Synthesis and Characterization of an Extremely Versatile Structural Motif Called the "Plum-Pudding" Gel

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The "plum-pudding" gel is a composite gel structure composed of responsive microgel particles randomly dispersed in a bulk gel medium. Microgel particles can be responsive to a variety of stimuli (temperature, pH, light, etc.), and the bulk gel can be any cross-linkable material. Thus an infinite variety of materials of different mechanical and responsive properties can be envisioned based on this simple structural motif. The novelty of the plum-pudding gel is that it separates the concepts of functionality and mechanical strength. The "plum-pudding" nature of the gel was confirmed by laser scanning confocal microscopy: the fluorescently labeled PNIPAM microgel particles resembled plums in a pudding. A model for the structure was proposed, where the growing network chains grew through the pores of the swollen microgel particles and were unaffected by their presence, resulting in an unchanged network structure at the concentrations of microgel particles studied (up to 20 mol % of the monomer content). Two examples of the diversity of the plum-pudding gel as a structural motif are illustrated. PNIPAM microgel particles are used in the first example to enhance the positive thermoresponsiveness of responsive bulk materials (NIPA-*co*-BAM-*co*-DAM gels) and in the second example to induce positive thermoresponsiveness into nonresponsive bulk gels (DAM gels).

Introduction

Chemically cross-linked networks composed of *N*-isopropylacrylamide (NIPA gels) show interesting phase behavior in aqueous solution. At low temperatures they exist as expanded (swollen) networks where as much as 95% of their weight can be water. Raising the temperature gradually causes the polymer chains in the network to contract slightly, and the network shrinks. When the temperature reaches a critical temperature, called the collapse or transition temperature (T_C), the network volume changes dramatically as the gel undergoes a transition from expanded to collapsed network, and water is forced out of the network. Thus, at temperatures above the critical temperature, the gel exists as a collapsed (shrunken) network. The volume phase transition of this system is not fully understood as yet, but it may result, in part, from the fact that with increasing temperature the isopropyl groups become increasingly hydrophobic and eventually the entropy-driven hydrophobic effect overcomes the energy-driven hydrogen bonding between the amide groups and the surrounding water, causing the side chains to become attractive to each other and contract.[1,2] Other interactions are also involved, but the detailed balance between these is at present unknown.

A range of applications of NIPA gels have been developed that rely on the swelling−shrinking properties of the gel network.[3−5] Many of these applications are limited by the gels response time to environmental changes, and could be improved if the swelling and shrinking times of the gels were faster. Additionally, conventional gels have problems associated with the surface layers shrinking more rapidly than the internal gel, resulting in a dense collapsed skin-layer forming on the gel surface. This skin layer acts as a barrier to prevent the release of internal water, and hugely delays the shrinking process.

Several approaches to faster shrinking kinetics have been reported in the literature, for example, Kaneko et al. grafted freely mobile polymer chains into gels and these shrink rapidly pulling the network with them.[6] Wu et al. and Gotoh et al. have synthesized macroporous gels and reported rapid shrinking.[7,8] Hirotsu prepared NIPA gels incorporating long chains of polyacrylamide which acted as water-release channels, speeding up the shrinking process.[9] Kaneko et al. have achieved a similar effect by introducing poly(ethylene oxide) channels into NIPA gels.[10]

Microgels, which are also called microspheres, latex particles, or submicron gel beads, are intermediate between branched polymers and macroscopic gels. The overall dimensions of microgels are comparable with high molecular weight polymers, but their internal structure resembles a typical network.[11] Poly(*N*-isopropylacrylamide) (PNIPAM) microgels undergo a quick and sharp temperature-dependent volume phase transition at 35 °C in aqueous solution.[12] Below the transition temperature the microgels are spongelike structures, with the interstitial spaces filled with water. When the temperature is raised above the transition temperature, the particles shrink (reversibly) and become hard and sphere shaped.[12] A number of applications of PNIPAM microgels[13−15] have been developed utilizing the fact that their response time to environmental change is many times faster than that of macro or bulk gels as well as the much greater surface area-to-volume ratio of microgels, which leads to increased accessibility and higher loading of solutes.[13]

From the above description of PNIPAM microgels it seems likely that they will prove useful for applications relying on rapid response to environmental change. Such applications include both positive and negative thermoresponsiveness which are used in controlled- and targeted-release applications. Thus, much scientific effort is currently being devoted to the develop-

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ment of hydrogel systems for applications in drug delivery etc. However, the current idea of using the same polymeric material to provide functionality (controlled release) and mechanical strength (durability, drag, compliance, etc.) is extremely limiting, as in general materials which are responsive to their environment are mechanically poor, while materials with good mechanical properties do not provide the necessary functionality. Thus, what appears to be missing to date is a simple and cohesive structural motif that can be applied to an extensive range of applications, and which separates the concepts of functionality and mechanical strength.

In this work, we have synthesized and characterized a simple composite gel structure, which we call the plum-pudding gel. The basic structural motif is to embed responsive microgel particles in a bulk gel medium. By altering the stimulus to which the microgel is responsive, a vast range of materials can be designed and tailored to specific applications. By altering the nature of the bulk gel, materials with diverse mechanical properties can be prepared, and issues such as compliance can be considered.

Two examples of the structural motif are described. The first uses the plum-pudding gel to overcome the problems associated with bulk NIPA gels where the shrinking process is dramatically slowed by the formation of a surface "skin-layer". To this end, PNIPAM microgels are incorporated into the network of a conventional macrogel (composed of loosely cross-linked NIPA-*co*-BAM-*co*-DAM (70:10:20)) and the effect on the shrinking kinetics determined. The kinetics of the bulk gel have been studied in detail,[16] and serve as a model to which the kinetics of the plum-pudding gel are compared. Thus changes in the shrinking kinetics can be attributed to the presence of the PNIPAM microgel particles in the composite gel. The second example of the structural motif involves the introduction of responsive microgel particles into a nonresponsive bulk gel, and we show that the entire gel can be made responsive. In this case PNIPAM microgel particles are introduced into a nonresponsive DAM gel, causing the entire plum-pudding gel to shrink in response to increasing temperature.

Experimental Section

Materials. *N*-Isopropylacrylamide (NiPAAm) monomer (purity >99%) from Acros Organics (Geel, Belgium) was recrystallized twice from hexane. The following chemicals were used as supplied: *N*-*tert*-butylacrylamide (BAM), *N*,*N*-dimethylacrylamide (DAM), and *N*,*N*^{1}-methylene-bisacrylamide (BisAM) from Fluka (Dorset, England); acrylamide (AM) and ammonium peroxydisulfate (APS) from Aldrich (Dorset, England); *N*,*N*,*N*^{1},*N*^{1}-tetramethylethylenediamine (TEMED) from Sigma (Dorset, England); acryloyl chloride (purity 98%) from Aldrich (Steinhein, Germany); fluoresceinamine, isomer 1, from Aldrich Chem. Co. (Wisconsin, USA); and fluorescein isothiocyanate-dextrans of various MW (4 400, 9 500, 19 500, and 42 000) from Sigma (Dorset, England). THF was distilled before use. Paraffin oil from BDH (Dublin, Ireland) was washed with deionized water before use. All water used was of Milli-Q (Millipore) quality, and was degassed before use.

Synthesis of PNIPAM Microgels. PNIPAM microspheres were synthesized by dispersion polymerization according to the method of Li and Bae.[17] NiPAM (0.2 g, 442 mmol) and BisAm (0.02 g, 3.2 mmol) were dissolved in 36 mL of water and 1 mL of 0.1 wt % Triton solution was added. The solution was heated to 70 °C and degassed by bubbling with N_2. APS (0.02 g) was dissolved in 4 mL of water, degassed, and added slowly to the stirring monomer solution, under an N_2 atmosphere. The reaction was left for 12 h at 70 °C. The resulting 1 wt % of microsphere in water dispersion was cleaned by dialysis, and freeze-dried before use.

Synthesis of Acryloyl-fluorescein Monomer. Acryloyl-fluorescein was prepared according to the method of Munkholm et al.[18] Acryloyl chloride (90 μL) and fluoresceinamine (isomer 1, 90 mg) were dissolved in distilled THF (3 mL) and left in the dark overnight. Product was collected by filtration, washed with acetone, dried by air evaporation, and stored in the dark.

Synthesis of Fluorescently Labeled PNIPAM Microgel Particles. Fluorescently labeled microgel particles were prepared exactly as above with the addition of 0.005 g of acryloyl-fluorescein to the monomer solution.

Characterization of Microgels. The transition temperature of the microgel particles was determined to be 35 °C by UV, using a Pharmacia LKB-Ultrospec III UV/visible spectrophotometer and a wavelength of 450 nm. Temperature control was provided by a Neslab RTE-211 water bath and the heating rate was 0.5 °C/min. Microgel solutions were extremely monodisperse as indicated by the fact that solutions were iridescent (Bragg scattering), and this was confirmed by light scattering where the polydispersity was less than 5%. Particle size was determined by light scattering to be 400 nm in the swollen state.

Synthesis of Spherical Gels with Incorporated Microspheres. Submillimeter spherical gel beads were prepared by inverse polymerization according to the method of Matsuo et al.[19] A 30-mL sample of paraffin oil was washed with Milli-Q water, heated to 100 °C for 1 h, cooled to 20 °C, and degassed by bubbling with N_2. All gels had 0.8 wt % cross-linking, and the pre-gel concentration was 700 mM monomer (490 mM NIPA, 70 mM BAM, 140 mM DAM) in 4 mg of water. PNIPAM microspheres (70 or 140 mmol) were added to the pre-gel solution. The pre-gel solution was degassed under vacuum, and 15 μL of TEMED was added. The initiator concentration was 40 mg in 1 mL of water, of which 70 μL was added. A 1- mL sample of this solution was added via syringe to the vigorously stirring oil. The reaction was purged after 1 h by adding water. The oil was removed and unreacted materials were removed by washing with copious amounts of distilled water.

Synthesis of Thin Gel Film with Incorporated Fluorescent Microspheres. The pre-gel solution was prepared exactly as for spherical gels, using fluorescentlylabeled microgel particles, and the solution was injected between two glass slides separated by distances of 0.15 or 0.3 mm. The plates were refrigerated for 24 h while gelation took place. Gels were washed with deionized water for 24 h to remove unreacted materials.

Laser Scanning Confocal Microscopy. A Leica DM IRB confocal microscope, which had an argon laser operated at 488.0 nm, was used to confirm the "plum-pudding" structure of the gels. A series of optical slices through thin films were obtained in the fluorescent mode. The objective used was an oil-immersion UV $\times$40 NA 1.25 objective, which resulted in a resolution of 20−30 nm in the *z*-direction, ensuring that the PNIPAM microgel particles were easily visible and that a depth of 3 μm between optical slices was reasonable.

Determination of Pore Size Distribution. The pore size distributions of the various gels were characterized by the solute exclusion technique with fluorescein isothiocyanate-dextran (FITC-dextran) fractions as molecular probes, as described by Wu et al.[7] Gel disks of diameter 20 mm and thickness 3 mm were prepared for each of the gel structures, and dried overnight in a vacuum oven. Each gel was equilibrated at room temperature overnight in 0.02% sodium azide solutions, before being

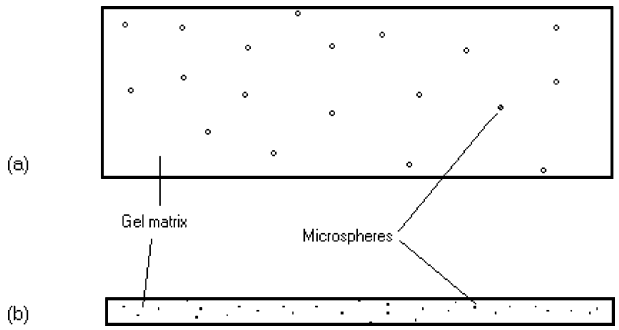

Figure 1. Schematic representation of the two-component or "plum-pudding" gel, where the "plums" are randomly dispersed PNIPAM microgel particles: (a) top view and (b) side view. The dimensions are not representative, as in reality the microgel particles are ~400 nm compared to the gel thickness of ~300 μm.

placed into sodium azide solutions containing different FITC-dextran fractions (200 μg/mL). The FITC-dextran concentration was monitored daily with a Perkin-Elmer Luminescence spectrometer LS50B (485-nm excitation, 515-nm emission) until the FITC-dextran concentration stopped changing. This limiting concentration was called C_0 (mg/mL). The gel disks were transferred to 100 mL of sodium azide solution for 2 days for exhaustive extraction, and the concentrations (C_e) were determined. Based on the assumptions that (a) all water in the gel is available to dissolve dextran molecules, (b) there is no interaction between the dextran molecules and the polymer matrix, and (c) the concentration of FITC-dextran in the total gel water is the same as in the external bulk water, the volume of pores accessible to each FITC-dextran fraction, V_a, may be estimated by the equation

$$V_a = 100\ (\text{mL}) \times C_e\ (\mu\text{g/mL})/C_0\ (\mu\text{g/mL}) \qquad (1)$$

The volume fraction of pores larger than the probing molecule is expressed by V_a/V_t, where V_t was the total volume of water in the gels, this being determined gravimetrically.

Kinetics of the Temperature-Induced Volume Phase Transition. Details of the T-jump apparatus and procedure were given previously.[16] Briefly, an aliquot of the gel beads in water (containing a range of gel sizes) is inserted onto a "thermoslide" made of conductive glass and heated by applying a current. The temperature was increased by a temperature jump (T-jump) from a starting temperature of 30 °C to final temperatures in the range 34−42 °C. The change in diameter (either the diameter at time t divided by the initial diameter ($D_t\backslash D_0$) or the renormalized diameter $\{(D_t/D_0 - D_f/D_0)/(1 - D_f/D_0)\}$) (where D_f is the final diameter) was plotted as a function of time. From these plots the relaxation time, or the time taken for the gel to reach its equilibrium size at the new temperature, was established.

Results and Discussion

The Structural Motif: The "Plum-Pudding" Gel. The plum-pudding gel is a composite structure composed of responsive microgel particles randomly embedded in a conventional hydrogel network. A schematic illustration of the structure of the gel is given in Figure 1. An infinite variety of such structures can be envisioned, as both of the components can be altered independently of each other. The core idea is that microgel particles are prepared first, and then randomly incorporated into a gel film as it forms. The structural motif described here separates the concepts of functionality and mechanical strength. Functionality is provided by the responsive microspheres which can be synthesized to have almost any size in the range 100−1000 μm, and can be made responsive to almost any stimulus imaginable (temperature, pH, light, electrical current, solutes, enzymes, etc.) Mechanical strength, elasticity, or other bulk material properties are controlled by the choice of the bulk network polymer, which can be any natural or synthetic polymer, including polymers already used in the development of coatings or wound-dressings, thus reducing the cost of developing such composite films. A major advantage of this structural motif is that cheap but nonresponsive polymeric hydrogels can be made responsive, as is shown later for the nonresponsive DAM hydrogel.

To illustrate the concept, and enable detailed characterization of the composite gel structure, a model plum-pudding gel was prepared. The gel was composed of PNIPAM microgel particles (diameter 400 nm, concentration 140 mM, which is 20 mol % of monomer concentration) embedded in a terpolymer gel composed of NIPA-*co*-DAM-*co*-BAM (70:20:10). The reason for the choice of the bulk gel will be explained later.

Incorporating the PNIPAM microgel particles into the bulk gel is easily achieved as there is no tendency for the microgels to aggregate in solution, due to the presence of surface charges which result from the synthesis procedure.[17] The PNIPAM microgel particles are added to the pre-gel solution and become randomly entrapped in the gel network as it forms, resulting in a plum-pudding structure, where the "plums" are the microgel particles. As the gel is synthesized at 20 °C (which is well below the transition temperature of the microgel particles (35 °C)) the microgel particles exist as swollen coils and thus we propose that the propagating chains of the bulk gel grow through the pores of the bulk gel, thus entrapping the microgel particles into the gel.

Characterization of the Plum-Pudding Gel Structure. Direct visual evidence for the "plum-pudding" nature of the composite gel was obtained with laser scanning confocal microscopy. The composite gel (PNIPAM microspheres in a NIPA-*co*-DAM-*co*-BAM (70:20:10) bulk gel) was prepared as a flat sheet and the microgel particles were labeled with acryloyl fluorescein. A series of pictures was taken in the fluorescence mode, starting at the gel surface and moving noninvasively through the gel. The "plums" showed up as fluorescent blobs, confirming the gel structure. Comparison of pictures at different depths shows how the structure changes through the gel, and how the microgel particles appeared and disappeared as the depth of the slice changed. Figure 2 shows two adjacent slices through a gel containing fluorescently labeled microgel particles (PNIPAM and acryloyl fluorescein, diameter ~0.4 μm) taken in the fluorescent mode. The background gel matrix is entirely dark and the green fluorescent dots represent microgel particles. It can be clearly seen in Figure 2 that the microgel particles visible at a depth of 3 μm are no longer visible at a depth of 6 μm, and microgel particles that were not visible at 3 μm depth have appeared at 6 μm. Thus it can be definitely stated that the PNIPAM microgel particles are embedded in the bulk-gel network to form a "plum-pudding"-like gel.

The slices represented in Figure 2 were analyzed to determine the volume fraction of microgel particles per 3-μm slice. Taking the volume of an individual sphere to be $^4/_3\pi r^3 = 0.268\ \mu\text{m}^3$, where $r = 0.4\ \mu$m, and the average number of spheres per slice to be 32 (obtained by counting over a number of slices), the volume of the gel occupied by microgel particles was determined. Dividing by the total volume of the gel slice ($31.3 \times 31.3 \times 3$) μm^3, the volume fraction of microgel particles per gel slice, ϕ_{exp}, was determined to be 2.9×10^{-3}. The theoretical volume fraction of microgel particles, ϕ_{theory}, was determined

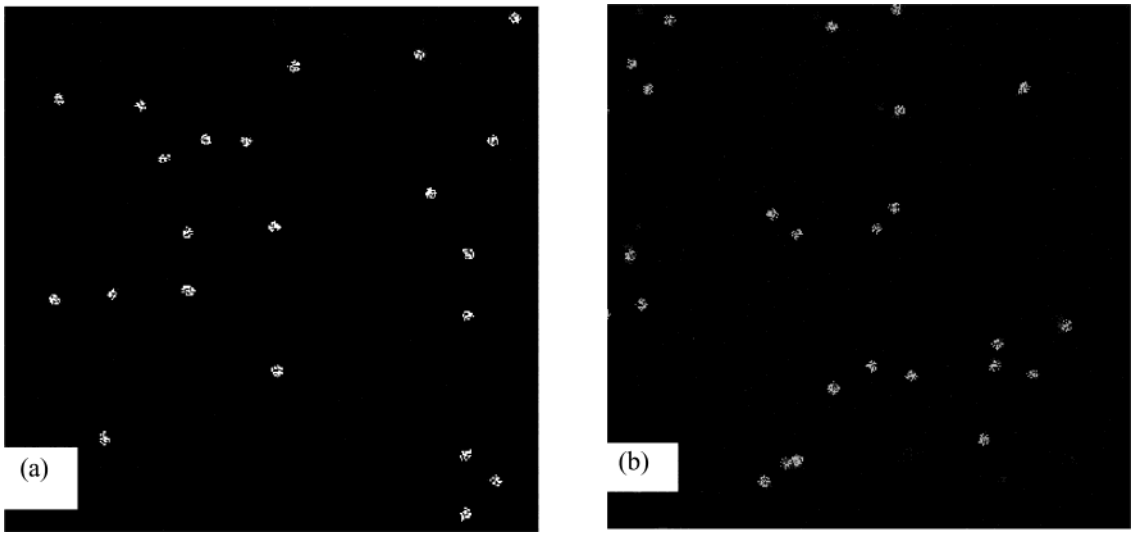

Figure 2. Laser scanning confocal microscopy images of fluorescently labeled "plum-pudding" gel. Microspheres were composed of BAM:NIPA: acryloyl fluorescein. The gel matrix was composed of NIPA. Microsphere concentration: 20 mol % of initial monomer concentration. Fluorescence mode; objective UV × 40, 1.25 NA; depth (a) 3 μm and (b) 6 μm.

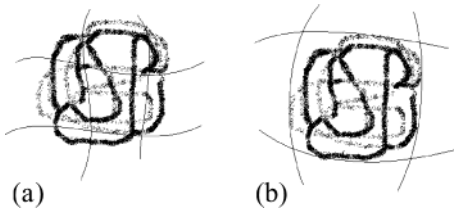

Figure 3. (a) Schematic representation of the proposed internal structure of the "plum-pudding" gel, showing the network chains passing through the microgel particles. (b) Schematic representation of the alternative case where the presence of the microgels affects the network structure.

from the amount of microgel particles added and the total gel volume to be 3×10^{-3}. Thus there is excellent agreement between the theoretical volume fraction and the volume fraction determined from the laser scanning confocal microscopy images of the two-component or plum-pudding gel.

Description of the Bulk Gel/Microgel Particle Interface. The synthesis of the composite gel is such that the spherical microgel particles are added to the pre-gel solution prior to gelation. Since gelation occurs at 20 °C, which is well below the transition temperature of the PNIPAM microgel particles, these exist as swollen spongelike particles, with long dangling outer chains, and cross-link density increasing toward their center.[12] The process of gel formation is by radical initiation, which means that the gel forms as a series of growing chains which occasionally encounter a bifunctional cross-link unit and thus take on a 3-dimensional structure. Due to the large degree of swelling of the PNIPAM microgel particles at 20 °C, we propose that the growing chains are essentially unaware of the presence of the microgel particles, and thus the microgel particles have essentially no effect on the gelation process, or on the structure of the resultant gel. On the basis of this hypothesis, a structure for the composite plum-pudding gel is proposed, where the network chains pass though the swollen microgel particles and thus the microgel particles become constrained within the gel. A schematic of this structure is given in Figure 3a.

To confirm the proposed structure, we investigated the effect of microgel particles on the resultant gel macro- and microstructure, in terms of degree of swelling at room temperature and pore size distribution. The results of these investigations

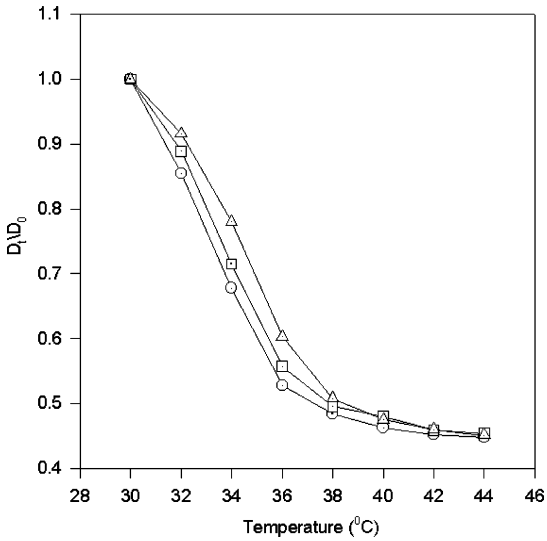

Figure 4. Comparison of the equilibrium shrinking curves of the bulk gel and the "plum-pudding" gel containing 20 mol % of PNIPAM particles: (○) bulk gel (NIPA-*co*-DAM-co BAM) and (△) "plum-pudding" (NIPA-*co*-DAM-*co*-BAM gel + 20 mol % of PNIPAM microspheres).

show that on both the macro- and microscopic scales, the presence of the microgel particles did not alter the network structure significantly, as can be seen in Figures 4 and 5. The degree of swelling of the bulk gel and the composite gel as a function of temperature is compared in Figure 4, and it is clear that there is no significant change in the degree of swelling, despite the fact that the microgel particles exist as highly swollen particles. Thus on the macroscopic scale, the presence of the microgel particles did not alter the network structure, as swelling is extremely closely related to network structure. In Figure 5a the pore size distribution at 20 °C of the plum-pudding gel is compared to that of the bulk gel alone. If the presence of the microgel particles forced the growing polymer chains to grow around them (as opposed to the chains growing through them and the network structure being unaffected by the presence of the microgel particles) we would expect to see an increase in the number of large pores, as the polymer chains would be more heterogeneously distributed with increased regions of dense and dilute polymer chains, as shown schematically in Figure 3b. If

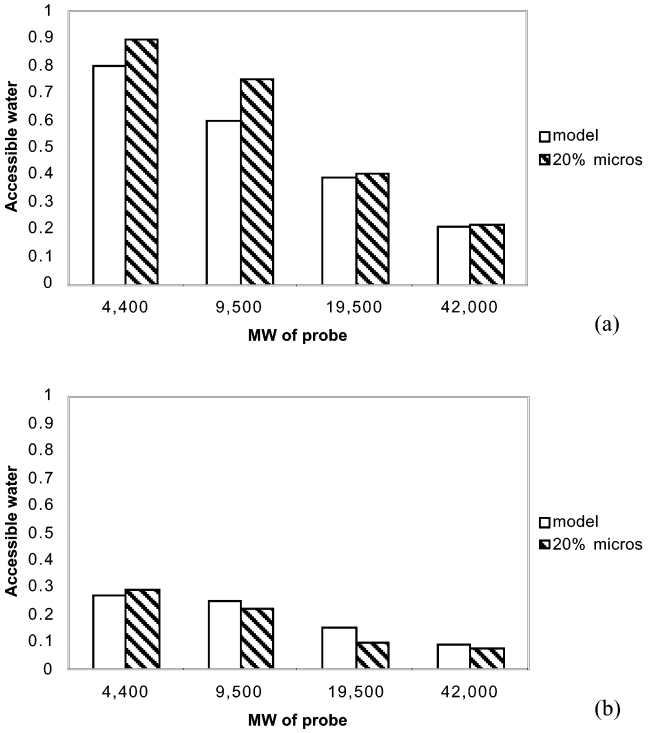

Figure 5. Pore size distribution of the bulk gel and the 20 mol % "plum-pudding" gel at 20 (a) and 34 °C (b).

the microgel particles were to disrupt the network formation or result in increased network inhomogeneity, the resultant gel would have a very different microstructure, and this would result in a significantly different pore size distribution profile. The fact that there is no major difference between the pore size distribution of these two gels is very strong evidence for the structure proposed in Figure 3a. The slight increase in the number of small and medium pores is presumably due to the porous nature of the microgel particles themselves. Thus we can conclude that the structure proposed in Figure 3a for the plum-pudding gel agrees with the experimental evidence.

Effect of Temperature on Bulk Gel/Microgel Particle Interface. It is necessary to determine the nature of the bulk gel/microgel interface after shrinking has occurred also, as this will play a crucial part in determining the effect of the presence of the microgel particles on the network structure. If the microgel particles affected the network structure, forcing the growing chains to pass around them, the shrinking of the microgel particles should result in the formation of voids (large pores) as described by Ichikawa et al. for a system containing 20% of PNIPAM-coated microgel particles in an ethylcellulose matrix.[20] Such a situation is represented schematically in Figure 6a and would result in a dramatic difference between the pore size distribution profile of the "plum-pudding" gel and bulk gel at temperatures above the transition temperature, and in particular an increase in the number of large pores in the plum-pudding gel. However, as can be seen from the pore size distribution of the gels at 34 °C in Figure 5b, this does not appear to be the case, and the pore size distribution of the plum-pudding gel shows no dramatic differences from that of the bulk gel alone. This would suggest that our proposed structure is correct where the network chains pass through the microgel particles, and that as the microgel particles shrink, they actually pull the bulk gel network with them, as shown schematically in Figure 6b.

Examples of the Versatility of the Plum-Pudding Gel as a Structural Motif. *1. Enhancement of the Positive Thermo-responsiveness of Bulk Responsive Gels.* The structure of the

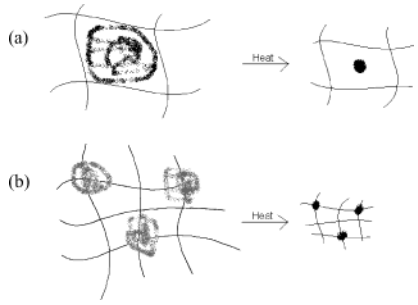

Figure 6. Schematic representation of possible shrinking mechanisms for the "plum-pudding" gel: (a) plums shrink rapidly resulting in the appearance of holes (voids) in the gel network structure; (b) rapid shrinking of plums pulls the network chains with it, resulting in rapid shrinking of the entire network.

plum-pudding gel, with the chains of the network passing through the pores of the microgel particles, combined with the sponginess and rapid shrinking properties of the PNIPAM microgel particles seemed like a possible mechanism for speeding up the shrinking process of bulk gels, which are often hampered by the formation of a dense layer of collapsed polymer on the gel surface which slows down the subsequent shrinking dramatically. Our thinking was 2-fold: first that the presence of the collapsing PNIPAM microgel particles would provide hydrophobic patches throughout the gel which would act to nucleate the collapse process, and second that the collapse of the PNIPAM microgel particles would pull the network chains that pass through them together and thus the entire gel should have faster response times to changes in the surrounding temperature.

The gel used to test this postulate was the terpolymer gel composed of 70:20:10 NIPA-*co*-DAM-*co*-BAM containing 10 or 20 mol % of PNIPAM microgel particles, described before. The bulk gel was chosen because its shrinking has been studied extensively and is well characterized, and it undergoes a continuous transition that removes the difficulties associated with studying gel-phase transitions.[16] Thus the bulk gel acts as a model gel, to which the shrinking kinetics of the composite gel are compared. Any differences are then attributable directly to the presence of the PNIPAM microgel particles in the network. The shrinking process of the bulk gel (to which we will compare the shrinking of the plum-pudding gel) was studied in detail,[16] and two distinct shrinking patterns were found, depending on the depth of the temperature jump. T^* was defined to be the temperature at which the gel first reaches the fully collapsed state, and is 38 °C for the 70:20:10 NIPA:DAM:BAM gel. The shrinking behavior was found to depend on whether the final temperature after the T-jump (T_f) was above or below T^*. In the case of $T_f < T^*$, the gel collapses exponentially with time, the shrinking process occurs simply by network diffusion, and the network has time to rearrange as it is never far out of equilibrium. Thus the shrinking occurs in a single step. There was no shape distortion, and no appearance of opacity. However, in the case of $T_f > T^*$, the gel collapses in two distinct steps. The first step is a rapid initial shrinkage, which is also due to network diffusion. However, due to the fact that the gel is far from equilibrium the outer gel layers respond faster than the internal gel, resulting in the formation of a dense layer of collapsed gel at the surface of the gel. This is evidenced by the appearance of opacity, and it prevents the internal water from being released and slows down the shrinking process. As the internal water tries to escape there is a buildup of pressure inside the gel, which manifests itself as bubbles appearing on the gel

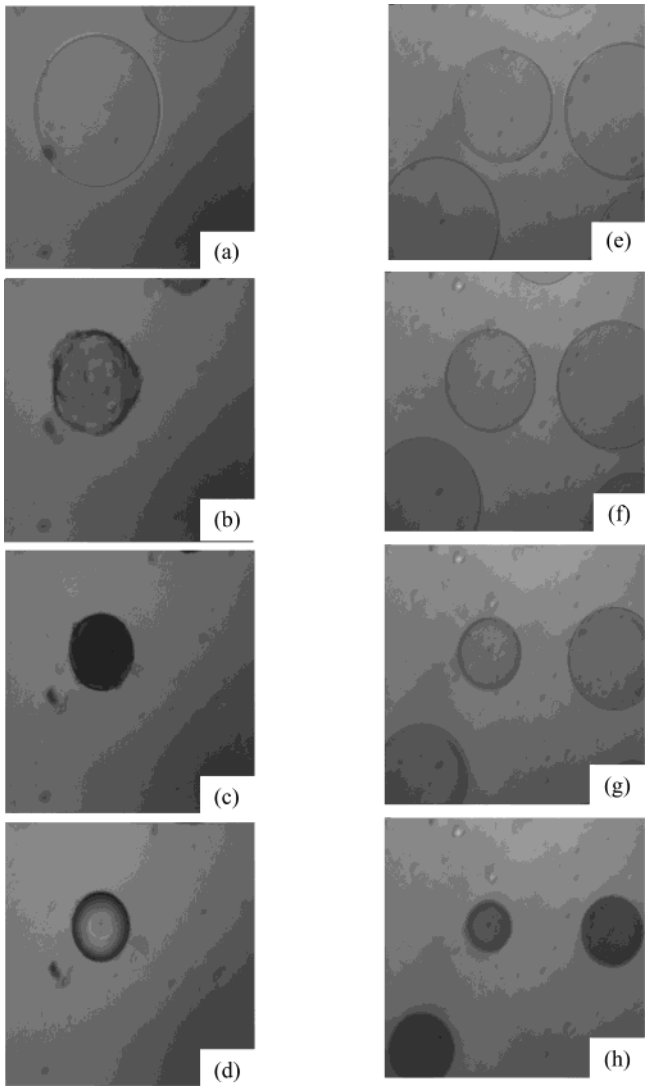

Figure 7. Photographs showing the shrinking for the gels following T-jumps from 30 to 38 °C. Bulk gel: (a) 0, (b) 10, (c) 30, and (d) 850 s. Plum-pudding gel containing 20 mol % of PNIPAM microgel: (e) 0, (f) 5, (g) 20, and (h) 50 s.

surface. The second shrinkage stage is the slow relaxation of the gel to its equilibrium size, and is seen as the gradual disappearance of the opacity, which begins from the edges. The shrinking process after T-jumps to $T_f > T^*$ is shown in the series of photographs in Figure 7a−d.

The transition temperature of the two-component gel is 34 °C, and is thus unchanged from that of the model gel. Figure 4 compared the equilibrium collapse curves of gels with increasing amounts of microgel particles. The shrinking pattern for the plum-pudding gels is quantitatively similar to that of the bulk gel after T-jumps to temperatures below T^*, but deviates significantly after T-jumps to temperatures above T^*. Below T^*, the plum-pudding gels shrink rapidly, and without any appearance of opacity. In all gel sizes studied the shrinking of the plum-pudding gels is exponential at temperatures up to and including T^*. Above T^*, the shrinking pattern differed from that of the bulk gel in that the two-stage shrinking process is much less pronounced. Additionally, there is much less appearance of opacity, which implies that a less dense surface layer forms. This is also evidenced by the fact that there is no appearance of bubbling implying that there is less pressure buildup and thus less water trying to escape. The shrinking process of the plum-pudding gel is shown in the series of

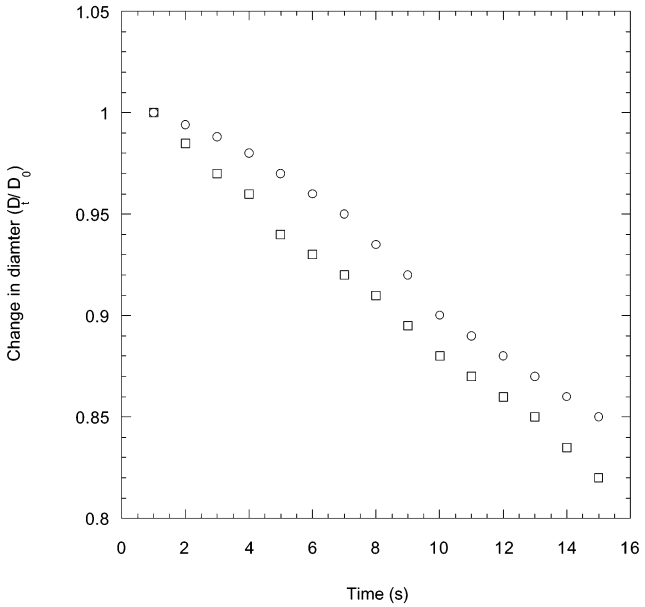

Figure 8. Initial rapid shrinking of the bulk gel (○) and plum-pudding gel with 20 mol % of PNIPAM microgel particles (□) following T-jumps from 30 to 34 °C.

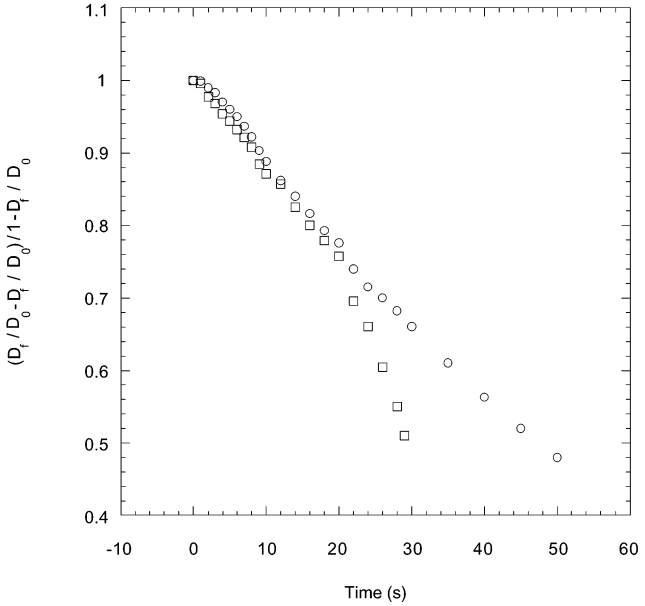

Figure 9. Shrinking profiles of the bulk gel (○) and the plum-pudding gel containing 20 mol % of PNIPAM microgel particles (□) after T-jumps from 30 to 38 °C.

photographs in Figure 7e−h. The exponential shrinking profile of the bulk gel and the plum-pudding gel containing 20 mol % of PNIPAM microspheres after T-jumps to 34 °C (below T^*) are shown in Figure 8. Clearly, the presence of the PNIPAM particles enhances the shrinking rate, since the plum-pudding gel shrinks more than the bulk gel. The shrinking profiles of the bulk gel and the plum-pudding gel containing 20 mol % of PNIPAM microspheres after T-jumps to 38 °C (above T^*) are shown in Figure 9. Here, there is not much difference in the shrinking rate during the first initial burst of shrinking, but during the second slower shrinking stage the presence of the PNIPAM microspheres clearly enhances the rate of shrinking. Thus, as well as achieving rapid, continuous collapse, addition of microgel particles prevents the formation of the dense layer of collapsed gel at the surface. Instead a thin surface layer forms

TABLE 1: Comparison of the Shrinking Times, τ (s), for ~200 μm Gel Beads of the Model Gel, 10 mol % of PNIPAM Microspheres Gel, and 20 mol % of PNIPAM Microspheres Gel

	T-jump temp (°C)					
gel description	34	35	36	37	38	40
model gel, 212 μm	38	43	41	48	42	21
10 mol % micros, 190 μm	34	36	33	32	29	16
20 mol % micros, 220 μm	26	29	39	24	23	12

TABLE 2: Relaxation Times, τ (s), Calculated from Experimental Data, for 20 mol % of PNIPAM Microspheres Gel

	gel diameter (μm)		
T-jump temp (°C)	160	220	275
34	25	26	51
35	27	29	44
36	24	38	42
37	15	24	35
38	11	23	30
40	9	12	21

that has a limited effect on the shrinking process, resulting in a less pronounced two-stage shrinking process at temperatures above T^*.

Quantitatively, the addition of as little as 10−20 mol % of microgel particles to the bulk gel is enough to significantly speed up the shrinking process, especially after T-jumps to $T_f > T^*$. The presence of 10 mol % of PNIPAM microspheres reduced the shrinking times for a ~200 μm gel bead from 38 s (bulk gel) to 34 s for a T-jump from 30 to 34 °C, and from 42 s (bulk gel) to 29 s for a T-jump from 30 to 38 °C. This represents a reduction of ~18% in the shrinking times below T^* and a reduction of ~35% in the shrinking times above T^*. The presence of 20 mol % of PNIPAM microspheres reduced the shrinking times from 38 s (bulk gel) to 26 s for a T-jump from 30 to 34 °C, and from 42 s (bulk gel) to 22 s for a T-jump from 30 to 38 °C. This represents a reduction in the shrinking times of ~30% below T^* and ~50% above T^*. The shrinking profiles of the bulk gel and the plum-pudding gel containing 20 mol % of PNIPAM microgel particles are shown in Figure 9 following T-jumps from 30 to 38 °C. The shrinking times for the bulk gel, a plum-pudding gel containing 10 mol % of PNIPAM microgel particles, and a plum-pudding gel containing 20 mol % of PNIPAM microgel particles are compared in Table 1. In all cases the gel size was about 200 μm. The relaxation or shrinking times are obtained from the shrinking profile by curve fitting. The process was described in detail in a previous paper.[16] The shrinking times of a range of sizes of the plum-pudding gel containing 20 mol % of PNIPAM microspheres are shown in Table 2 and it can be seen that increasing the gel size results in increased shrinking times. The same trend was found for the plum-pudding gel containing 10 mol % of PNIPAM microgel particles, but the data are not shown.

The shrinking data confirm that the presence of the responsive microgel particles reduces the impact of skin-layer formation on the shrinking of bulk gels, resulting in faster shrinking times. Where $T_f < T^*$ the shrinking of the plum-pudding gel remained exponential but was slightly faster than that for the bulk gel. The reason for this is that the collapse transition temperature of the microgels has not been reached and so they do not undergo full collapse, but only shrink slightly. However, due to their extreme sponginess, they still responded to changes in their surroundings faster than the surrounding network, and due to the structure of the composite gel, where the network chains pass through the microgel particles, the rapid shrinking of the microgel particles pulled the associated network with them as they adjusted to the new temperature. The most dramatic increase in the shrinking time of the network resulted from T-jumps to temperatures above T^*. Here, the entire network underwent dramatic and rapid shrinking. Again this was due to the sponginess of the microgel particles, which underwent a rapid phase transition, and the structure of the composite gels. The shrinking of the microgel particles results in local regions of collapsed hydrophobic polymer appearing throughout the gel (as opposed to just at the surface in the case of skin-layer formation). These hydrophobic regions cause the entire network to collapse rapidly, as a result of the hydrophobic effect, in combination with the effect of the shrinking microgel particles pulling the associated network polymer with them as they collapse. Due to the fact that the plum-pudding gels shrink more rapidly than the model gel, more water is expelled during the initial shrinking stage, and thus less water is trapped inside the gel when the skin layer forms. Also, the skin layer that forms is much less dense than that in the case of the model gel, and there is no appearance of bubbling during the shrinking process.

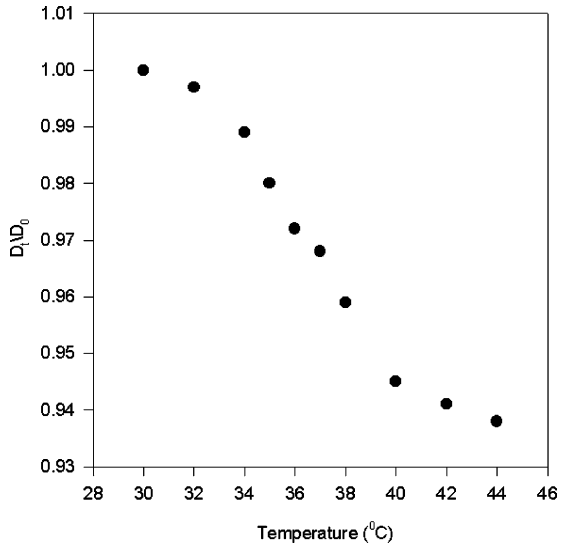

Figure 10. Equilibrium shrinking curve of nonthermoresponsive *N*,*N*-dimethylacrylamide gel + 20 mol % of PNIPAM microgel particles.

2. Use of the Plum-Pudding Gel to Induce Responsiveness in Nonresponsive Materials. In much the same manner as the presence of the responsive microgel particles speeded up the overall collapse of a responsive bulk gel, by pulling the associated polymer network with them as they shrank, it was envisioned that incorporation of PNIPAM microgel particles into nonthermoresponsive gels would cause thermoresponsive behavior in the entire gel. Thus, PNIPAM microgel particles were incorporated into a hydrophilic DAM hydrogel, and the equilibrium collapse curve for a 220-μm cylindrical DAM gel containing 20 mol % of PNIPAM microgel particles is shown in Figure 10. The presence of the microgel particles causes the degree of swelling of the gel to decrease with increasing temperature. This is an important result as it increases the range of gels that can be used for stimuli-controlled applications. DAM was chosen to illustrate this application of the structural motif as it was convenient, but any gelling material (natural or synthetic) could be used as the bulk phase. For example, one could imagine carrageenan or chitosan gels with embedded PNIPAM particles, as such gels have already been prepared as blends or interpenetrating networks with PNIPAM polymers.[21,22] The main requirement is that bulk gel material must be relatively

soft (have a low Young's modulus) for the particles to be able to exert an effect. For example, the Young's modulus of *N*-isopropylacrylamide gels is 2.83 KPa at 25 °C,[23] and that of the DAM gel is expected to be similar due to their similar compositions. While the degree of shrinking shown in Figure 10 with 20 mol % of microgel particles is only 10%, it must be noted that the microsphere particles are more than 500 times smaller than the bulk gel, and the fact that such tiny particles can affect the degree of swelling of the bulk gel is very interesting. Obviously, if the ratio of the microsphere particle size relative to the gel thickness was decreased the effectiveness of the shrinkage would be increased. The ideal microgel particle size to gel thickness ratio as well as the most efficient microgel particle concentration for maximum deswelling is currently being investigated, and the results of this study will be reported separately. Other methods of imparting thermoresponsiveness onto nonresponsive materials include formation of block copolymers with one block being thermoresponsive and one block being mechanically strong, or interpenetrating networks (IPNs).[24,25] Both of these methods result in a blending of the properties of the two components. It has been shown here that the microgel particles can be embedded in a nonthermoresponsive bulk gel, and impart thermoresponsiveness on the entire system without altering the properties of the bulk material. This opens up even greater possibilities for use of such a two-component gel as a controlled release device, since the use of NIPA gels is limited by its poor mechanical properties[24] and its expensiveness as a raw material.

Thus we have shown that the addition of PNIPAM microgel particles to a bulk gel has a profound effect on the shrinking behavior of the bulk gel, regardless of whether the bulk gel has responsive properties or not. Further extensions to the structural motif are conceivable if microgel particles are added to the bulk gel in their collapsed state. In this case there will be no enhancement to the kinetics, but this leads to a second potentially more useful application of these two-component gels. The microgel particles could be used as reservoirs for drug molecules. By forming the gel at a temperature above the microgel particle collapse transition, the microgel particles will exist as dense collapsed balls within the network, from which the drug molecules will diffuse very slowly. This potential application of plum-pudding gels will be the subject of another paper.[26]

An alternative approach to rapid shrinking kinetics with plum-pudding type gels could be to introduce hydrophilic microgel particles, such as polyacrylamide (PAM), which would remain swollen even at high temperatures. These microgel particles would perhaps soak up the water being expelled by the bulk gel, and act as water release channels, in analogy to the gels of Hirotsu[9] and Kaneko et al.[10] We have already shown that 20 mol % of polyacrylamide polymers incorporated into bulk gels results in extremely rapid shrinking kinetics.[27] Again, the presence of a second component did not alter the equilibrium swelling behavior or the pore-size distribution of the gel to any significant degree.[28]

Conclusion

A simple composite gel structure, which we call the plum-pudding gel, was prepared and characterized. The basic structural motif is responsive microgel particles embedded in a bulk gel medium. By altering the stimulus to which the microgel is responsive a vast range of materials can be designed and tailored to specific applications. By altering the nature of the bulk gel, materials with diverse mechanical properties can be prepared, and issues such as compliance can be considered. The gel is described as a "plum-pudding" gel, since the randomly incorporated microgel particles resemble plums. The structure of the gel was confirmed by laser scanning confocal microscopy in the fluorescent mode. Pore size distribution measurements were used to show that the presence of the microgel particles in the pre-gel solution did not affect the formation of the bulk gel network, and thus did not affect the gel microstructure. On the basis of these experiments a structure was proposed whereby the network chains pass through the swollen microgel particles.

Two examples of the structural motif are described. The first uses the plum-pudding gel to overcome the problems associated with bulk NIPA gels where the shrinking process is dramatically slowed by the formation of a surface "skin layer". To this end, PNIPAM microgels are incorporated into the network of a conventional macrogel (composed of loosely cross-linked NIPA-*co*-BAM-*co*-DAM (70:10:20)) and the effect on the shrinking kinetics determined. Incorporation of as little as 10−20 mol % of PNIPAM microgel particles decreases the relaxation time by 20−50%, and dramatically reduced the effect of skin-layer formation, following temperature jumps to temperatures above *T**. This was explained as being due to the formation of hydrophobic domains throughout the gel network which are attractive to the bulk network, and thus induce shrinkage in the entire network.

The second example of the structural motif involves the introduction of responsive microgel particles into a nonresponsive bulk gel, and we show that the entire gel can be made responsive. Plum-pudding gels composed of *N*,*N*-dimethylacrylamide containing 20 mol % of PNIPAM microgel particles were shown to undergo a shrinkage of 10% with a temperature change of 10 °C. This is an important result, as it is an interesting way of imparting thermoresponsive properties on nonthermoresponsive gels. Unlike interpenetrating networks or block copolymers for example, the fundamental properties of the network remain unchanged and there is the addition of thermoresponsiveness.

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