Dual Lower Critical Solution Temperature Polymer Networks Based on Block, Laminate, and Interpenetrating Network Structures Composed of *N*-Alkylacrylamides and *N,N*-Dialkylaminoethyl Methacrylates

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ABSTRACT: Novel materials that display two lower critical solution temperatures (LCSTs) were developed by forming block copolymers, laminate structures, and interpenetrating networks of crosslinked polymer systems that displayed temperature sensitivity independently. A number of LCST polymers and copolymers were investigated, including those based on *N*-isopropylacrylamide, *N,N*-diethylacrylamide, *N,N*-diethylaminoethyl methacrylate, and *N,N*-dimethylaminoethyl methacrylate. The polymer structure was found to profoundly influence the thermal sensitivity, as polymer formulation techniques led to materials with varying degrees of temperature sensitivity. Random and block copolymerization, along with interpenetrating networks and laminate systems, were studied, with only the structures having the greatest physical separation between pendent chains of different types having the ability to separate temperature transitions. Experiments were conducted to characterize the equilibrium swelling behavior and thermal transitions in the polymer systems. © 2003 Wiley Periodicals, Inc. J Appl Polym Sci 88: 2974–2981, 2003

Key words: temperature sensitive; lower critical solution temperature; hydrogel; phase behavior; interpenetrating network

INTRODUCTION

Among the recent work with environmentally sensitive polymers, many have been used in regulating polymer behavior with respect to a change in pH or temperature or other environmental inputs.[1] In these materials, pH and temperature sensitivity can be used to trigger a thermodynamic transition in polymer structures to control, among other things, swelling behavior. These materials are have been shown to be capable of controlling diffusion in membranes for size exclusive separations and in porous networks for controlled drug delivery.[2,3] Temperature-sensitive polymers have also been investigated extensively for biomolecule entrapment, and thermal switching abilities for a number of aqueous-based applications. These systems have been well researched, and much attention in the drug delivery area has turned to systems that have proportional control over the diffusion and release rate. This can be accomplished using a material that responds incrementally to some of the same triggering mechanisms, but to be robust (and not change properties with small perturbations), the material must have an intermediate region between transition points where the thermodynamic properties, including the hydrophilic/hydrophobic balance, are relatively unchanged, as depicted in Figure 1. This type of dual-sensitive polymer would allow incremental control of diffusion, providing advancement over the on/off behavior that has been achieved by a several researchers.[4–7]

The options available for creating polymers with multiple phase transitions are somewhat limited, but there is some flexibility in the design of systems. For pH-sensitive polymers, the thermodynamic transition occurs as the pH crosses the pk_a or pk_b values for the ionizable pendent chain, which is typically a carboxylic acid or amine group.[8] With pH-sensitive materials, the transitions available for the design of controlled release vehicles is limited, with most pk_a values in a narrow pH range from 4.5 to 5.5, and pk_b values around 7, without the possibility of designing a stepwise pH-sensitive material. However, polymers based on amino acids have potential for specific pH-sensitive design, but many of these acids and bases are very weak and would not support the magnitude of electrostatic repulsion needed to separate or swell polymer chains.

For temperature-sensitive polymers, the transition temperature can be tailored based on the hydrophilic/hydrophobic content of copolymers. *N*-isopropylac-

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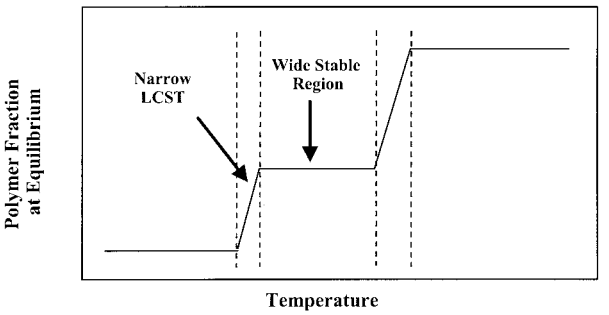

Figure 1 Schematic of proposed dual temperature-sensitive system, Separating LCSTs individually. Low polymer fractions correspond to highly swollen materials, such as PNIPAAm, at temperatures below its LCST.

rylamide (NIPAAm) polymers are the most researched materials in this class, with a sharp lower critical solution temperature (LCST) transition around 32°C.[9,10] Copolymers have been shown to increase[11] [e.g., acrylic acid (AA) and methacrylic acid (MAA)], or decrease[12] (e.g., butyl methacrylate) this temperature.[13] Once the temperature is decreased so that the net behavior of the polymer has become hydrophilic, it is soluble in water (or for crosslinked gels, it swells), and above the LCST, it phase separates into a concentrated hydrophobic mass in aqueous solutions. Another important observation is that the temperature sensitivity is dependent not only on composition, but the molecular structure of polymers containing thermosensitive groups, such as NIPAAm. Because the LCST behavior is attributed to a cooperative conformational transition in pendent groups,[14] so once the composition has become random enough to separate large sections of NIPAAm, the temperature sensitivity is reduced significantly.[11,15] However, creating a material with different compositions (or a gradient in copolymer content), allows multiple LCSTs to be incorporated into the same polymer structure. As Jones and Lyon[16] have shown, it is possible to incorporate thermosensitive materials with different thermal transition points into the same material, using layered microspheres composed of NIPAAm and AA. By incorporating the transitions into a single bulk polymer, instead of microspheres, the material can be used to control drug delivery or membrane diffusion.

The desired material would have the advantage of controlling diffusion rates with some proportional control instead of the typical on/off response in many environmentally responsive systems. This could be useful in designing drug delivery strategies where the release rate is more finely tuned, or in bioseparations, where a single membrane could be used for molecular separations for four different size ranges, simply based on the temperature surrounding the membrane (Fig. 2).

The structures that display temperature sensitivity have a common pendent group structure, and include hydrophilic and hydrophobic sections, such as alkylacrylamides[17–19] and alkylaminoethyl methacrylates.[20] In contrast to pH-sensitive systems where the thermodynamic transition takes place near the pk_a of a polyacidic or polybasic material, regardless of the copolymer composition, the LCST of these thermosensitive materials can be tailored by controlling the composition and structure of the polymer. For example, a hydrophobic comonomer (such as butyl methacrylate) shifts the LCST to lower temperatures, as the copolymer displays net hydrophobic behavior at lower temperatures than the homopolymer of NIPAAm. On the other hand, hydrophilic comonomers, such as methacrylic acid, have been shown to increase the transition temperature to higher values, as the polymer is compatible with and solvated by water up to higher temperatures. Based on these observations, along with work that has shown the need for block structures (or high concentrations of NIPAAm) to maintain a sharp transition, it is possible to create thermosensitive materials that have distinct and multiple temperature-induced phase transitions.

Strategies that have been used to improve the temperature sensitivity of LCST polymers include block and interpenetrating network (IPN) structures. Vakkalanka et al.[15] showed that a block-preferential structure of NIPAAm in polymer gels retained temperature sensitivity with as little as 10 mol % NIPAAm in terpolymers containing AA and 2-hydroxyethyl methacrylate. This block structure has been used increasingly in micellar and nanostructured systems, where the temperature sensitivity can aid in self-assembly or in reversibly controlling interfacial properties for drug delivery or capture and recovery of species in aqueous solutions.[16,21] IPNs have also been successfully used to isolate the temperature-sensitive segments into an overall structure that retains temper-

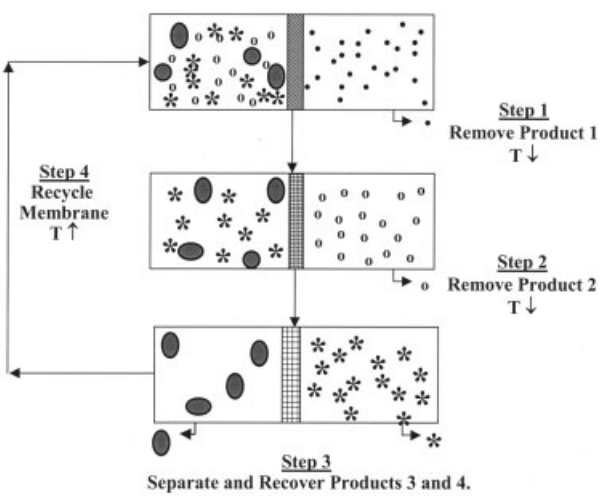

Figure 2 Application of dual temperature-sensitive Networks in membrane separations.

TABLE I
Monomers Used to Create Temperature-Sensitive Gels

Monomer	Abbreviation	Supplier
N-Isopropylacrylamide	NIPAAm	Polysciences (Warrington, PA)
N,N-Diethylacrylamide	DEAAm	Polysciences (Warrington, PA)
2-Diethylaminoethyl methacrylate	DEAEMA	Aldrich (St. Louis, MO)
2-Dimethylaminoethyl methacrylate	DMAEMA	Aldrich (St. Louis, MO)

ature sensitivity while allowing a second network to impart mechanical strength, biodegradability, or sensitivity to other environmental conditions, such as pH.[21–26] These IPNs are particularly well suited to isolating the multiple transitions needed to impart environmental sensitivity under varied conditions, but the physical structure of the material is complicated by the swelling transitions, as the mesh space is not necessarily decreased when one of the intermeshed networks collapses; Zhang and Peppas[26] reported results that indicate that one network may collapse directly onto another, still swollen network, leading to a net increase in mesh space available for diffusion, instead of restricting solute transport.

Membrane transport is one of the important applications for environmentally responsive systems, as the diffusion rate can be controlled by external conditions so that the material can screen different-sized solutes with a change in temperature or pH. Diffusion of model solutes in temperature-sensitive polymer networks has proven difficult to categorize, as the collapsing/expanding process as the gel crosses its LCST has been reported to allow diffusion when the polymer is expanded and to release drugs rapidly during the collapsing process. For membranes, as long as the material has been equilibrated at its environmental conditions, the solute size exclusion is a robust process.[26–29]

OBJECTIVE

Our work sought to create polymer networks with multiple thermal transitions that would affect the bulk properties of a membrane, which could be used for membrane separations or thermally activated controlled release. The desired material properties are depicted in Figure 1.

MATERIALS

Polymers and copolymers were formed using combinations of temperature-sensitive monomers listed in Table I. NIPAAm was purified by recrystallization in hexane/benzene (both 99% pure from Acros Organics, Fairlawn, NJ); other monomers were used as received. A 50 vol % aqueous solution of methanol (Acros Organics, Fairlawn, NJ) was used as a polymerization solvent. Methylene bisacrylamide (MBAAm, 99%), ammonium persulfate (AMPS, 98%), *N,N,N′,N′*-tetramethylethylenediamine (TEMED, 99%), and 2,2-dimethoxy-2-phenylacetophenone (DMPA, 99%) were used as received (all from Aldrich, St. Louis, MO).

EXPERIMENTAL

Synthesis

Monomers of NIPAAm, DEAEMA, DMAEMA, and DEAAm were reacted by free radical polymerization into homopolymers, random copolymers, block copolymers, and IPNs. The specific structures were chosen to enhance the cooperative thermal transition at the LCST, and isolate the different polymers to achieve multiple swelling transitions. The specific polymer systems investigated are listed in Table II, with their expected and observed LCST behavior.

Homo- and copolymerization

Homopolymer gels of NIPAAm and DEAAm were synthesized by free radical solution polymerization in 75 vol % aqueous methanol solutions (50/50 vol/vol methanol/water) using 1 wt % each of AMPS and TEMED and 1 mol% (of monomers) MBAAm as a crosslinking agent. The reactions were carried out at 5°C for 24 h. Polymer samples were recovered and rinsed thoroughly for several days in deionized water to extract unreacted monomer. Copolymer hydrogels of 50/50 mol/mol NIPAAm/DEAAm and 50/50 mol/mol NIPAAm/DEAEMA were made in a similar fashion.

Interpenetrating networks

Interpenetrating networks of PNIPAAm with P(NIPAAm-co-DEAAm) were synthesized by first reacting the PNIPAAm homopolymer by the above procedure, then soaking the polymer in a monomer solution consisting of 50/50 NIPAAm/DEAAm, 1 mol % MBAAm, water/methanol, and 1 wt % DMPA, used as a photoinitiator. The comonomer solution was imbibed into the PNIPAAm gel to equilibrium, by soaking for three days at 5°C. Excess monomer solution was rinsed off of the polymer, and the sample was placed under ultraviolet light to initiate the formation of a P(NIPAAm-co-DEAAm) network within the ex-

TABLE II
Polymer Systems Investigated, with their Expected and Observed LCSTs

Polymer	Abbreviation	Description	Expected LCST(s)	Observed LCST(s)[a]
1	PNIPAAm	Homopolymer gel	32	32
2	PDEAAm	Homopolymer gel	29	32[b]
3	P(NIPAAm-co-DEAAm)	Random copolymer Gel; Composition 50 mol % NIPAAm, 50 mol % DEAAm	21, 32	21 only
4	P(NIPAAm-co-DEAEMA)	Random copolymer Gel with 50 mol % NIPAAm, 50 mol % DEAEMA	50	33
5	P(NIPAAm-ipn-[NIPAAm-co-DEAAm]	IPN of Polymers 1 and 3	21, 32	33 only
6	P[NIPAAm-lam-(NIPAAm-co-DEAAm)]	Laminate structure of polymers 1 and 3	21, 32	24, 33
7	P[NIPAAm-b-(NIPAAm-co-DEAAm)]	Block copolymer gel of polymers 1 and 3	21, 32	21 only[c]
8	P[NIPAAm-b-[NIPAAm-co-DEAEMA)]	Block copolymer gel of polymer 1 with a 50/50 copolymer of NIPAAm with DEAEMA	32, 50	32, 59[b,c] 32, ~52[b,d]
9	P[NIPAAm-b-(NIPAAm-co-DMAEMA)]	Block copolymer gel of polymer 1 with a 50/50 copolymer of NIPAAm with DMAEMA	32, 58	34, 60[b,c]

[a] As measured by DSC.
[b] Determined from swelling experiments.
[c] Polymerization of NIPAAm carried out for 2 min prior to addition of comonomer.
[d] Polymerization of NIPAAm carried out for 6 min prior to addition of comonomer.

isting polymer gel. The reaction was carried out for 3 h at 25°C under ultraviolet (UV) light.

Laminate gels

Laminate systems were formed by reacting a second monomer solution that had contacted only the surface of a preformed hydrogel, to allow interpenetration that adhered the two segments. A laminate hydrogel system, P[NIPAAm-lam-(NIPAAm-co-DEAAm)], was formed by first forming a random copolymer of 50/50 mol/mol NIPAAm/DEAAm as described above and contacting this gel with a solution to make a PNIPAAm homopolymer. The reaction was set up to keep the first gel (the copolymer) suspended above, but touching, the NIPAAm/MBAAm/TEMED/AMPS solution. The PNIPAAm layer was formed by redox polymerization at 5°C for 24 h. Teflon® spacers were used between glass plates to control sample thickness.

Block-preferential copolymers

Because the temperature-induced phase transition in PNIPAAm-based systems requires a cooperative transition, the segregation of pendent groups in the final structure is of utmost importance. Block copolymers were formed by a simplified scheme to begin the polymerization with a homopolymer of NIPAAm and subsequently add (while free radicals were still active) a second monomer, resulting in a structure that began entirely as a homopolymer of NIPAAm, followed by a copolymer structure as the second monomer was added. DEAEMA, DMAEMA, and DEAAm were each used as the comonomer that was added at various times after initiation. A representation of the theoretical linear structure is represented as in Figure 3. This reaction was carried out by mixing NIPAAm, MBAAm, AMPS, TEMED, and aqueous methanol solvent (as above), and reacting at room temperature for a specific period of time prior to adding the comonomer solution (the second monomer with MBAAm in aqueous methanol). The time allowed for homopolymerization prior to addition of the second monomer was varied, but kept small to ensure that the reaction was still active. Time period of 2 and 6 min were found to successfully incorporate both monomers. These gels all had a net crosslinking ratio of 1.0 mol %, and had a total comonomer feed of 2:1 mol:mol NIPAAm:(second monomer). No additional initiator was included with the comonomer solution.

Equilibrium swelling

Dry sample weights were established by thoroughly drying hydrogel samples in a vacuum oven at 25°C

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Figure 3 Representation of the block-preferential copolymer structure formed by NIPAAm (N) with a comonomer (D) added later in the polymerization.

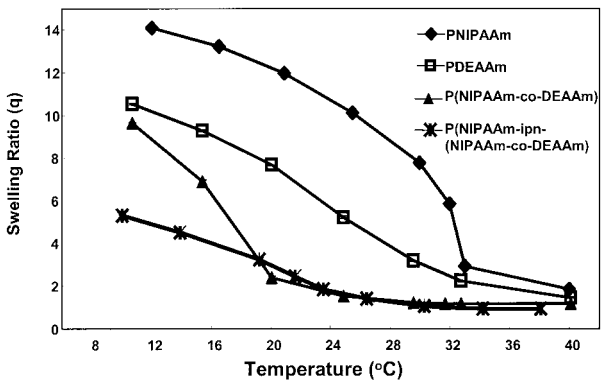

Figure 4 Equilibrium swelling behavior of homopolymers and copolymers of *N*-isopropylacrylamide and *N,N,*-diethylacrylamide. Error bars representing the standard deviation for three experiments are smaller than the data symbols.

until they reached constant weight. Samples were then equilibrated in deionized water at specified temperatures from 4 to 60°C, and the swollen weight was recorded after surface water was removed by blotting the sample surfaces. Swelling ratios, q, were calculated as the wet weight divided by the dry sample weight.

Differential scanning calorimetry (DSC)

DSC was used to monitor the temperature(s) of phase transition(s) in LCST polymers. Approximately 10 mg samples of swollen hydrogels, kept at 4°C, were weighed and placed in hermetically sealed aluminum pans before placing in a triple bomb calorimeter (Model 2920 MDSC, TA Instruments, Newcastle, DE). The samples were subjected to a temperature ramp from 0 to 70°C at 2°C/min, with the heat flow recorded as a function of temperature.

RESULTS AND DISCUSSION

With the goal of achieving a material with two separate, independent LCSTs, polymerization strategies were used to create different molecular architectures that would isolate temperature-sensitive groups. These structures included random and block copolymers, IPNs, and laminate polymers. Swelling experiments were used to quantify the thermodynamic behavior of the polymers, through gradual and sharp transitions, while DSC was used to measure the temperature(s) of phase separation due to increasing temperature. The polymer systems investigated are summarized in Table II.

Homopolymers and copolymers

PNIPAAm and PDEAAm hydrogels displayed LCST behavior, both swelling in aqueous solutions below 32°C (Fig. 4). PNIPAAm had a sharp transition around 32.5°C, while PDEAAm samples swelled in a more linearly increasing pattern with decreasing temperature. (Note: While this gradual change in swelling may be adequate for temperature-proportional control of phase behavior, this material is not robust enough to maintain a stable state with small fluctuations in temperature, and PDEAAm does not provide the sharp contrast that other LCST polymers do.) A 50/50 copolymer of NIPAAm with DEAAm showed a decrease in the LCST while retaining the sharp transition from collapsed to swollen as the transition temperature dropped to near 20°C. This decrease in LCST is attributed to a disruption of the segmental homogeneity of the pendent groups when the monomers were mixed at even molar ratios, similar to the disruption caused by hydrophobic moieties. This behavior did have utility in further experiments, however.

DSC confirmed the observations made in the swelling experiments (Fig. 5: thermograms A, B, and C). The PNIPAAm sample had a sharp transition around 32°C, the P(NIPAAm-co-DEAAm) sample had an LCST around 21°C, and there was little detectable transition for the PDEAAm gel, consistent with the gradual deswelling with temperature as predicted by the swelling experiments. P(NIPAAm-co-DEAEMA) random copolymers were expected to have a high LCST, based on the hydrophilicity of DEAEMA and previous reports,[20] but DSC indicated only a single transition, at 33°C. Although the DSC experiments provided a rapid assessment of the LCST transition, the swelling experiments provided greater information about chain extension, which can be correlated to solute diffusion for membrane or controlled release processes.

IPNs

Based on the differing LCSTs of the PNIPAAm homopolymer and the 50/50 P(NIPAAm-co-DEAAm) random copolymer, IPNs, P[NIPAAm-ipn-(NIPAAm-co-DEAAm)], were created to combine the materials into a single structure as an attempt to create a network with dual temperature sensitivity. The IPN was more rigid than the single network materials due the entanglements between the two networks and the higher density of polymer chains. Thus, the swelling ratio was smaller for the IPN at all temperatures (Fig. 4). Although the temperature-sensitive components the IPN were separated so that covalent bonds were isolated on either the homopolymer or copolymer gel, the IPN displayed only a single LCST, at around 25°C. This transition, when observed through equilibrium swelling data, was less sharp than PDEAAm, possibly due to the additional physical crosslinks induced by the intermeshed networks.

DSC on the IPN confirmed that any transitions were much smaller in magnitude than was observed in the

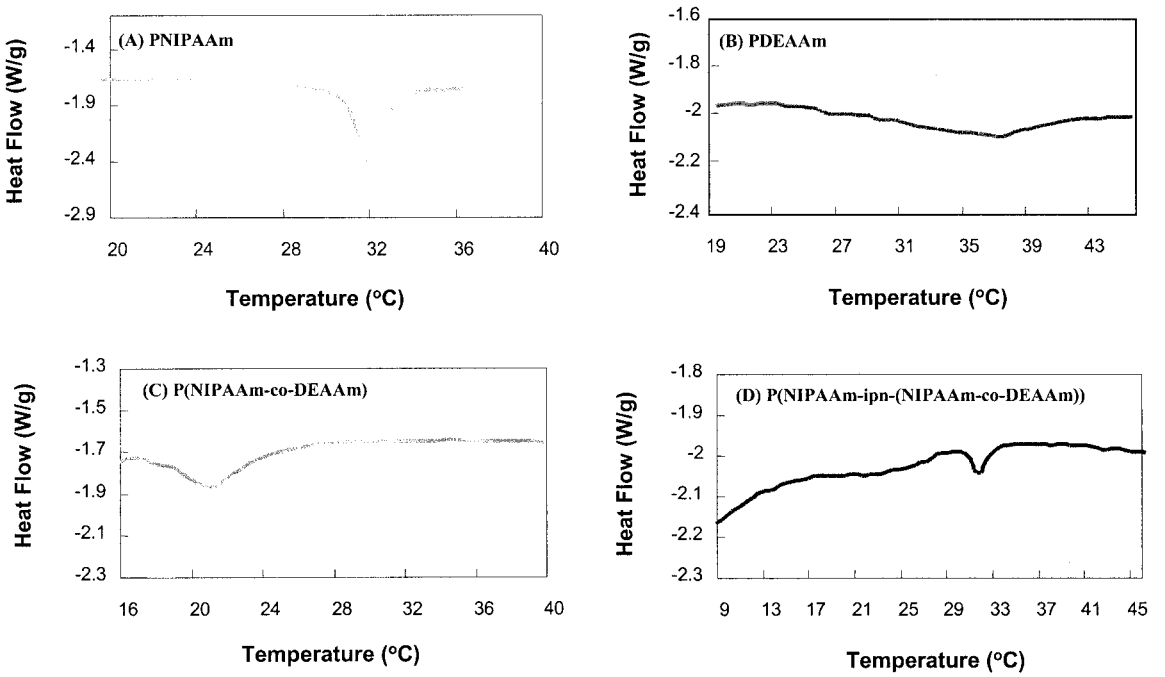

Figure 5 DSC thermograms for temperature-sensitive hydrogels. Polymers were swollen to equilibrium at 4°C prior to running the experiment. The materials used in each experiment are listed within the thermograms.

homopolymers and copolymers (Fig. 5: thermogram D). The IPN had a relatively sharp phase separation peak around 32°C, indicative of the LCST of pure PNIPAAm, but due to the smaller magnitude, it was not a significant factor in the swelling behavior of the IPN. Also, the presence of two intertwined networks has a complicating effect on the swelling behavior (as noted by Zhang and Peppas[26]), where one polymer network may collapse onto the second, still swollen, structure; thus while there is no distinct change in swelling, DSC detects the phase transition for the collapsing network. This can have a significant impact on diffusion, as the collapsing network may cause the mesh space available for diffusion to increase without a significant change in swelling capacity. For the goals of our work, the importance of these experiments are that the proximity of the polymer segments are too close to permit distinct thermal transitions (or perhaps the copolymer's transition was not strong enough when placed into the IPN).

Block and laminate copolymers

Since the IPN synthesized was unsuccessful at isolating different polymers with distinct thermal transitions, block copolymer structures were synthesized beginning with a NIPAAm segment and a copolymer structure constituting the remainder of the network, as depicted in Figure 3. The block-preferential polymers were not characterized specifically to determine the molecular structure, but the technique used to synthesize these materials was able to isolate backbone segments with blocks of NIPAAm separated by random copolymers of NIPAAm with (A) DEAAm, (C) DEAEMA, and (D) DMAEMA. The equilibrium swelling behavior of these polymers as functions of temperature are shown in Figure 6. Of the block copolymer structures, the P[NIPAAm-b-(NIPAAm-co-DEAEMA)] samples displayed three distinct stable swelling zones, with detectable thermal transitions at approximately 32 and 59°C (for the sample where the comonomer was added after 2 min of NIPAAm polymerization). By allowing the polymerization of NIPAAm to continue for 6 min prior to the addition of DEAEMA, the 32°C transition was preserved, and is attributed to the transition of the block NIPAAm segments, while the second transition was lowered to approximately 52°C (Table II). These transitions were easily observed by swelling experiments, but DSC was less conclusive, indicating a single transition around 32°C, with a broad endotherm between 50 and 60°C. Regardless of the disparate results, these block copolymers show promise as bulk materials that can incorporate multiple LCSTs.

Another strategy employed to segregate pendent groups was the use of laminate structures. By polymerizing a second gel with only an interfacial penetration into a preformed P(NIPAAm-co-DEAAm) hydrogel, the resulting material had two distinct layers, with only a small region of an interpenetrating network. This resulted in a material with sharp thermal transitions due separately to the copolymer and the

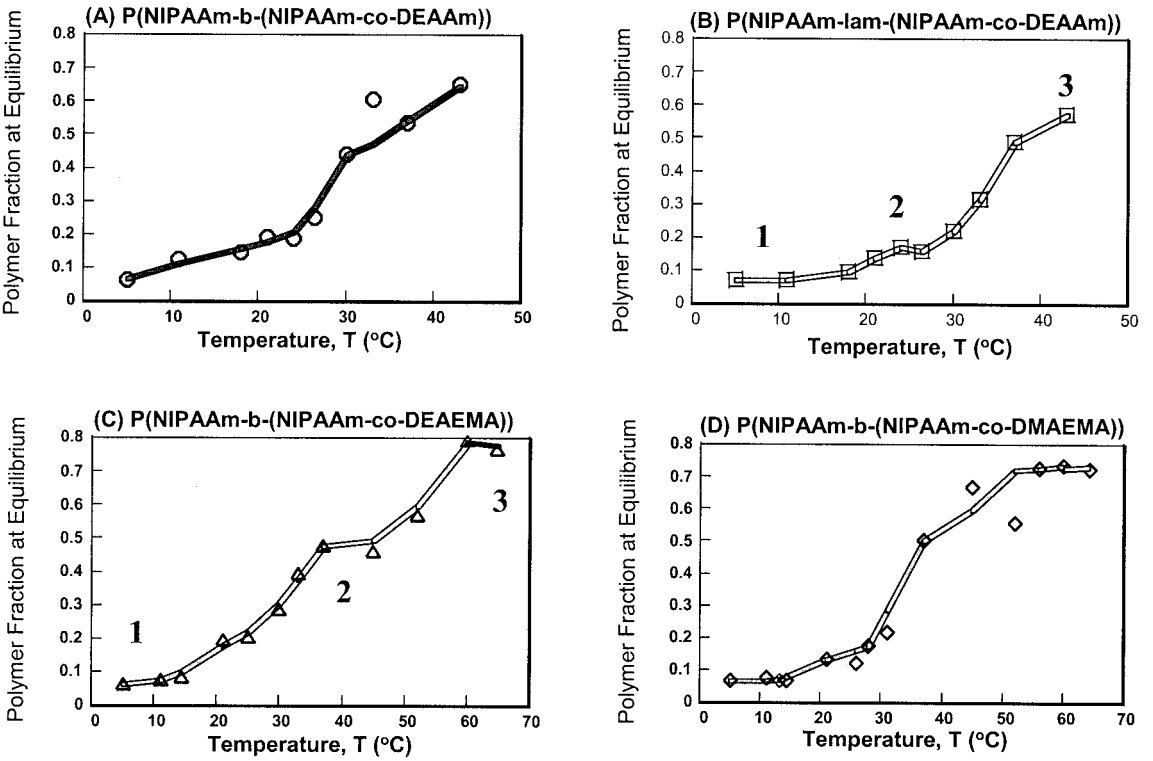

Figure 6 Equilibrium polymer fractions in water for block and laminate thermosensitive Gels as functions of temperature. The materials tested are indicated (A–D) above each graph. The numbers (1–3) indicate regions where the polymer system was stabilized. Region 1 indicates that the polymer is highly swollen below all LCSTs, while region 3 is above the LCSTs of all components. Region 2 is between the multiple LCSTs.

homopolymer PNIPAAm, at around 21 and 37°C. DSC confirmed this behavior, where sharp, distinct endothermic peaks indicated the phase separation temperatures for hydrated gels when heated (Fig. 7). This idea is similar to the work of Lyon and coworkers,[16] who have developed micro- and nanospheres with unique thermal swelling properties in concentric layers. While these structures and laminate materials are both capable of separating the phase transitions for multiple LCSTs, the bulk properties needed for membrane separations require a material with more uniform structure throughout, such as the block copolymers.

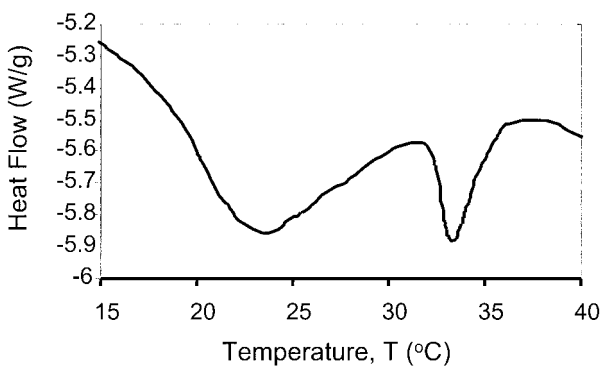

Figure 7 DSC thermogram for laminate copolymer hydrogel, P[NIPAAm-lam-(NIPAAm-co-DEAEMA)].

Since the ultimate goal of creating materials with multiple transitions is to develop systems with three or more stable diffusive characteristics, the next steps will involve analyzing the transport properties of these polymer gels for use as size-exclusion membranes and variable rate drug delivery devices. Transport in hydrogels is largely governed by the mesh space between polymer chains. This mesh space in stimuli-sensitive polymer gels changes predictably with the environment (high temperatures causes PNIPAAm gels to collapse, with a corresponding decrease in mesh space). However, in multiple-transition polymers, the collapse of part of the polymer network may not affect the mesh size in the same way (i.e., the collapsed polymer may preferentially segregate near the swollen polymer at the intermediate swelling stage, thus creating a network with a larger mesh size than the fully swollen gel). Zhang and Peppas[30] have discussed these complications in regard to IPNs composed of one temperature-sensitive and one pH-sensitive component. Another transport issue for drug delivery is achieving different polymer swollen states than can allow different rates of diffusion of the same drug based

on temperature stimuli. There is a sharp molecular weight cutoff for most polymer membranes, below which solute diffusivities are orders of magnitude higher than for drugs of larger size. Because of this, drug release will most likely still be on/off from multisensitive polymers. However, these materials may be useful at size-exclusion separations or at delivery of multiple drugs with differing molecular weights, since each drug could be liberated as the polymer mesh size expands.

CONCLUSIONS

With the results reported here, we have taken the first step in developing materials with stepwise responsive behavior. Further development of these temperature-responsive materials relies on understanding the importance of polymer design on the thermodynamic behavior of LCST polymers. Equilibrium water sorption data confirm the need for advanced structures in developing dual temperature sensitivity. Promising polymer structures investigated include block copolymers and interpenetrating networks, as well as laminate systems. The thermal transitions observed in swelling experiments were confirmed by DSC, indicating that the phase separations were unique and independent. One added benefit of the selection of materials used here is that polymers containing DEAEMA or DMAEMA have cationic groups on the pendent groups, which impart pH sensitivity on top of the temperature sensitivity discussed in this article.

The results detailed herein provide insight into the development of environmentally sensitive systems with multiple stable regions. This will impact drug delivery and membrane permeation technologies by allowing temperature-proportional control of the rate of diffusion.

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