the product precipitated directly from the solution. The white crystal product was recovered by filtration and recrystallized from chloroform to give a yield above 60%. The melting point of the product was 120–121 °C. The infrared spectrum (FTIR, KBr pellet) shows major peaks at 3253, 3067, 1653, 1622, 1555, 1312, 1254, 1238, 1075, 992, 961, and 806 $cm^{-1}$. $^1$H-NMR spectrum ($CDCl_3$) gave δ 2.9 (2H, triplet), 3.7 (2H, quartet), 5.6 (1H, multiplet), and 6.1 (2H, multiplet).

**Terpolymer Poly(NiPAAm-*co*-SA-*N*-*n*-alkylacrylamide) Networks.** NiPAAm-*co*-SA-*co*-*N*-*n*-alkylacrylamide networks were synthesized by micellar copolymerization using either MBAAm or BAC as a cross-linker. For aqueous redox polymerization, ammonium persulfate (AP) and TEMED were used as initiators. At first, various amounts of hydrophobic monomers, *N*-*n*-butyl-, *N*-*n*-octyl-, *N*-*n*-decyl-, *N*-*n*-dodecyl, *N*-*n*-tetradecyl-, and *N*-*n*-octadecylacrylamide, were stabilized by either SDS or Brij 30 (1–5%) in a transparent aqueous solution with proper stirring and temperature control. Then aqueous solutions of various amounts of mixed comonomers (NiPAAm and SA), cross-linker (MBAAm or BAC), and TEMED were carefully added into the micelle solution with stirring and $N_2$ bubbling for 15 min. The total monomer content in water was 10 wt % unless specified. After the addition of AP, the complete mixture was injected between precooled clean glass plates separated by 2-mm-thick gaskets (2-mm-o.d. cross-linked silicone rubber O-rings) with extreme care taken to avoid the introduction of air bubbles into the solution. The plates were clamped securely and suspended in an ice/water bath at temperatures less than 5 °C for 24 h. The resulting gel films were then separated from the plates and allowed to swell in deionized water/methanol (60/40) for a week, followed by swelling in pure deionized water at room temperature until no release of surfactant was detected. Swollen terpolymer gel membranes were subsequently cut into disks of 1-cm diameter using a cork borer, dried ambiently for 1 day, and dried under vacuum for 3 days at room temperature.

**Swelling Measurements.** For measurements at pH 7.3, 0.05 M phosphate buffers were used. Dried hydrogel disks were initially immersed and equilibrated in buffer solutions in glass vials at 20 °C for 2 days. These vials were in turn immersed in a shaking water bath (American Scientific Model YB-521) at a series of temperatures from 20 to 70 °C until gel weight changes were less than 0.1%. Each sample was then removed from the water bath and from its respective vial, tapped with a dampened Kim-wipe towel to remove excess surface water, and weighed directly using an electrobalance (Ohaus GA200D). The dry weights were measured on the same balance after desiccating the

**Table 1. Characterization of *N*-*n*-Alkylacrylamide Monomers**

| alkylacrylamide monomer | mp (°C) | FTIR bands ($cm^{-1}$) | $^1$H-NMR (ppm) (in $CDCl_3$) |
|---|---|---|---|
| octyl- | | 3300, 3057, 2956, 2926, 1656, 1625, 1543, 1476, 1408, 1375, 1313, 1239, 990, 952 | 6.0–6.2, 6.2–6.4, 5.5–5.7, 3.3, 1.7–2.0, 1.4–1.6 |
| decyl- | 44–45, 45–46[a] | 3280, 3071, 2957, 2927, 1659, 1626, 1550, 1467, 1408, 1362, 1220 | 6.0–6.4, 5.6–5.65, 3.3–3.4, 2.2, 1.2–1.6, 0.9 |
| dodecyl- | 54–55, 55.5[b] | 3271, 3072, 2957, 2922, 1653, 1622, 1550, 1469, 1406, 1378, 1309, 1244, 989, 952 | 6.0–6.4, 5.5–5.7, 3.7–3.8, 3.3, 2.2 |
| tetradecyl- | 63.5–64, 61.5–62[c] | 3273, 3072, 2955, 2919, 1653, 1622, 1549, 1471, 1407, 1379, 1310, 1240, 993, 963 | 6.0–6.4, 5.6–5.65, 3.3, 2.2 |
| octadecyl- | 68.5–69, 69[d] | 3303, 2957, 2918, 1654, 1624, 1542, 1408, 1377, 1311, 1238, 992, 953 | 6.0–6.4, 5.6–5.65, 3.3, 2.2, 1.2–1.6 |

[a] Reported value from ref 31. [b] Reported value from ref 32. [c] Reported value from ref 32. [d] Reported value from ref 33.

same gels for 3 days under vacuum at room temperature until constant dry weights were maintained. Swelling ratios (SW) were calculated from the following formula:

$$\text{SW} = (\text{wet weight} - \text{dry weight})/(\text{dry weight}) \text{ or } (W_t - W_d)/W_d \quad (1)$$

where $W_t$ = gel weight at temperature $t$, $W_d$ = gel dry weight, and $W_0$ = fully hydrated weight of the gel.

**Model Amphiphile SDS Loading and Release Measurements.** The model amphiphile SDS was loaded into terpolymer gels as part of the *in situ* gel polymerization method. Release measurements of SDS from gels began immediately after gel membranes were separated from the glass plate molds, cut, and equilibrated in pure water for 24 h. Release of SDS was measured by both HPLC assay and gel swelling ratio monitoring over time. The HPLC (Waters) analytical conditions were as follows: $\mu$-Bondapak $C_{18}$ column as a stationary phase, water as a mobile phase, UV ($\lambda$ = 225 nm) detection, 0.8 mL/min flow rate, 10-$\mu$L injection volume, temperature = 21 °C, internal standard method as quantitation calculation. The swelling ratio monitoring method stems from the changes in gel swelling ratios as ionic SDS is released. Due to the Donnan equilibria approximation at constant temperature, SDS release is correlated to gel swelling by the relation

$$\frac{M_t}{M_\infty} = \frac{\text{SW}_0 - \text{SW}_t}{\text{SW}_0 - \text{SW}_\infty} \quad (2)$$

where $M_t$ is the amount of SDS measured at each time interval, $M_\infty$ the equilibrium value, $\text{SW}_0$ the initial swelling ratio measured, $\text{SW}_t$ the swelling ratio at each time interval, and $\text{SW}_\infty$ the equilibrium swelling ratio. Overall release measurements were conducted under either "normal" conditions (no changes of the 20-mL aqueous release media) or "sink" conditions (equal volumes of fresh aqueous media exchanged for 500-$\mu$L sampling volumes in 20 mL of total release media). In all cases, the total released SDS concentration amounted to less than 10% of the SDS critical micelle concentration.

## Results and Discussion

**Thermosensitive Swelling Behavior of Amphiphilic Terpolymer Networks.** Figures 2 and 3 show differences in temperature-dependent swelling equilibria for four network systems—poly(NiPAAm-*co*-SA-*co*-*N*-*n*-butyl-, *N*-*n*-octyl-, *N*-*n*-dodecyl-, or *N*-*n*-tetradecylacrylamide)—with the same copolymer compositional ratio, 95/3/2, and cross-linker MBAAm (Figure 2) or BAC (Figure 3), respectively. All four networks containing either MBAAm or BAC show their reversible critical collapse temperature between 30 and 35 °C.

The networks demonstrate higher swelling capability at temperatures below their critical points and shrink dramatically (swelling ratio near unity) as temperatures increase above their respective critical points. After introducing a hydrophobic comonomer, *N*-*n*-alkylacrylamide, with varying alkyl side chain length, the networks decrease their swelling ratios at temperatures below their

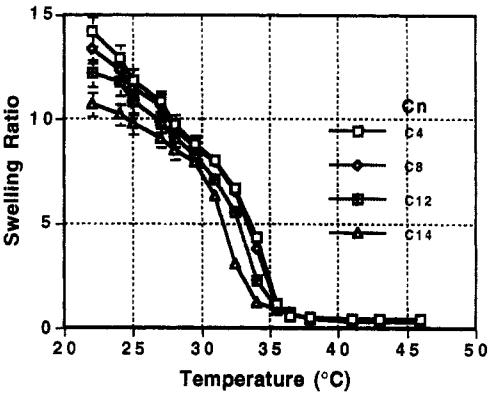


**Figure 2.** Thermosensitive swelling behavior of terpolymer (NiPAAm/SA/C*n*, 95/3/2, 0.8 mol % MBAAm) gels in 0.05 M phosphate buffer (pH 7.3).

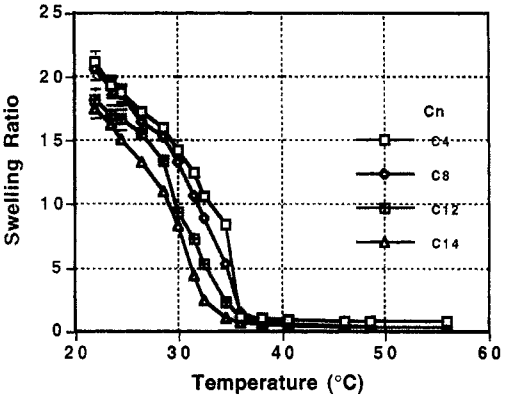


**Figure 3.** Thermosensitive swelling behavior of terpolymer (NiPAAm/SA/C*n*, 95/3/2, 1.5 mol % BAC) gels in 0.05 M phosphate buffer (pH 7.3).

critical points, and their critical temperatures decrease with increasing length of the alkyl side chain.

Figure 4 shows temperature-dependent swelling equilibria for poly(NiPAAm-*co*-SA-*co*-*N*-*n*-butylacrylamide) networks with fixed amounts of hydrophilic comonomer (SA) incorporation (3 mol %) and four different amounts of hydrophobic comonomer (*N*-*n*-butylacrylamide) incorporation (1, 2, 4, 6 mol %). All four networks demonstrate their thermosensitive swelling behavior with critical points between 28 and 35 °C. Figure 5 shows the temperature-dependent swelling equilibria for poly(NiPAAm-*co*-SA-*co*-*N*-*n*-dodecylacrylamide) networks with fixed amounts of (SA) incorporation (3 mol %) and four different amounts of *N*-*n*-dodecylacrylamide incorporation (1, 2, 4, 6 mol %). All four networks demonstrate their thermosensitive swelling behavior with critical temperatures between 27 and 35 °C. Figures 4 and 5 show nearly identical results in response to the amount of hydrophobic comonomer, either *N*-*n*-butyl- (C4) or *N*-*n*-dodecylacrylamide (C12), incorporated. Swelling ratios consistently

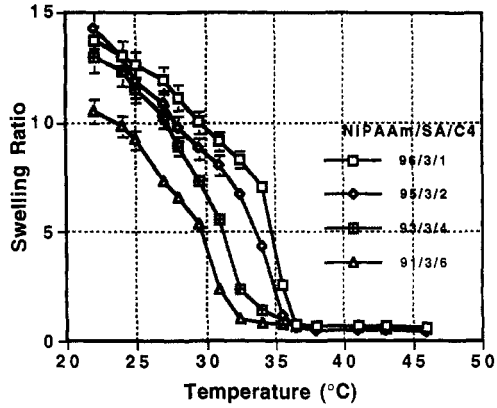


**Figure 4.** Thermosensitive swelling behavior of terpolymer (NiPAAm/SA/C4, 0.8 mol % MBAAm) gels in 0.05 M phosphate buffer (pH 7.3).

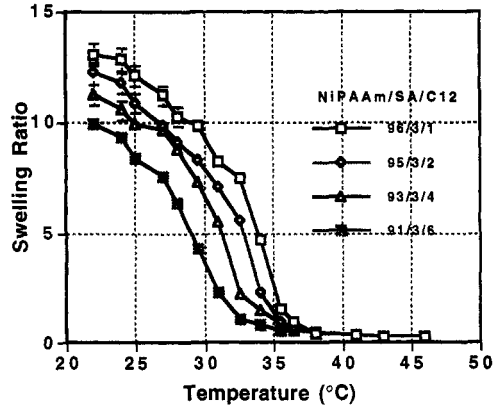


**Figure 5.** Thermosensitive swelling behavior of terpolymer (NiPAAm/SA/C12, 0.8 mol % MBAAm) gels in 0.05 M phosphate buffer (pH 7.3).

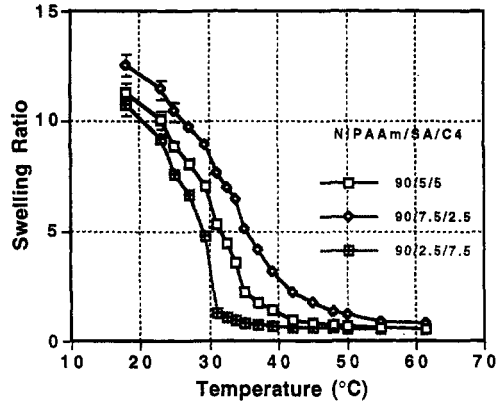


**Figure 6.** Thermosensitive swelling behavior of terpolymer (NiPAAm/SA/C4, 0.8 mol % MBAAm) gels in 0.05 M phosphate buffer (pH 7.3).

decrease and critical points shift to lower temperature as the amount of network hydrophobic comonomer incorporation increases.

Figure 6 shows temperature-dependent swelling equilibria for three poly(NiPAAm-*co*-SA-*co*-*N*-*n*-butylacrylamide) networks, with three different copolymer ratios: 90/7.5/2.5, 90/5/5, 90/2.5/7.5. Figure 7 shows temperature-dependent swelling equilibria for three poly(NiPAAm-*co*-SA-*co*-*N*-*n*-tetradecylacrylamide) networks, with three different copolymer ratios: 95/4/1, 95/2.5/2.5, 95/1/4. Generally, both figures show similar results for network swelling with regard to hydrophilic/hydrophobic comonomer ratio changes. When the amount of hydrophilic comonomer (SA) incorporation increases, network temperature-dependent swelling profiles shift to higher swelling ratios and higher critical temperature points. On the other hand, network swelling profiles shift to lower swelling ratios and lower critical temperature points as the amount of hydrophobic comonomer, either *N*-*n*-butyl- (C4) or *N*-*n*-tetradecylacrylamide (C14), incorporation increases. Network swelling is balanced by the function of incorporated hydrophilic or hydrophobic comonomer species to increase or decrease the transition temperature and magnitudes, respectively, into these networks.[8]

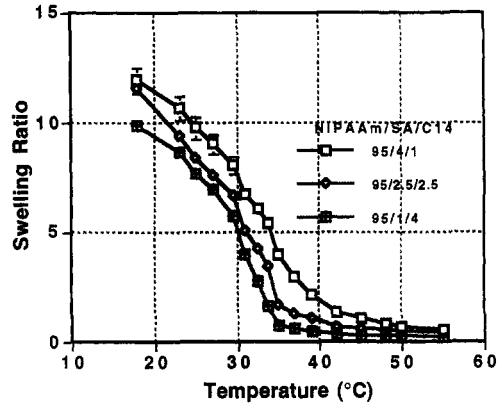


**Figure 7.** Thermosensitive swelling behavior of terpolymer (NiPAAm/SA/C14, 0.8 mol % MBAAm) gels in 0.05 M phosphate buffer (pH 7.3).

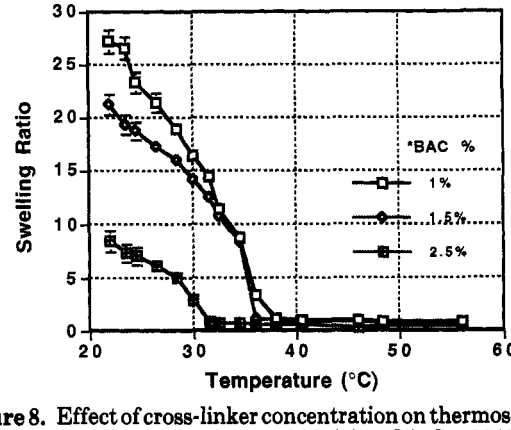


**Figure 8.** Effect of cross-linker concentration on thermosensitive swelling behavior of terpolymer (NiPAAm/SA/C4, 95/3/2) gels in 0.05 M phosphate buffer (pH 7.3) (*mol % to monomer).

Figure 8 shows temperature-dependent swelling equilibria for poly(NiPAAm-*co*-SA-*co*-*N*-*n*-butylacrylamide) (95/3/2) networks with three different amounts of the cross-linker, BAC (1, 1.5, and 2.5%). Network thermosensitive swelling behavior and critical points do not change, except that swelling ratios decrease as network cross-linking density increases. Like the often-used cross-linker MBAAm, the bis(acryloyl)cystamine cross-linker behaves as a normal cross-linking agent in network synthesis, but with the advantage that it might be cleaved with reducing agents to solubilize the network.

Figure 9 summarizes the mutual effects of network hydrophilic and hydrophobic (C4) comonomer ratios on temperature-dependent swelling equilibria for PNiPAAm amphiphilic networks. The reversible swelling–deswelling transition is shifted as a function of the balanced respective influences of SA and RAAm components. However, none of the currently existing theoretical models[35-41] accurately describe the temperature-dependent critical swelling behavior of PNiPAAm gels quantitatively, particularly the mixing component of the gel free energy expression. The influence of ionized hydrophilic comonomer SA can be estimated properly using an ideal Donnan equilibria approach (see eq 10) as the networks have very high

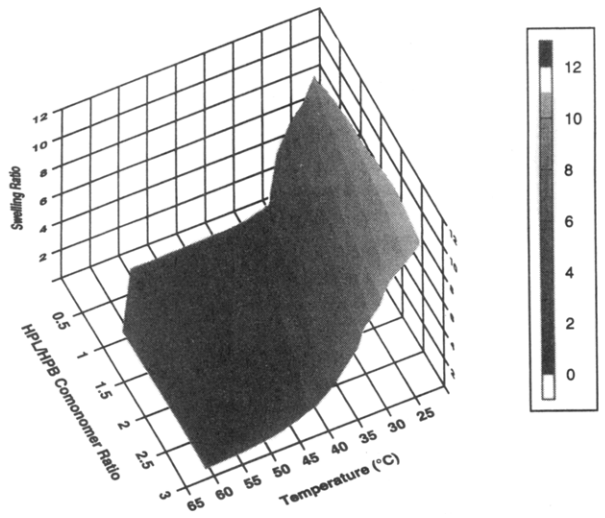


**Figure 9.** Temperature-dependent swelling equilibria of amphiphilic networks, cross-linked poly(NiPAAm-*co*-SA-*N*-*n*-butylacrylamide), versus hydrophilic SA and hydrophobic RAAm comonomer ratio in 0.05 M phosphate buffer (pH 7.3).

swelling ratios (high solvent uptake), have very low incorporation of ionized SA (less than 10 mol %), and remain in equilibrium.

To explain the thermosensitive critical swelling behavior observed for PNiPAAm gels, most gel theories basically contain four additive terms reflecting the changes in free energies of mixing, specific interactions, elasticity, and osmotic effects for a gel in aqueous media.[35-41] The extensively used model invoked to describe gel swelling behavior—Flory–Huggins mean-field theory[42]—expresses the Gibbs free energy of mixing as

$$\Delta G_{mix} = kT[n \ln(1-\varphi) + \chi n\varphi] \quad (3)$$

where $\Delta G_{mix}$ is the free energy change for mixing a pure solvent and a polymer network, $n$ the number of the solvent molecules in the gel, $\varphi$ the volume fraction of the polymer network, $\chi$ the polymer–solvent interaction parameter, $k$ Boltzmann's constant, and $T$ the absolute temperature. However, the Flory–Huggins theory is based on a random-mixing lattice model which assumes that interaction potentials for solvent and polymer segments are homogeneous over the segment surfaces. *This theory does not account for orientation-dependent interactions (i.e., hydrogen bonds and hydrophobic interactions) which dramatically influence the behavior of PNiAAm gels in aqueous systems and result in temperature-dependent hydration.*

The hydrophobic contribution to the mixing term of gel free energy has been expressed[38] as

$$\Delta G^{hydrophobic} = C_a + C_b T + C_c T^2 \quad (4)$$

where $C_a$, $C_b$, and $C_c$ are system-dependent parameters related to the nature (amount and length of the alkyl side chain) of the hydrophobic species in the networks.[40]

The thermosensitive swelling behavior of PNiPAAm gels has been recently addressed by some very different approaches, such as quasi-chemical approaches,[39] equation-of-state (compressible) approaches,[36,40] and "blob theory" approaches.[43,44] Nevertheless, a theoretical expression adequately accounting for the mixing term for PNiPAAm gels in water is far from complete. Further work addressing hydrogen bonding/hydrophobic interactions, as well as network structural characterization, will be required for constructing a valid and rigorous analytical solution.

Modern network theories can successfully deal with the two ideal networks: affine[42] and phantom[46] types. *However, real networks conform to neither of the two limiting cases.* A modified model of chemical potential change ($\Delta\mu$) due to network elastic contributions[47,48] can be written as

$$\Delta\mu_{elas} = \Delta\mu_{elas}^{phantom}(1-F) + \Delta\mu_{elas}^{affine}F \quad (5)$$

$$\Delta\mu_{elas}^{affine} = \frac{1}{2}RT(\phi_2^0/\chi_c)\lambda^{-1}(2-\lambda^{-2}) \quad (6)$$

$$\Delta\mu_{elas}^{phantom} = \frac{1}{2}RT(\phi_2^0/\chi_c)\lambda^{-1} \quad (7)$$

where $\chi_c$ is the average number of segments per network chain (where a segment is defined to have the same volume as that of a solvent molecule), $\phi_2^0$ the volume fraction of the gels in the reference state (i.e., at preparation), and $\lambda = (\phi_2^0/\phi_2)^{1/3}$. Forces exerted on the network are expressed by

$$F = K(\lambda,\kappa)/(1-\lambda^{-2}) \quad (8)$$

where $F$ varies between 0 (no constraints on junctions) and 1 (complete constraints on junctions) given by the Flory–Erman theory.[47] Parameter $\kappa$ is a measure of constraints on junction fluctuations and is related to the degree of network interpenetration through[48]

$$\kappa = \frac{1}{4}P\phi_2^{0\,1/2}\chi_c \quad (9)$$

where a dimensionless number, $P$, is determined by the type of polymer and the molar volume of the solvent. For a specific polymer/solvent (gel) system, $P$ remains constant and $\kappa$ depends only on network composition (cross-link density and monomer concentration at preparation).

Fixed charges on a network are confined (along with an equal number of counterions) to the gel phase, resulting in an unequal distribution of unbound ions between the gel and surounding solution and a resulting osmotic pressure difference between the two phases.[42] The osmotic difference introduces an additional mixing contribution (of ions with solvent) to the swelling free energy and therefore to the solvent chemical potential. Semiquantitative Donnan equilibria for describing this contribution can explain only some basic features of polyelectrolyte gel swelling.[49] In ideal Donnan equilibria theory

$$\Delta G_{ion} = \Delta G_{ion}^{gel} - \Delta G_{ion}^{ext} = -\bar{\nu}RT\sum_j (c_j^{gel} - c_j^{ext}) \quad (10)$$

where $\bar{\nu}$ is the solvent partial molar volume, and $c_j^{gel}$ and $c_j^{ext}$ are respectively ion concentrations within the gel and in the surrounding solution. The summation over $j$ includes all mobile (unbound) ions.

Despite the ability to explain constituent behaviors (i.e., electrostatic, hydrophobic) in ideal gel networks, application of any known theories to accurately account for nonideal Donnan effects, temperature-dependent segment–solvent interactions, and hydrophobic segmental clustering in nonideal networks in the gel free energy expression remains an intractable analytical problem. Trends observed in these ionized hydrophobic NiPAAm gels cannot be accurately modeled with any of the theories mentioned above for these reasons.

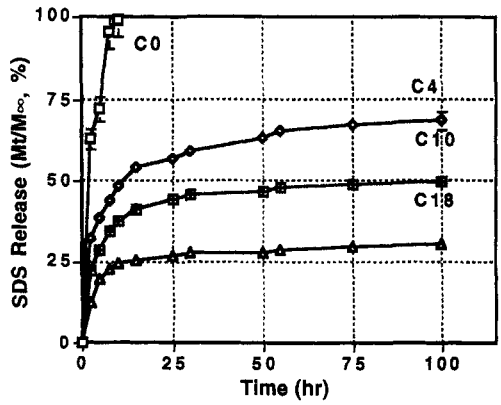


**Figure 10.** SDS release from terpolymer gels (PNiPAAm/SA/Cn, 95/2.5/2.5, 0.8 mol % MBAAm) in water under normal conditions at 25 °C measured by the HPLC method.

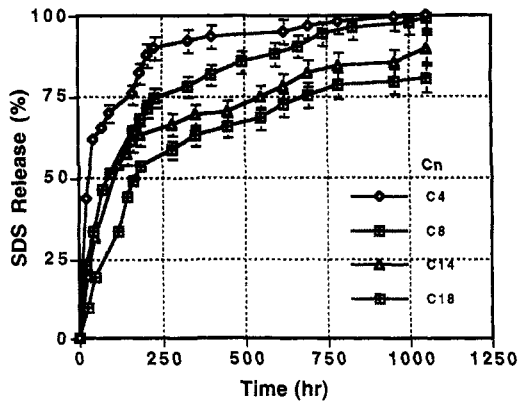


**Figure 11.** SDS release from terpolymer gels (PNiPAAm/SA/Cn, 95/2.5/2.5, 0.8 mol % MBAAm) in water under "sink" conditions at 25 °C measured by changes in swelling ratios over time.

**Model Amphiphile SDS Release from Amphiphilic Terpolymer Networks.** Figure 10 shows sodium dodecyl sulfate (SDS) release profiles from four different networks: nonhydrophobized, cross-linked poly(NiPAAm-*co*-SA) (95/5) and poly(NiPAAm-*co*-SA-*N*-*n*-butyl-, *N*-*n*-decyl-, and *N*-*n*-octadecylacrylamide) (95/2.5/2.5) in water at 25 °C asayed using HPLC measurement. Except for the poly(NiPAAm-*co*-SA) gels, all three of the other samples' release profiles demonstrate first-order (first 25 h) to pseudo-zero-order (after 25 h) kinetics. Release rates decrease dramatically as network alkyl chain length increases. This is proposed to result from increasing hydrophobic interactions between SDS hydrocarbon chains and the network alkyl side chains. Release profiles from poly(NiPAAm-*co*-SA) gels (no pendent alkyl side chains introduced) show very rapid, complete, first-order release kinetics (within 10 h). Rapid responses of swelling changes in ionized NiPAAm hydrogels to media temperature, pH, ionic strength, and network ionic charge have been described in our previous work.[9]

Figure 11 shows SDS release profiles from four different networks: poly(NiPAAm-*co*-SA-*co*-*N*-*n*-butyl-, *N*-*n*-decyl-, *N*-*n*-tetradecyl-, *N*-*n*-octadecylacrylamide) (95/2.5/2.5) in water by monitoring swelling ratios under a fixed temperature of 25 °C. All release profiles exhibit interesting long-term pseudo-zero-order release kinetics over the initial 200-h period, particularly in networks containing long alkyl side chains. Release rates decrease as network alkyl chain lengths increase due to increasing gel-surfactant hydrophobic chain–chain interactions. While we cannot be entirely certain that 100% SDS release is achieved at the end of these measurements, the lack of further release

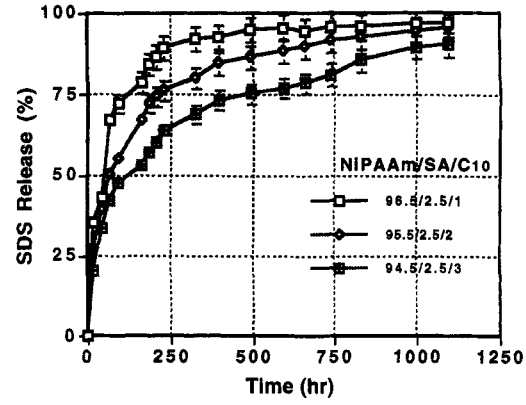


**Figure 12.** SDS release from terpolymer gels (PNiPAAm/SA/C10, 0.8 mol % MBAAm) in water under "sink" conditions at 25 °C measured by changes in swelling ratios over time.

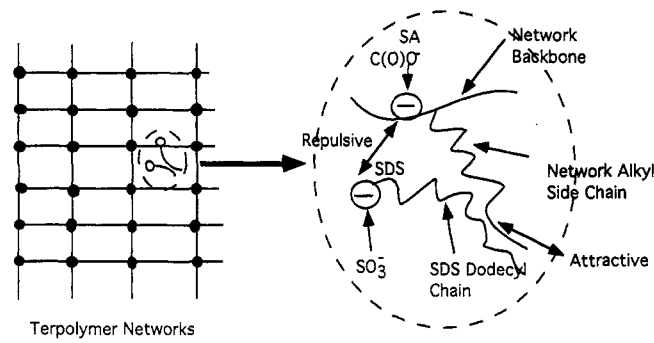


**Figure 13.** Schematic diagram of hydrophobic chain–chain interactions between terpolymer networks and SDS which influence amphiphile diffusion in these networks.

after plateau (as detected by HPLC; Figure 10) correlates with plateaus in Figures 11 and 12, indicating the swelling and SDS release both came to equilibrium concomitantly.

Figure 12 shows SDS release profiles from three different networks of poly(NiPAAm-*co*-SA-*N*-*n*-decylacrylamide) with fixed SA content (2.5 mol %) and different amounts of *N*-*n*-decylacrylamide comonomer incorporation (1, 2, and 3 mol %, respectively) measured by swelling ratio changes over time at 25 °C. All release curves show the same kinetic pattern. However, release rates decrease as the amount of hydrophobic components increases due to enhancement of hydrophobic interactions between SDS and network alkyl chains. Swelling-based data shown in Figures 11 and 12 consistently corroborate SDS release data quantified by HPLC (Figure 10) as SDS releases hydrophobic regions in the gels which act as pinpoints inhibiting swelling. Removal of SDS accelerates gel swelling, allowing the two methods to be closely correlated over the first release period (<100 h).

Figure 13 shows a schematic diagram of proposed molecular associations in the gel networks due to hydrophobic chain–chain interactions between amphiphilic networks of cross-linked poly(NiPAAm-*co*-SA-*co*-RAAm) and SDS. Their partial structural similarity is also illustrated in this figure. Correlations with thermodynamic data reported for hydrophobic binding between alkyl chains in two different polymers[45,50] show standard free energies of interaction which are a linear function of alkyl chain length from $n = 1$ to $n = 16$. This indicates that each methylene group of the alkyl chain makes equivalent contributions to total hydrophobic interactions with SDS. Such a model forms the basis for a semiquantitative analysis of results for SDS release versus network hydrophobicity, including both length and amount of alkyl side chains. While the simplest Fickian laws of diffusion have

been extensively applied to describe the solute diffusivity in hydrogels, resulting in frequent models for first-order release kinetics, solute diffusivity in amphiphilic terpolymer gels may be better interpreted by considering both time- and position-dependent diffusivities of permeating species through a multicomponent controlled diffusion theory approach. Further detailed discussions about solute diffusivity in these terpolymer networks will appear in our future publications.[51]

## Conclusions

Amphiphilic terpolymer networks based on cross-linked poly[(*N*-isopropylacrylamide)-*co*-(sodium acrylate)-*co*-(*N*-*n*-alkylacrylamide)] demonstrate some remarkable and interesting thermosensitive matrix swelling behaviors in water as well as amphiphile diffusion kinetics. Network swelling and thermosensitive critical points are readily adjusted by controlling levels of hydrophilic and hydrophobic comonomers. Network amphiphile (surfactant) release kinetics are controlled using this tunable network swelling: fine tuning by type and amount of alkyl side chain incorporated and broad control by network cross-link density. Molecular-scale hydrophobic domains in the networks are proposed to play a significant role in achieving long-term zero-order release for amphiphiles.

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## References and Notes

(1) Yu, H.; Grainger, D. W. *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)* **1993**, *34*, 820.
(2) Ivan, B.; Kennedy, J. P.; Mackey, P. W. In *Polymeric Drugs and Drug Delivery Systems*; Dunn, R. L., Ottenbrite, R. M., Eds.; ACS Symposium Series 469; American Chemical Society: Washington, DC, 1991; pp 194–212.
(3) Yu, H.; Grainger, D. W. In *Proceedings of the 20th International Symposium on Controlled Release of Bioactive Materials*; Roseman, T. J., Peppas, N. A., Grabelnick, H. L., Eds.; Controlled Release Society: Deerfield, IL, 1993; pp 28–29.
(4) Schlid, H. G. *Prog. Polym. Sci.* **1992**, *17*, 163.
(5) Baker, J. P.; Stephens, D. R.; Blanch, H. W.; Prausnitz, J. M. *Macromolecules* **1992**, *25*, 1955.
(6) Hirotsu, S.; Hirokawa, Y.; Tanaka, T. *J. Chem. Phys.* **1987**, *87*, 1392.
(7) Feil, H.; Bae, Y. H.; Feijen, J.; Kim, S. W. *Macromolecules* **1992**, *25*, 5528.
(8) Kafono, H.; Sanui, K.; Ogata, N.; Okano, T.; Sakurai, Y. *Polym. J.* **1991**, *23*, 1179.
(9) Yu, H.; Grainger, D. W. *J. Appl. Polym. Sci.* **1993**, *49*, 1553.
(10) Winnik, F. M.; Ringsdorf, H.; Venzmer, J. *Macromolecules* **1991**, *24*, 1678.
(11) Kungwatchakun, D.; Irie, M. *Makromol. Chem., Rapid Commun.* 1988, *9*, 243.
(12) Snyder, W. D.; Kotz, I. M. *J. Am. Chem. Soc.* **1967**, *97*, 4999.
(13) Elaissaf, J. *J. Appl. Polym. Sci.* **1978**, *22*, 873.
(14) Nguyen, A. L.; Luong, J. H. T. *Enzyme Microb. Technol.* **1990**, *12*, 663.
(15) Fujishige, S. *Polym. J.* **1987**, *19*, 297.
(16) Schild, H. G.; Tirrell, D. A. *Langmuir* **1991**, *7*, 665.
(17) Wooten, W. C.; Blanton, R. B.; Coover, H. W. *J. Polym. Sci.* **1957**, *XXV*, 403.
(18) Otake, K.; Inomata, H.; Konno, M.; Saito, S. *Macromolecules* **1990**, *23*, 283.
(19) Chiklis, C. K.; Grasshoff, J. M. *J. Polym. Sci., Part A* **1970**, *8*, 1617.
(20) Heskin, M.; Guillet, J. E. *J. Macromol. Sci., Chem.* **1969**, *2*, 1441.
(21) Schild, H. G.; Tirrell, D. A. *Macromolecules* **1991**, *24*, 948.
(22) Priest, J. H.; Murray, S. L.; Nelson, J. R.; Hoffman, A. S. In *Reversible Polymeric Gels and Related Systems*; Russo, P. S., Ed.; ACS Symposium Series 350; American Chemical Society: Washington, DC, 1987; pp 255–263.
(23) Shields, D. J.; Cover, H. W. *J. Polym. Sci.* **1959**, *XXXIX*, 532.
(24) Kennedy, J. P.; Otsu, T. *J. Macromol. Sci., Rev. Macromol. Chem.* **1972**, *C6* (2), 237.
(25) Mortimer, G. A. *J. Appl. Polym. Sci.* **1974**, *18*, 2847.
(26) Zurakowaska-Orszagh, J. *Polymer* **1978**, *19*, 720.
(27) Yamada, N.; Okano, T.; Sakai, H.; Karikusa, F.; Sawasai, Y.; Sakurai, Y. *Makromol. Chem., Rapid Commun.* **1990**, *11*, 571.
(28) Turner, S. R.; Siano, D. B. U.S. Patent 4 520 182, 1985.
(29) Butler, K.; Thomas, P. R.; Tyler, G. J. *J. Polym. Sci.* **1960**, *48*, 357.
(30) Erickson, J. G. U.S. Patent 2 451 436, 1948.
(31) Erickson, J. G. *J. Am. Chem. Soc.* **1952**, *74*, 6281.
(32) Jordan, E. F., Jr.; Riser, G. R.; Parker, W. E.; Wrigley, A. N. *J. Polym. Sci., Polym. Phys. Ed.* **1966**, *4*, 975.
(33) Specht, E. H., Neuman, A.; Neher, H. T. U.S. Patent 2 773 063, 1956.
(34) Kranzlein, G.; Corell, M. Ger. Patent 752 481, 1952.
(35) Hirotsu, S.; Hirokawa, Y.; Tanaka, T. *J. Chem. Phys.* **1987**, *87*, 1392.
(36) Marchetti, M.; Prager, S.; Cussler, E. L. *Macromolecules* **1990**, *23*, 3445.
(37) Lee, K. K.; Cussler, E. L.; Marcheti, M.; McHugh, M. A. *Chem. Eng. Sci.* **1990**, *45*, 766.
(38) Otake, K.; Inomata, H.; Konno, M.; Saito, S. *J. Chem. Phys.* **1990**, *91*, 1345.
(39) Prange, M. M.; Hooper, H. H.; Prausnitz, J. M. *AIChE J.* **1989**, *35*, 803.
(40) Marchetti, M.; Prager, S.; Cussler, E. L. *Macromolecules* **1990**, *23*, 1760.
(41) Lundberg, R. D. *Encyclopedia of Polymer Science and Engineering*; Wiley-Interscience: New York, 1987; Vol. 8, p 393.
(42) Flory, P. J. *Principles of Polymer Chemistry*; Cornell University Press: Ithaca, NY, 1963.
(43) Fujishige, S.; Kubota, K.; Ando, I. *J. Phys. Chem.* **1989**, *93*, 3311.
(44) Kubota, K.; Fujishige, S.; Ando, I. *J. Phys. Chem.* **1990**, *84*, 5154.
(45) Nemethy, G.; Sheraga, H. A. *J. Chem. Phys.* **1962**, *66*, 1773.
(46) James, H. M.; Guth, E. *J. Chem. Phys.* **1947**, *15*, 669.
(47) Flory, P. J.; Erman, B. *Macromolecules* **1982**, *12*, 2782.
(48) Flory, P. J. *J. Chem. Phys.* **1977**, *66*, 5720.
(49) Ricka, J.; Tanaka, T. *Macromolecules* **1984**, *17*, 2916.
(50) Molyneux, P.; Cornarakis-Lentzos, M. *Colloid Polym. Sci.* **1979**, *257*, 855.
(51) Yu, H.; Grainger, D. W. *J. Controlled Release*, submitted.