Studies on Preparation and Swelling Properties of the *N*-Isopropylacrylamide/Chitosan Semi-IPN and IPN Hydrogels

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ABSTRACT: Semi-interpenetrating network (semi-IPN) polymer gels and interpenetrating network (IPN) polymer gels with thermosensitivity were prepared by introducing a biodegradable polymer, chitosan, into the *N*-isopropyacrylamide (PNIPAAm) gel system. The swelling behavior, temperature sensitivity, pH sensitivity, gel strength, and drug-release behavior of PNIPAAm/chitosan semi-IPN and IPN hydrogels were investigated. The results indicated that the NIPAAm/chitosan semi-IPN and IPN hydrogels exhibited pH and temperature-sensitivity behavior and could slow drug release and diffusion from the gels. From the stress–strain curves of the hydrogels, the compression moduli of IPN gels containing crosslinked chitosan were higher than those of semi-IPN gels. This is because IPN gels have a more compact structure. The morphology of PNIPAAm/chitosan hydrogels was also investigated. © 2001 John Wiley & Sons, Inc. J Appl Polym Sci 82: 2487–2496, 2001

Key words: hydrogel; interpenetrating network; *N*-isopropylacrylamide; chitosan

INTRODUCTION

Hydrogels are crosslinked, three-dimensional hydrophilic polymer networks, which swell but do not dissolve when brought into contact with water. There are some hydrogels which sometimes undergo a volume change in response to a change in surrounding conditions such as temperature,[1–3] pH,[4–7] ion strength,[8] electric field,[9–11] light (ultraviolet[12] or visible[13]), and certain chemicals.[14–16] Therefore, they are extensively applied in biochemistry systems.

A thermosensitive hydrogel, one of the environmental stimuli-response hydrogels, collapses at elevated temperature above the lower critical solution temperature (LCST). The volume change occurs within a quite narrow temperature range. An "on–off" switch, according to the environmental temperature, can change the permeability of water through the gel. Therefore, such materials can be used in many fields such as in drug-delivery systems and for enzyme-activity control.[17–24]

N-Isopropyacrylamide (NIPAAm) hydrogels demonstrate a nearly continuous volume transition and associated phase transition from, at a low temperature, a highly swollen gel network, to, at a high temperature, a collapsed phase near its critical point between 31 and 35°C.[25] Hirotsu[26] investigated the phase behavior of the NIPAAm gel/water/alcohol system and explained its thermoshrinkage by the destruction of hydrogen bonds between the water molecules and amido groups of NIPAAm. The swelling behaviors for a series of hydrogels synthesized from NIPAAm and cationic monomers,[27–29] anionic monomers,[30,31] and sulfobetaine monomers[32–34] have been studied in our laboratory.

Chitosan (2-amino-2-deoxy-(1→4)-β-D-glucopyranan), a polyaminosaccharide, normally ob-

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tained by alkaline deacetylation of chitin,[35] is the principal component of living organisms such as fungi and crustacea. Chitosan has been reported to be a promising polymer not only in the chemical field, but also in medical and industrial areas.[36,37] Chitosan, a linear polymer of mainly anhydroglucosamine which behaves as a linear polyelectrolyte at acidic pH, is nontoxic and bioabsorbable.[38] At pH below 6.5, chitosan in solution carries a high positive charge density, one charge per glucosamine unit. Since chitosan is one of the few cationic polyelectrolytes, it is an exception to the current industrial high molecular weight polysaccharides, which are mostly neutral or polyanionic, and provides a great variety of potential applications. Since most living tissues carry negative charges (e.g., proteins, anionic polysaccharides, nucleic acids), the positive charge of chitosan interacts strongly with negative surfaces to give an electric neutrality. Because of its vast number of $—NH_3^+$ groups, it readily forms film on biopolymers such as bone, hair, and skin, which are composed of negatively charged mucopolysaccharides and proteins. Thus, the binding of chitosan to living cells of all types is a very important property for its use in biomedical applications. It was documented that oral administration of chitosan with drugs enhanced their absorption from intestines into blood in animals.[39,40] Chitosan is being evaluated in a number of biomedical applications, including wound healing and dressing, dialysis membranes, contact lenses, fibers for digestible sutures, liposome stabilization agents, antitumor uses, and drug-delivery and controlled-release systems. In these uses, chitosan's key properties are (1) biocompatibility, (2) nonantigenicity, (3) nontoxicity (its degradation products are known natural metabolites), (4) the ability to improve wound healing and/or clot blood, (5) the ability to absorb liquids and to form protective films and coatings, and (6) selective binding of acidic liquids, thereby lowering serum cholesterol levels.[41–43]

The phase separation and morphology of two combined polymers has been an attractive subject of research, especially in the case of interpenetrating polymer networks (IPNs), where specific topological network structures provide smaller domains of phase-separated material.[44,45] Their miscibility level leads to multiphase polymer blends with a wide variety of structural order ranging from nanometer to micrometer scale. The formation of IPNs is practically the only way to combine two or more crosslinked polymers in a fine dispersion. This technology offers the possibility to obtain materials with combined properties of the components.[46–49] In semi-IPNs, one of the two polymers has a linear structure; in IPNs, both polymers have crosslinked structures.

The main purpose of this article was to prepare a series of semi-IPN and IPN hydrogels based on NIPAAm/chitosan and to discuss the swelling behavior and drug-release behavior. In addition, the pH sensitivity and the temperature sensitivity for the PNIPAAm/chitosan semi-IPN and IPN hydrogels were investigated. The gel strength and the morphology for the PNIPAAm/chitosan gels were also investigated.

EXPERIMENTAL

Materials

NIPAAm (Wako Pure Chemical Co. Ltd., Osaka, Japan) was further purified by recrystallization. Chitosan ($\bar{M}_n \sim 1.5 \times 10^5$; Fluka Chemical Co., Switzerland), *N,N′*-methylenebisacrylamide (NMBA; Sigma Chemical Co., St. Louis, MO) as a crosslinker, and *N,N,N′,N′*-tetramethylethylenediamine (TEMED; Fluka Chemical Co.) as an accelerator were used as received. Ammonium persulfate (APS) (Wako Pure Chemical Co. Ltd.) as an initiator was further purified by recrystallization.

Preparation of Hydrogels

Semi-IPN Hydrogel

Various ratios of NIPAAm, chitosan, and 3 mol % NMBA based on the total monomers were dissolved in 10 mL of a 1% acetic acid solution (See Table I). To this solution, 1 wt % APS and 1 wt % TEMED as redox initiators were added, and the mixture was immediately injected into the space between two glass plates. The thickness of the gel membrane was adjusted with a silicone spacer between the two glass plates. Polymerization was carried out at 5°C for 1 day. After the gelation was completed, the gel membrane was cut into disks and immersed in an excess amount of deionized water for 7 days to remove the residual unreacted monomers. Swollen polymer gels were dried at room temperature for 2 days, and these samples were further dried in a vacuum oven for 1 day at 60°C. The thickness of the dried gel was about 1–1.5 mm and the diameter was about 4–5 mm.

IPN Hydrogel

Various ratios of NIPAAm, chitosan, and 3 mol % NMBA based on total monomers were dissolved

Table I Characterization of the PNIPAAm/Chitosan Hydrogels

Style	No.	NIPAAm Concentration (*M*)	Chitosan (wt %)	Glutaraldehyde 1% (mL)	Swelling Ratio (g/g)
PNIPAAm	N0	1	0	0	7.42
	N3		3		7.10
Semi-IPN	N6	1	6	0	7.08
	N9		9		6.97
	IPN3		3		5.43
IPN	IPN6	1	6	1	5.38
	IPN9		9		5.29
	G15	1	6	1.5	4.87

in 9 mL of a 1% acetic acid solution. To these solutions, 1 wt % APS and 1 wt % TEMED as redox initiators and 1 mL of a 1% glutaraldehyde solution as a crosslinker were added. The mixtures were immediately injected into the space between two glass plates. The thickness of a gel membrane was adjusted with a silicone spacer between the two glass plates. Polymerization was carried out at 5°C for 1 day. The gel membrane was then cut, washed with excess deionized water, and then dried.

Measurement of Swelling Ratio

The dried gels were immersed in 10 mL of deionized water at different temperatures or in various buffer solutions with different pHs at 25°C until swelling equilibrium was attained. The pHs of the various solutions adjusted by an aqueous solution of HCl and NaOH were measured with a pH meter (Radiometer PHM95) calibrated by a standard buffer solution. The weight of the wet sample (*Ww*) was determined after removing the surface water by blotting with filter paper. The weight of the dry sample (*Wd*) was determined after drying the gel in a vacuum oven for 1 day. The swelling ratio (*Q*) based on *Ww* and *Wd* was then calculated from the following equation:

$$\text{Swelling ratio } (Q) = (Ww - Wd)/Wd \qquad (1)$$

Dynamic Swelling

The dried gels were immersed in 10 mL of deionized water at 25°C. The "*Q*" was obtained by weighing the initial and swollen samples at various time intervals.

Caffeine-release Experiment

The dry gels were equilibrated in 30 mg caffeine/10 mL of deionized water at 25°C for 1 day to load caffeine into the gels. The caffeine-release experiments were carried out by transferring previously incubated drug gels into 10 mL of deionized water at 37°C. The gels were repeatedly removed and transferred into 10 mL fresh deionized water at each fixed time interval. The released caffeine was analyzed at 272 nm by an ultraviolet spectrophotometer (JASCO V-530).

Caffeine-diffusion Experiment

Side-by-side diffusion cells were used to perform drug-diffusion studies. Temperature was maintained at 25°C by circulating a constant temperature fluid through the water jackets. For continuous agitation, each half-cell also contained a magnetic stirrer. A preequilibrated hydrogel membrane was clamped between the half-cells before they were secured into place. In a typical experiment, 25 mL of deionized water was poured into the receptor compartment and 25 mL of a 3000 ppm caffeine solution was poured into the donor compartment. Drug concentration was analyzed at 272 nm by the ultraviolet spectrophotometer.

Uniaxial Compression Experiment

The swollen sample gels were tested using a universal tester (LLOYD LRX), with a crosshead speed at 1 mm/min. The following equation can be used to calculate the shear moduli of gels[50,51]:

$$\tau = F/A_0 = G(\lambda - \lambda^{-2}) \qquad (2)$$

where τ is the compression stress; F, the compression load; A_0, the undeformed cross-sectional area of the swollen gels; λ, the compression strain (L/L_0); and L_0, the undeformed sample length. At low strains, a plot of shear stress versus $-(\lambda$

$-\lambda^{-2}$) will yield a straight line whose slope is the shear modulus (G). The effective crosslinking density (ρ_x) can then be calculated from the shear modulus and polymer swelling ratio (Q) as follows[50,51]:

$$\rho_X = GQ^{1/3}/RT \quad (3)$$

where R is the gas constant (8.48×10^4 gcm mol^{-1} K^{-1}), and T, the absolute temperature (298 K).

Morphology

Xerogel samples were equilibrated in deionized water for 2 days. The swollen gels were frozen in liquid nitrogen for 5 min, then fractured and freeze-dried. The fractured specimens were covered with gold vapor, and then the morphology of the fractured surface of the hydrogels were observed by scanning electron microscopy (SEM) using a JEOL JXA8600 microscope with an acceleration voltage of 15 kV.

RESULTS AND DISCUSSION

Characterization of the PNIPAAm/Chitosan Gels

The characterization of the PNIPAAm/chitosan hydrogels with various feed compositions is shown in Table I. N0 represents the PNIPAAm hydrogel; N3, N6, and N9 represent 3, 6, and 9 wt % chitosan dispersed in the network of the PNIPAAm hydrogel, respectively; IPN3, IPN6, and IPN9 represent 3, 6, and 9 wt % crosslinked chitosan dispersed in the network of the PNIPAAm hydrogel, respectively; and G15 represents 6 wt % chitosan crosslinked with 1.5 mL of 1% glutaraldehyde dispersed in the network of the PNIPAAm hydrogel. The results in Table I shows that the swelling ratios of IPN gels are lower than those of semi-IPN gels. The reason is that the addition of crosslinked chitosan in the PNIPAAm hydrogel makes the network structure of the gel denser and more hydrophobic. The swelling ratios, as a function of time for PNIPAAm/chitosan semi-IPN gels at 25°C in deionized water, are shown in Figure 1. The results indicate that the swelling ratios of PNIPAAm/chitosan gels slightly decrease with the addition of chitosan, but the swelling ratios are not significantly affected by the amount of chitosan added to the PNIPAAm gel. The swelling ratios, as a function of time for the PNIPAAm, semi-IPN, and IPN gels at 25°C in deionized water, are shown in Figure 2. The results show that the key factor in swelling is the crosslinking of chitosan, and the equilibrium swelling ratios of IPN gels decrease with an increase of glutaraldehyde content.

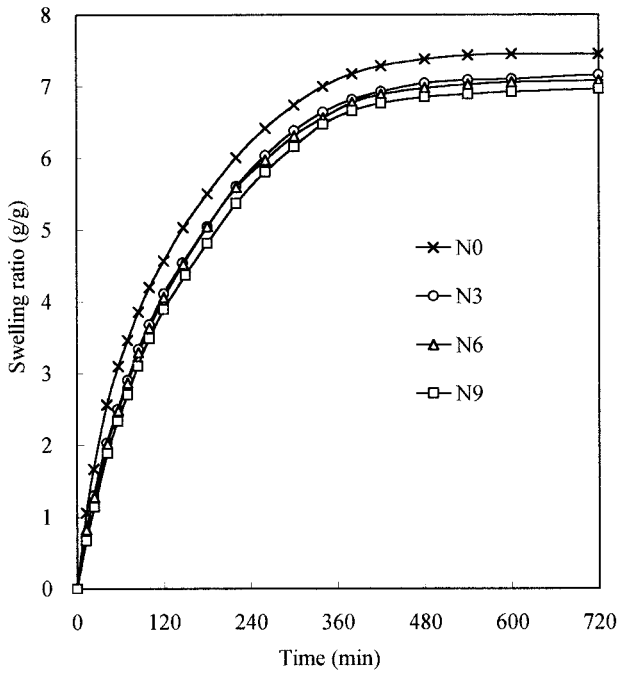

Figure 1 Swelling ratios as a function of time for PNIPAAm and PNIPAAm/chitosan semi-IPN hydrogels in water at 25°C.

Effect of Temperature on Swelling Ratio for PNIPAAm/Chitosan Gels

The effect of temperature on the equilibrium swelling ratios for a series of NIPAAm/chitosan hydrogels is shown in Figure 3. According to previous reports,[27–29,30–34] the NIPAAm molecule contains a hydrophilic group (amido-, —CONH—) and a hydrophobic group (isopropyl-). The hydrophilic group in the polymer structure will form an intermolecular hydrogen bond with surrounding water at low temperature (below the gel transition temperature). Hence, water penetrating into the PNIPAAm/chitosan hydrogels is in a bound state at low temperature. The water molecule will gain an enthalpy during the increase of temperature, and the hydrophilic group in the NIPAAm will be turned into an intramolecular hydrogen bond in this condition. At the same time, the hydrophobic force of the isopropyl group of PNIPAAm increases. These two results make the

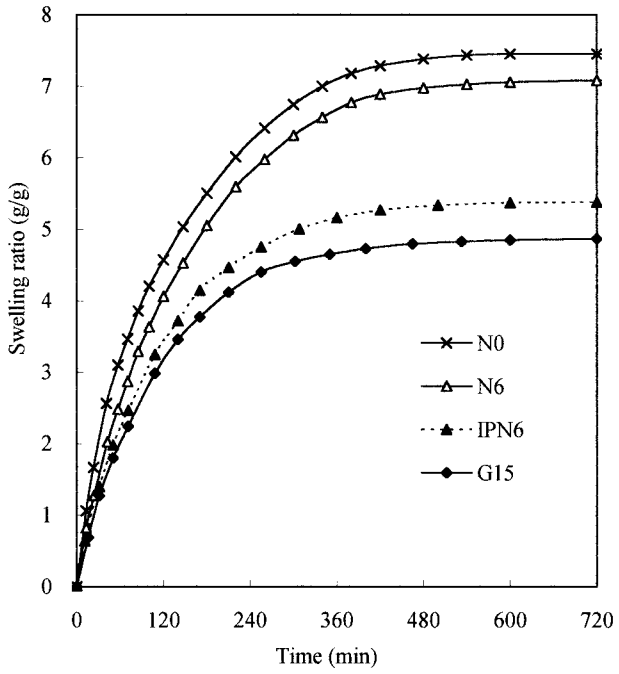

Figure 2 Swelling ratios as a function of time for PNIPAAm/ chitosan semi-IPN and IPN gels at 25°C.

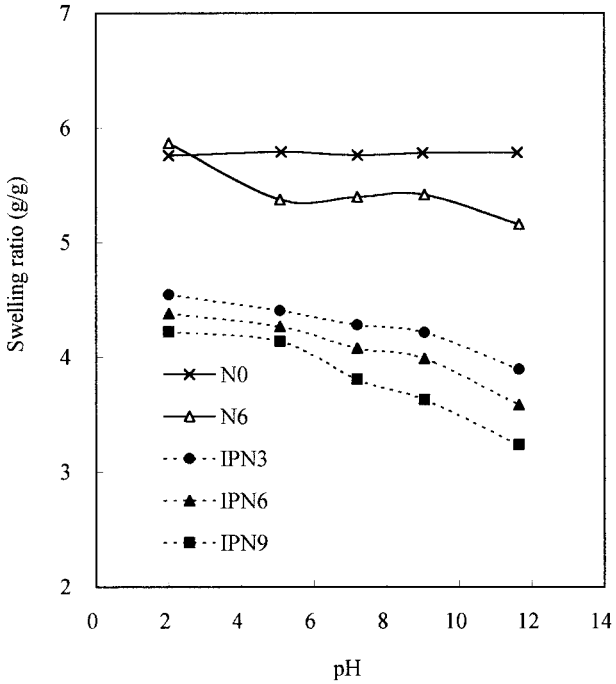

Figure 4 Equilibrium swelling ratios as a function of pH for PNIPAAm/chitosan gels at 25°C.

water molecule inside the gel change from a bound state to a free state and release from the gel. This phenomenon makes the swelling ratios of the hydrogels decrease rapidly at the gel transition temperature. Figure 3 shows that the PNIPAAm/chitosan semi-IPN and IPN hydrogels deswell more quickly at their gel transition temperatures. Figure 3 also shows that the gel transition temperature for the present gels is not affected by the addition of the chitosan component in the gels.

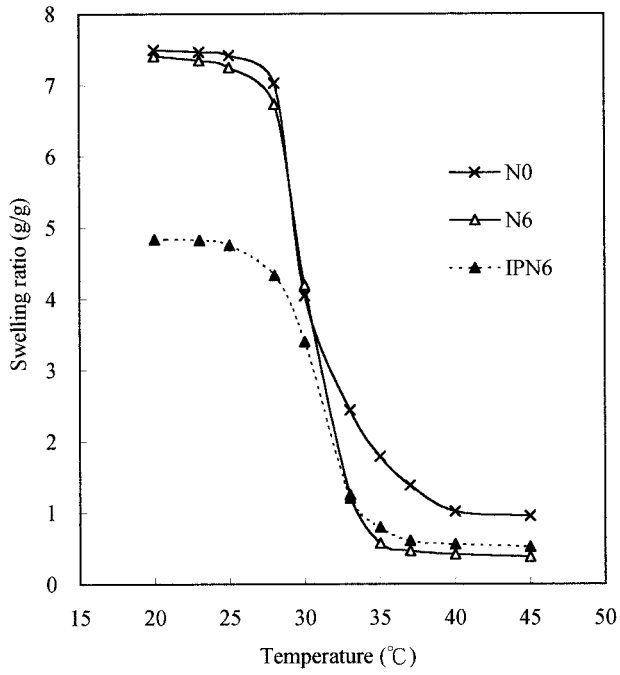

Figure 3 Equilibrium swelling ratios as a function of temperature for PNIPAAm/chitosan gels in water.

Effect of pH on Equilibrium Swelling Ratio for PNIPAAm/Chitosan Gels

The equilibrium swelling ratios for a series of NIPAAm/chitosan hydrogels in different pH solutions, shown in Figure 4, indicate that the swelling ratios decrease with an increasing pH value of the buffer solutions. This is because PNIPAAm gels do not have pH sensitivity in the buffer solution but chitosan has. In an acid solution, the protonation of amino groups (—NH_2) in the chitosan gel and dissociation of the hydrogen bonding, which induces gel swelling, develop an internal ion osmotic pressure.[52] Semi-IPN hydrogels contain uncrosslinked chitosan, which will be dissolved in an acid solution and increase the porosity of PNIPAAm/chitosan gels. In an alkali solution, there is a lower swelling ratio, which is due to the inherent hydrophobicity of the chitosan.

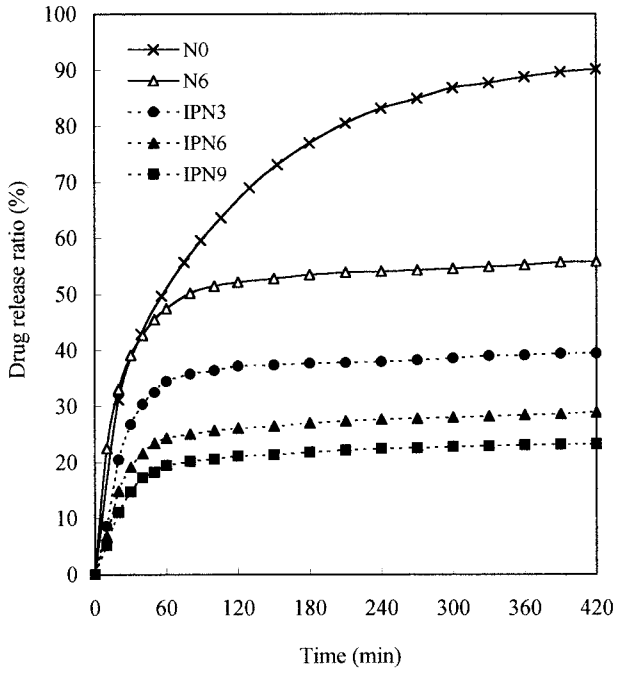

Figure 5 Caffeine-release profile for PNIPAAm/chitosan gels at 37°C.

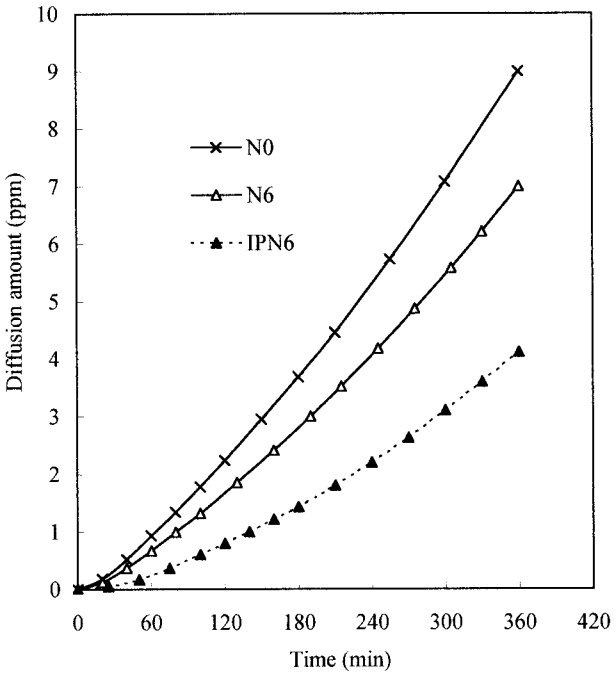

Figure 6 Caffeine-diffusion profile for PNIPAAm/chitosan gels at 37°C.

Yao et al.[52] reported that the degree of protonation of the amino group in the network had a strong effect on the swelling behavior. Figure 4 shows that the differences of the swelling ratio between pH 2 and pH 12 for IPN gels increase with an increasing content of crosslinked chitosan.

Caffeine-release Behavior for PNIPAAm/Chitosan Gels

Figure 5 shows the release profile of caffeine for the PNIPAAm/ chitosan gels, swelled at 25°C in the caffeine solution and deswelled at 37°C, in deionized water. Because the hygrogels shrink at 37°C, the caffeine in the gels will be released due to the driving force of the volume change and concentration gradient of the drug. In addition, Figure 5 also shows that the fractional release is directly proportional to their swelling ratios, that is, N0 > N6 > IPN3 > IPN6 > IPN9. This result indicates that the higher swelling ratios of hydrogels create larger surface areas to diffuse the drug. For example, the fractional release of PNIPAAm gel at 7 h is about 90%, but the fractional release of semi-IPN gel (N6) is about 55% due to the complex structure of the NIPAAm/ chitosan gel. However, the IPN gels possess two interpenetrating networks and restrict the releasing of the drug inside the hydrogels. Because the sample IPN9 contains the most crosslinked chitosan, this gel has the densest structure and releases the least amount of caffeine (about 20%).

Caffeine-diffusion Behavior for PNIPAAm/Chitosan Gels

Figure 6 shows the diffusion profile of caffeine through the PNIPAAm/chitosan hydrogels clamped between two diffusion cells at 25°. The results in Table II show the diffusion amount at 6 h and the linear diffusion rate after 2 h of diffusion. Experimental results show that the caffeine diffusion amount of the gels is directly proportional to their

Table II Drug-diffusion Amount and Diffusion Rate of the PNIPAAm/Chitosan Hydrogels at 25°C

Sample No.	Drug-diffusion Amount[a] (ppm)	Diffusion Rate[b] (ppm/h)
N0	9.0	1.69
N6	7.0	1.34
IPN6	4.1	0.85

[a] Diffusion amount at 6 h.
[b] Diffusion rate after 2-h diffusion.

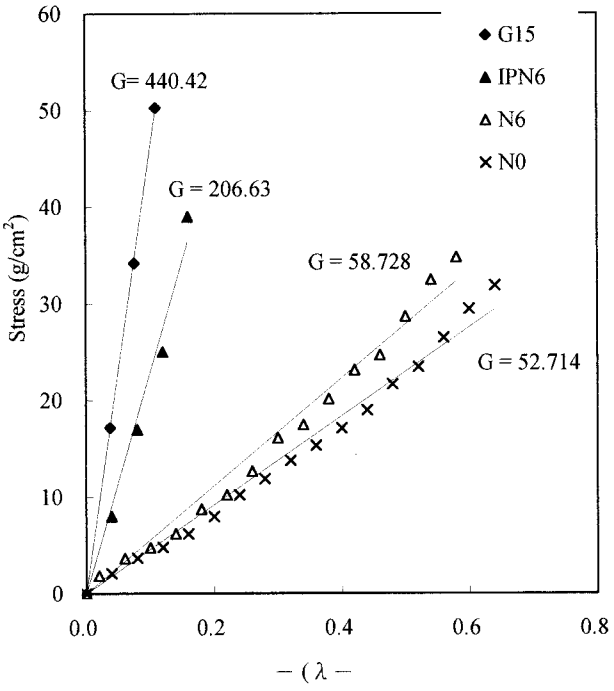

Figure 7 Compression curves for PNIPAAm/chitosan gels at 25°C, where $\lambda = L/L_0$.

swelling ratios, that is, N0 > N6 > IPN6. This result proves that the addition of chitosan to the NIPAAm gel can hinder the diffusion of caffeine and slightly slows the diffusion rate. This behavior is more significant in the diffusion curve of IPN gels. This is because the crosslinked chitosan has only small spaces for the passing of caffeine whose molecular weight is 194.19. However, the IPN hydrogel still allows the drug to penetrate through the network but does not lock the drug in.

Effect of Crosslinked Chitosan on Gel Strength and Crosslinking Densities for PNIPAAm/Chitosan Hydrogels

The stress–strain curves for a series of PNIPAAm/chitosan hydrogels, in the swollen state at 25°C, are shown in Figure 7. The slope of the straight line is the shear modulus (G), and the value represents the gel strength of the gels. The crosslinking densities of the hydrogels, calculated from eq. (5), are listed in Table III. Figure 7 shows that sample N6 has a higher G value than that of the PNIPAAm gel (N0). This is because the semi-IPN gel has a larger polymer density and makes the gel become stronger. In the same way, the IPN gels show the highest polymer density and make the gel strength steeply increase. Hence, the IPN gel, which contained 6% chitosan and 1.5 mL glutaraldehyde (G15), has the highest crosslinking density and gel strength. The data shown in Table III also indicate that the crosslinking densities of hydrogels increase with the increase of the shear modulus of the hydrogels. This can be explained by eq. (5). In this equation, the crosslinking density depends on the swelling ratio and the shear modulus. Because the values of $Q^{1/3}$ are nearly equal to 1.8 for all the gels (see Table III), the crosslinking densities of the gels are directly proportional to their shear moduli. Hence, the shear moduli for the PNIPAAm/chitosan gels play a determinant role in defining their crosslink densities.

SEM Analysis

Figure 8 shows SEM microphotographs of cross sections of the PNIPAAm/chitosan gels. Figure 8(a,c,e) represents the micrographs of the fractured surfaces of PNIPAAm, PNIPAAm/chitosan semi-IPN, and IPN hydrogels (magnification of 100), respectively. The results show that the hydrogels are porous, and the pore size of semi-IPN and IPN gels is smaller than that of the PNIPAAm gel. The pore distribution of the semi-IPN gel also is nondirectional, but the network of IPN gel exhibits a lamellar structure, supporting the fact that the IPN structure provides smaller domains of phase separation. Figure 8(b,d,f) represents microphotographs of fractured surfaces of PNIPAAm, PNIPAAm/chitosan semi-IPN, and

Table III Shear Moduli and Crosslinking Densities of the PNIPAAm/Chitosan Hydrogels

Sample No.	Swelling Ratio Q (g/g) 25°C	$Q^{1/3}$	Shear Modulus G (g/cm^2)	Crosslinking Density $\rho_X \times 10^6$ (mol/cm^3)
N0	7.42	1.95	52.71	4.07
N6	7.08	1.92	58.73	4.46
IPN6	5.38	1.75	206.63	14.3
G15	4.87	1.69	440.42	29.5

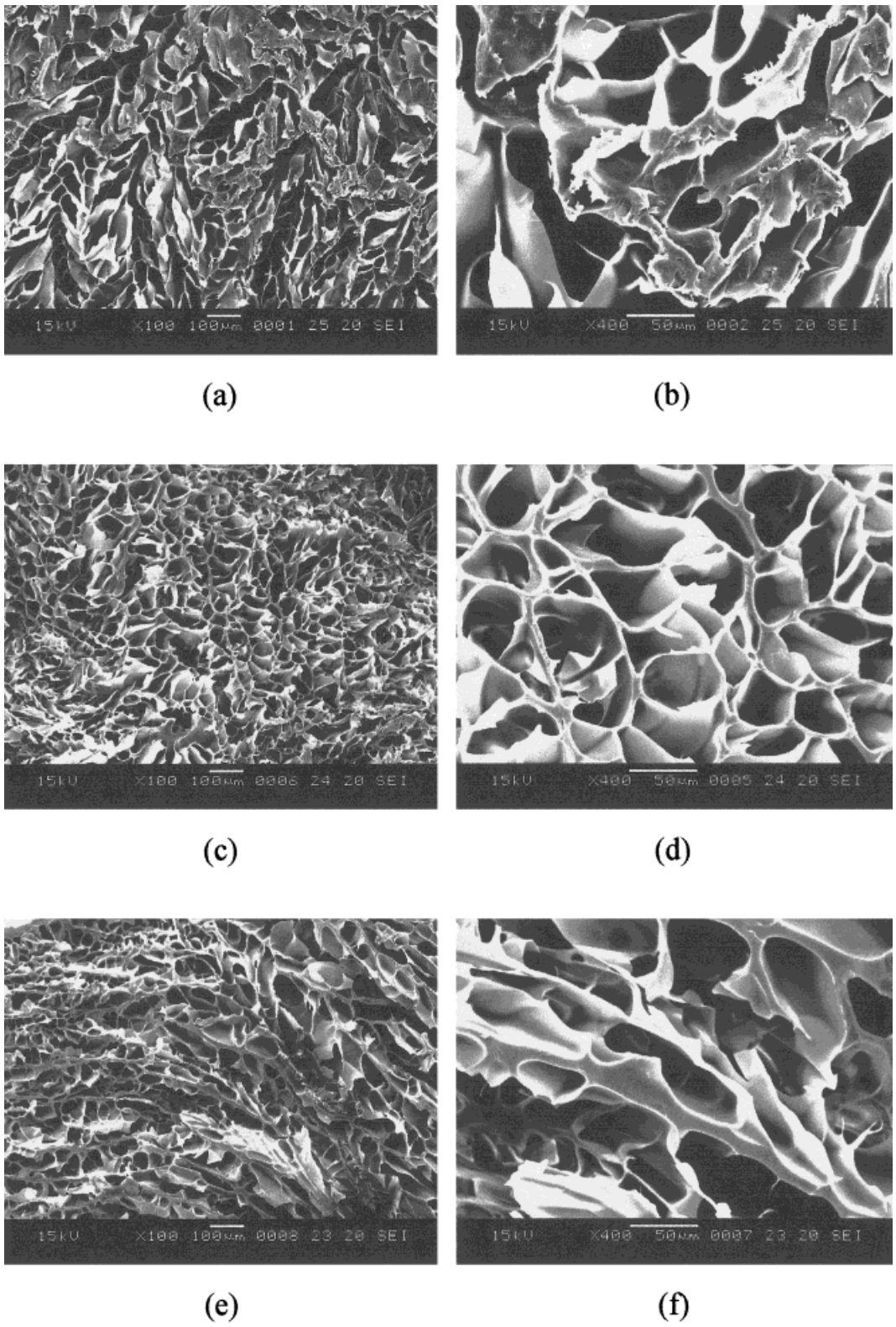

Figure 8 SEM of PNIPAAm/chitosan (a) ×100 and (b) ×400; PNIPAAm/chitosan semi-IPN (N6) (c) ×100 and (d) ×400; and IPN6 (e) ×100 and (f) ×400.

IPN hydrogels (magnification of 400), respectively. The results show that the pore walls of semi-IPN and IPN gels become thicker than those of the PNIPAAm gel and make the gel strength increase.

CONCLUSIONS

The experimental results showed that the addition of crosslinked chitosan to the PNIPAAm hydrogel made the network structure of the gel become denser and more hydrophobic. The swelling ratios of PNIPAAm/chitosan gels slightly decreased with the addition of chitosan, but the swelling ratios were not significantly affected by the amount of chitosan added to the PNIPAAm gel. The equilibrium swelling ratios of IPN gels decreased with increasing glutaraldehyde content in the IPN gels. The PNIPAAm/chitosan semi-IPN and IPN hydrogels had not only temperature sensitivity, which was the unique property of PNIPAAm, but also pH sensitivity, which was the property of chitosan. The addition of chitosan in the PNIPAAm hydrogel also would decrease the fractional release and diffusion amount. From the stress–strain curves of the hydrogels, the compression moduli of the IPN gels containing crosslinked chitosan were higher than those of the semi-IPN gels, due to the denser structure of the IPN gels. The SEM microphotographs of the PNIPAAm/chitosan hydrogels showed that all the hydrogels were porous and had a smaller pore size than that of the PNIPAAm gel. These results also sustain the fact that the IPN structure provided smaller domains of phase separation and increased the gel strength.

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