Swelling and Drug-Release Behavior of the Poly(AA-*co*-*N*-vinyl pyrrolidone)/Chitosan Interpenetrating Polymer Network Hydrogels

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Received 29 March 2003; accepted 23 July 2003
Published online 8 December 2003 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/app.13353

ABSTRACT: A series of novel hydrogels were prepared from acrylic acid (AA), *N*-vinyl pyrrolidone (NVP), and chitosan by photopolymerization. The swelling behavior, gel strength, and drug release behavior of the poly(AA/NVP) copolymeric hydrogels and corresponding interpenetrating polymer network hydrogels were investigated. Results showed that the swelling ratios for the present hydrogels decreased with an increase of NVP content in the gel, but the gel strength increased with an increase of NVP content in the gel. Results also showed that the drug-release behavior for the gels is related to the ionicity of drug and the swelling ratio of the gel. © 2003 Wiley Periodicals, Inc. J Appl Polym Sci 91: 2135–2142, 2004

Key words: interpenetrating polymer networks (IPN); hydrogels; biocompatibility; swelling; drug release

INTRODUCTION

Hydrogels are crosslinked, three-dimensional hydrophilic polymer network that swell but do not dissolve when brought into contact with water. There are some hydrogels that sometimes undergo a volume change in response to a change in the surrounding conditions such as temperature,[1,2] pH,[3] ionic strength,[4] and electric field.[5] Therefore, they are extensively applied in biochemistry. The biocompatibility of hydrogels is attributed to their high water content and their special surface properties. They have been investigated for applications ranging from solute separation to controlled delivery of solutes.[6–11]

Because of the presence of carboxylic acid, the swelling behavior of the poly(acrylic acid) (PAA) hydrogel is highly dependent on the pH of the surrounding medium.[12–17] For example, because the pK_a of PAA is between 4.5 and 5.0, PAA hydrogels swell significantly above pH 5, which is the pH of simulated intestinal juice. However, they do not swell significantly below pH 4, which is the pH of simulated gastric juice. Therefore, one of the major applications of acrylic acid gels is in a sustained gastrointestinal drug-delivery system.[18,19]

Poly(*N*-vinyl pyrrolidone) (PNVP) is a typical neutral water-soluble polymer. It has good solubility in water, methanol, ethanol, chloroform, and dichloromethane. Several reports have discussed the interaction of PNVP with other polymers, surfactants, and adsorbents.[20–22]

Chitosan, normally obtained by alkaline deacetylation of chitin, has been reported to be a promising polymer not only in the chemical field, but also in medical and industrial areas.[23,24] Chitosan, a linear polymer of mainly glucosamine, which behaves as a linear polyelectrolyte at acidic pH, is nontoxic and bioabsorbable. At pH below 6.5, chitosan in solution carries a high positive charge density, one charge per glucosamine unit. 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.[25,26]

Peniche et al.[27] reported the swelling behavior of chitosan/PAA interpenetrating network (IPN) gels that were prepared by radical polymerization of AA activated at low temperature, in an aqueous/alcoholic chitosan dispersion. Hu et al.[28] studied the chitosan–PAA complex nanoparticles, which were well dispersed and stable in aqueous solution, prepared by template polymerization of AA in chitosan solution. The complex nanoparticles are used as silk peptide release material. Cho et al.[29] reported on mucoadhesive polymer, composed of chitosan and PAA, that was prepared by template polymerization of acrylic acid in the presence of chitosan. Sen and Güven[30] reported on dynamic deswelling studies of poly(NVP/itaconic acid) (IA) hydrogel, prepared by γ-ray irradiation of a ternary mixture of NVP/IA and

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Contract grant sponsor: Tatung University; contract grant number: B91–1413-01.

TABLE I
Feed Compositions and Yields of the Poly(AA-*co*-VP) Hydrogels

Sample code	AA (mol %)	VP (mol %)	Chitosan (g)	Glutaraldehyde 2% (mL)	NMBA (mol %)	Yield (%)
N7	70	30	0	0	1	90
N8	80	20	0	0	1	92
N9	90	10	0	0	1	97
IPN7	70	30	0.0725	1.5	1	76
IPN8	80	20	0.0725	1.5	1	80
IPN9	90	10	0.0725	1.5	1	89

crosslinking agent, ethylene glycol dimethacrylate (EGDMA), in water at ambient temperature.

The main purpose of this work was to prepare a series of poly(AA-*co*-NVP) copolymeric hydrogels and poly(AA-*co*-NVP)/chitosan IPN hydrogels by photopolymerization and to investigate the swelling behavior and drug-release behavior of the gels. In addition, the pH sensitivity and the gel strength for these gels were also investigated.

EXPERMENTAL

Materials

Acrylic acid (AA), chitosan ($M_n \sim 1.5 \times 10^5$), and α,α-diethoxyacetophenone (DEAP) as photoinitiator were purchased from Fluka Chemical Company (St. Gallen, Switzerland). *N*-Vinyl pyrrolidone (NVP) was purchased from Aldrich Chemical Company (St. Louis, MO). *N,N'*-Methylene bis(acrylamide) (NMBA) as a crosslinker was purchased from Sigma Chemical Company (St. Louis, MO). Caffeine, vitamin B_{12}, phenol red, and neutral red as model drugs were purchased from Sigma and Fluka Chemical, respectively. All compounds were used as received, except that AA was purified by vacuum distillation under 29°C/6 mmHg.

Preparation of hydrogels

Poly(AA-*co*-NVP) copolymeric hydrogels

Various molar ratios of AA, NVP, and 1 mol % NMBA based on the total monomers were dissolved in 10 mL deionized water. To this solution, 1 mol % DEAP as photoinitiator was added, and the mixture was immediately injected into the space between two glass plates. The thickness of the gel membrane was adjusted with a 1.5-mm silicone spacer between two glass plates. Polymerization was carried out by exposing the monomer solution to UV light for 10 min. After the gelation was completed, the membrane was cut into disks and immersed in deionized water for 2 days to remove the residual unreacted monomers. Swollen polymer gels were dried at room temperature for 2 days, and then dried in a 60°C vacuum oven for 1 day. The thickness of the dried gel was about 1–1.5 mm and the diameter was about 4–5 mm.

Poly(AA-*co*-NVP)/chitosan IPN hydrogels

Various molar ratios of AA, NVP, chitosan (0.0725 g), and 1 mol % NMBA based on the total monomers were dissolved in 8.5 mL deionized water. To this solution, 1 mol % DEAP as photoinitiator and 1.5 mL of 2% glutaraldehyde solution as a crosslinker 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 1.5-mm silicone spacer between two glass plates. Polymerization was carried out by exposing the mixture to UV light. After the gelation was completed, the membrane was cut into disks and immersed in an excess amount of a 1% acetic acid solution for 2 days to remove the residual unreacted monomers and chitosan. Swollen polymer gels were dried at room temperature for 2 days, and then dried in a 60°C vacuum oven for 1 day. The thickness of the dried gel was about 1–1.5 mm and the diameter was about 4–5 mm. The feed compositions and yields for the synthesized gel are listed in Table I.

Measurement of equilibrium swelling ratio

The dried gels were immersed in 10 mL of deionized water, or in various pH buffer solutions, at 25°C until swelling equilibrium was attained. The pH values of the various solutions, adjusted by an aqueous solution of HCl, KCl, $KHC_8H_4O_4$ (potassium hydrogen phthalate), NaOH, KH_2PO_4, and H_3PO_3, were measured with a pH meter (Radiometer PHM95) calibrated by a standard buffer solution. The weight of the wet sample (W_w) was determined after removing the surface water by blotting with filter paper. The weight of the dry sample (W_d) was determined after drying the gel in a vacuum oven for 1 day. The swelling ratio (Q) based on W_w and W_d was then calculated by the following equation:

$$Q = \frac{W_w - W_d}{W_d} \quad (1)$$

Swelling kinetics

The dried gels were immersed in an excess of deionized water. The swelling ratio was obtained by weighing the initial and swollen samples at various time intervals. The amount of water sorbed W_t was reported as a function of time, and the equilibrium sorption at infinitely long time was designated as W_∞. Equation (2) can be used to calculate the diffusion coefficient D for $W_t/W_\infty \leqq 0.8$[31]:

$$W_t/W_\infty = (4/\pi^{0.5})(Dt/L^2)^{0.5} \quad (2)$$

where t is the time and L is the initial thickness of the dried gel.

Drug-release behavior

The model drugs used for the release experiment were caffeine, vitamin B_{12}, phenol red, and neutral red. The dry gels were equilibrated in 3 mg (caffeine, vitamin B_{12}, phenol red, neutral red)/10 mL of deionized water at 25°C for 2 days to load drug into the gels.

The drug-release experiments were carried out by transferring previously incubated drug gels into 10 mL fresh model gastric juices, model intestinal juice, or deionized water at 37°C. The gels were repeatedly removed and transferred into 10 mL fresh model gastric juices, model intestinal juice, or deionized water at each fixed time interval. The released drug was analyzed, at 273 nm for caffeine, at 360 nm for vitamin B_{12}, at 431 nm for phenol red, and at 275 nm for neutral red, by an ultraviolet spectrophotometer (Jasco V-530; Jasco, Tokyo, Japan).

Determination of partition coefficient

Two gel disks were swelled in deionized water for 1 day, and then immersed in 10 mL of 50 ppm drug solution until the diffusion of drug was completed. The final concentration of drug solution was determined by using a UV spectrophotometer for caffeine at 273 nm, Vitamin B_{12} at 360 nm,phenol red at 430 nm, and neutral red at 27 5nm. The partition coefficient (K_d) is defined as[32]

$$K_d = C_m/C_s = V_s(C_i - C_0)/V_mC_0 \quad (3)$$

where C_m and C_s are the concentrations of drug inside the membrane and in the surrounding solution at equilibrium, respectivel; C_i is the initial concentration of drug in the solution; C_0 is the concentration of drug at equilibrium; V_s is the volume of drug solution; and V_m is the volume of membrane at equilibrium of swelling.

Uniaxial compression experiment

The swollen sample gel was tested using a universal tester (Lloyd LRX, Hampshire, UK) with a crosshead speed at 1 mm/min. Equation (4) was used to calculate the shear modulus G of the gel.

$$\tau = F/A_0 = G(\lambda - \lambda^{-2}) \quad (4)$$

where τ is the compression stress, F is the compression load, A_0 is the initial cross-sectional area of the swollen gels, λ is the compression strain (L/L_0, where L_0 is the initial sample length). At low strains, a plot of τ versus $-(\lambda - \lambda^{-2})$ yields 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 fraction (υ_2) as follows[33]:

$$\rho_x = G\upsilon_2^{-1/3}/RT \quad (5)$$

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

RESULTS AND DISCUSSION

Characterization of the poly(AA-*co*-NVP)/chitosan gels

The feed compositions and yields of the presented hydrogels are as shown in Table I. N7, N8, and N9 represent 70, 80, and 90 mol % AA in the hydrogel, respectively; IPN7, IPN8, and IPN9 represent the corresponding interpenetrating hydrogels containing crosslinked chitosan. The yields of IPN gels, shown in Table I, are lower than those of the N-series gels. This is because the viscosity of polymerization medium increased as chitosan was added. The swelling ratios as a function of time for poly(AA-*co*-NVP)/chitosan hydrogels at 25°C in deionized water are shown in Figure 1. The results indicate that the swelling ratios of poly(AA-*co*-NVP)/chitosan gels increase with an increase of AA. The reason is that the more carboxylic groups (−COOH) would be dissociated when more AA was added in the gel. The results also indicate that the swelling ratio of IPN gel (IPN9) is lower than that of poly(AA-*co*-NVP) gel (N9). This is because the addition of crosslinked chitosan into the poly(AA-*co*-NVP) hydrogel causes the gel network to become denser.

Investigation of swelling kinetics in the xerogels

To investigate the diffusion model of the gel, the initial swelling data were fitted to the exponential heuristic equation for $W_t/W_\infty \leqq 0.6$.[34,35]

$$W_t/W_\infty = Kt^n \quad (6)$$

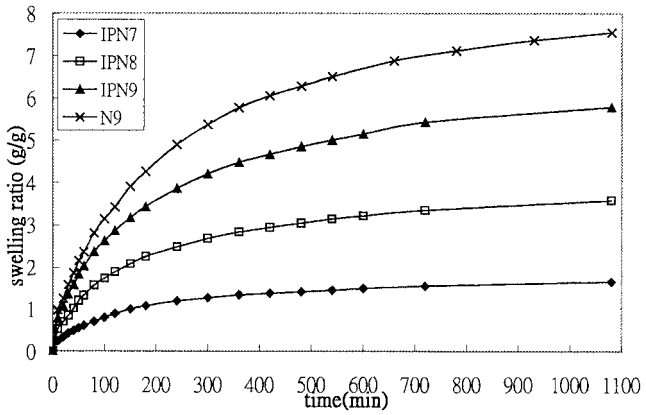

Figure 1 Swelling ratios as a function of time for poly(AA-*co*-VP) and poly(AA-*co*-VP)/chitosan IPN hydrogel in water at 25°C.

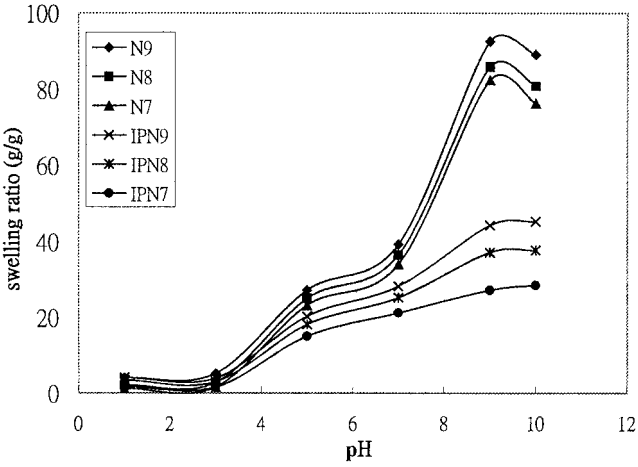

Figure 2 Equilibrium swelling ratios as a function of pH for poly(AA-*co*-NVP)/chitosan gels at 25°C.

where K is a characteristic constant of the gel and n is a characteristic exponent of the mode transport of the penetrate. Values n and K were calculated from the slopes and intercepts of the plot of $\log(W_t/W_\infty)$ against $\log t$, respectively. From eq. (2), the diffusion coefficient D can be calculated from the slope of the plot W_t/W_∞ against $(t/L^2)^{0.5}$. Hence, the results shown in Table II indicate that the values of n for the gels in deionized water are below 0.5, but the n values for the gels in pH 5 buffer solutions are above 0.5. These results imply that the transport mechanism belongs to Fickian transport and non-Fickian transport for the gels in deionized water and pH 5 buffer solution, respectively, according to the distinction of transport mechanism mode proposed by Alfrey et al.[36]

The data shown in Table II indicate that the diffusion coefficients D for the gels increase with increase in swelling ratio of the gels (i.e., N9 > N8 > N7; IPN9 > IPN8 > IPN7).

TABLE II
Initial Diffusion Coefficient of Water D, Kinetic Exponent *n*, and Characteristic Constant *k* Through Copolymeric Gel Under Deionized Water and pH 5 Buffer Solution

Sample code	n	k	$D \times 10^8$ (cm^2/s)	Q (g/g)
Deionized water				
N7	0.17	0.27	4.8	2.01
N8	0.26	0.16	5.1	3.98
N9	0.36	0.09	5.49	7.92
IPN7	0.15	0.33	3.52	1.81
IPN8	0.26	0.173	4.65	3.65
IPN9	0.32	0.12	5.33	5.92
pH = 5 buffer				
N7	0.59	0.82	7.11	22
N8	0.59	0.83	7.38	25
N9	0.6	0.86	7.9	28
IPN7	0.6	0.02	5.64	14.6
IPN8	0.59	0.02	6.63	17.8
IPN9	0.58	0.03	7.47	19.8

Effect of pH on equilibrium swelling ratio for poly(AA-*co*-VP)/chitosan gels

The equilibrium swelling ratios for the present hydrogels in different pH solutions, shown in Figure 2, indicate that the swelling ratios increase with an increase of pH value in the buffer solutions. This is because poly(AA-*co*-NVP) gels have pH sensitivity in the buffer solutions. In alkali solution, the deprotonation of carboxylic groups (–COOH) in the poly(AA-*co*-NVP) gel develops an internal ion osmotic pressure and induces the gel to swell. The results indicate that the swelling ratios of poly(AA-*co*-NVP) gels decrease with the addition of NVP. Similar results were observed from the IPN hydrogels, although the swelling ratios of poly(AA-*co*-NVP) gels decrease above pH 9. This is because the relaxed chains are compressed by

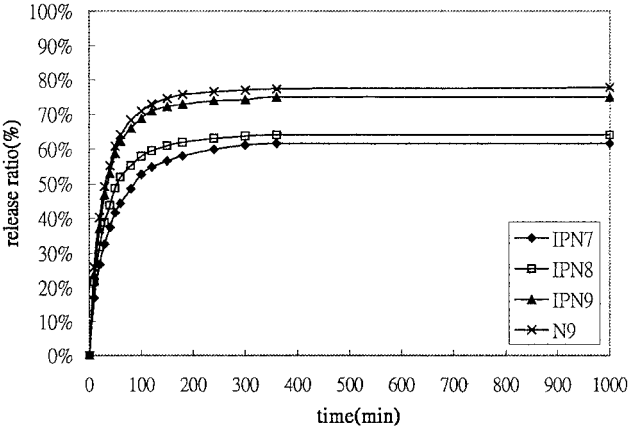

Figure 3 Caffeine release profile for poly(AA-*co*-NVP)/chitosan gels in deionized water at 37°C.

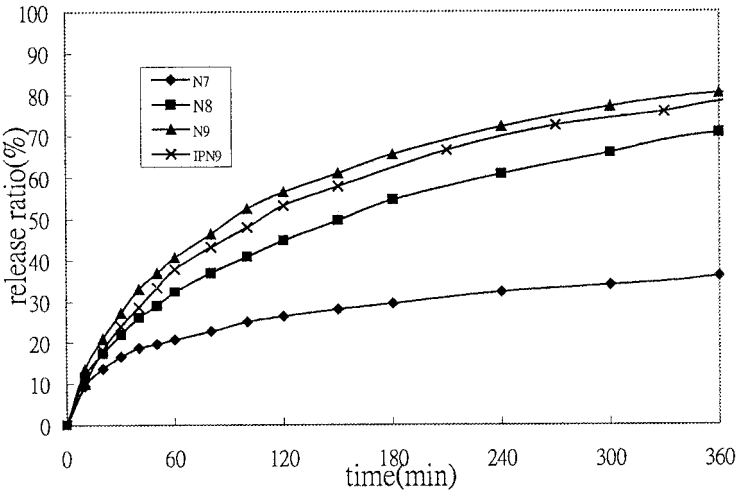

Figure 4 Vitamin B_{12} release profile for poly(AA-*co*-NVP)/chitosan gels in deionized water at 37°C.

ion strength of the buffer solution outside the gel; however, because the network structure of IPN gel is denser, the compression effect is not apparent.

Drug-release behavior for poly(AA-*co*-NVP)/chitosan gels

Figure 3 shows the release profile of caffeine for the poly(AA-*co*-NVP)/chitosan gels loading at 25°C in the caffeine solution and releasing at 37°C in deionized water. Because the drug release was carried out in deionized water at 37°C, the drug in the gels could be released as a result of the gel volume change and the concentration gradient of the drug. In addition, Figure 3 also shows that the fractional release is directly proportional to the swelling ratio of the gels, that is, N9 > IPN9 > IPN8 > IPN7 (also see Table II). This result indicates that the higher swelling ratios of the hydrogels create larger surface areas to diffuse the drug. However, the IPN gels possess two interpenetrating networks and restrict the releasing of the drug inside the hydrogels.

Figure 4 shows the vitamin B_{12} release profile for the poly(AA-*co*-NVP) and IPN9 gels. The tendency of vitamin B_{12} release is in the order N9 > IPN9 > N8 > N7, a tendency that also follows their swelling ratios (see Table II). The reason is the same as that of caffeine release in deionized water. However, the molecular size of vitamin B_{12} is larger than that of caffeine, and thus the release rate of vitamin B_{12} is slower.

Figure 5 shows the release profile of vitamin B_{12} for the poly(AA-*co*-NVP) gels and IPN9 gel loading at 25°C in the vitamin B_{12} solution and releasing at 37°C, in simulated gastric juice for the initial 2 h, then the incubated gel was transferred into simulated intestinal juice. Figure 5 shows that the fractional drug release is in the order N9 > IPN9 > N8 > N7. Because the initial environment of drug release is simulated gastric juices (pH = 2), the chains of the gels containing more AA (N9 or IPN9) would thus shrink more. This compression effect is more obvious for N9 or IPN9 gel. When the gels transferred into simulated intestinal juice (pH = 7.4), however, the carboxylic groups in the gels were dissociated and the formation of carboxylate groups caused the gel network structure to expand. This behavior is much in favor of N7 gel and increases the drug-release rate.

Figure 6 shows the release profile of phenol red (model anionic drug) for the gels loading at 25°C in the phenol red solution and releasing at 37°C in deionized water. It also shows that the tendency of the fractional release is in the order N9 > N8 > IPN9 > N7. This is attributed to the negative charge repulsion between the carboxylic group and the phenol red; thus the greater the amount of AA in the gel, the stronger the charge repulsion, and the higher the drug release.

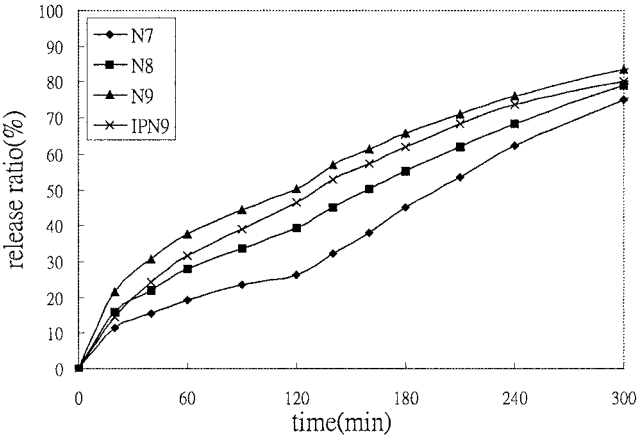

Figure 5 Vitamin B_{12} release profile for poly(AA-*co*-NVP)/chitosan gels in simulated gastric juice and in simulated intestinal juice at 37°C.

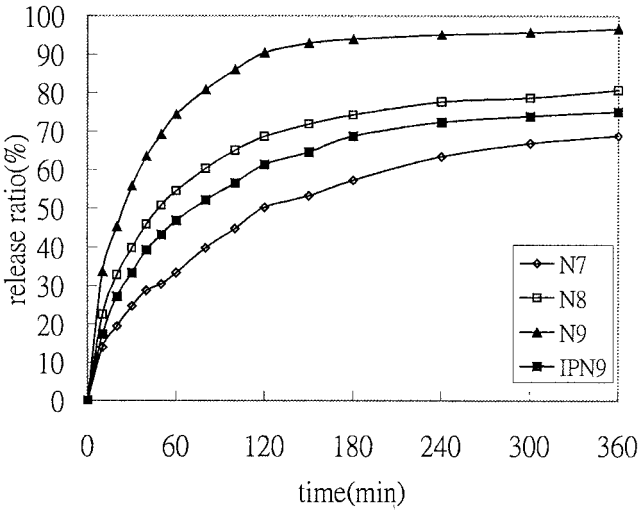

Figure 6 Phenol red release profile for poly(AA-*co*-NVP)/chitosan gels in deionized water at 37°C.

Figure 7 shows the release profile of cationic neutral red for the present gels loading at 25°C in the neutral red solution and releasing at 37°C in deionized water. The results in Figure 7 show that no drug was released from the gels, which is attributed to the stronger ionic attraction between the carboxylate group in the gel and the drug. To explain this behavior, the incubated-drug gels were released at 37°C in physiological saline (0.9 wt % NaCl). A significant release profile, different from that in Figure 7, is shown in Figure 8. This release behavior is attributed to the sodium ion to exchange the neutral red binding on the gels. This ion-exchange effect was also observed from our previous study.[37] The results in Figure 8 show that the fractional release of neutral red from the gels is in the order IPN9 > IPN8 > N7 > N9 > N8. Obviously, this release behavior is not related to the gel composition and the swelling ratio of the gel, but related to the drug loading amount, which is N9 = N8 (190 ppm) > N7 (100 ppm) > IPN9 = IPN8 (70 ppm). Hence, the fractional release of IPN9 is fastest because of the lower drug loading in the gel.

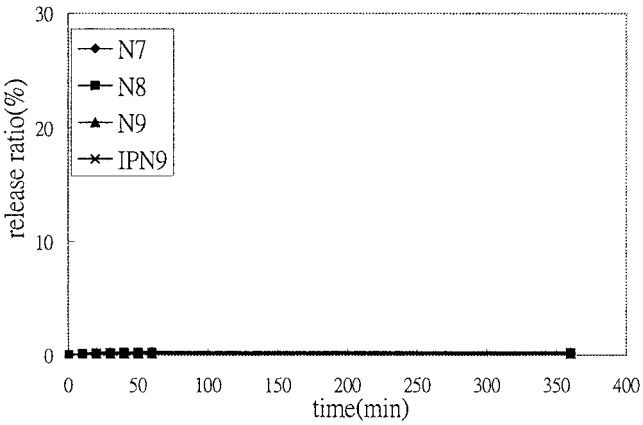

Figure 7 Neutral red release profile for poly(AA-*co*-NVP)/chitosan gels in deionized water at 37°C.

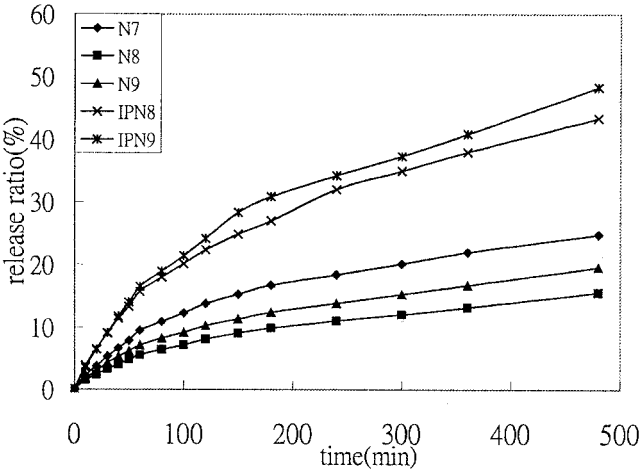

Figure 8 Neutral red release profile for poly(AA-*co*-NVP)/chitosan gels in physiological saline at 37°C.

Interaction between drug and gels

The partition coefficients (K_d) of various drugs in the present gels were examined. In general, the larger the K_d value, the stronger the interaction of drug to the gels and the more difficult was the drug release in the gel. The K_d values of various drugs in the synthesized gels are listed in Table III. For caffeine and vitamin B_{12}, the K_d values increase with an increase of AA in the gels. The K_d value of vitamin B_{12} is larger than that of caffeine, so the drug release is lower than that in caffeine (see Figs. 3 and 4). The K_d value of the caffeine is larger than that of phenol red, so the phenol red release is more rapid than that for caffeine (see Figs. 3 and 6). For a cationic drug, such as neutral red, the K_d value is largest because of the stronger ionic attraction between the gels and neutral red, so neutral red cannot be released from the gels (see Fig. 7).

TABLE III
Partition Coefficient of Various Drugs in Deionized Water for the Synthesized Hydrogel[a]

Sample code	Caffeine	Vitamin B_{12}	Phenol red	Neutral red
N9	420	2357	5	∞
N8	314	1692	6	∞
N7	205	1075	7	∞
IPN9	181	493	4	∞
IPN8	148	480	6	∞

[a] The initial drug loading amount is 300 ppm.

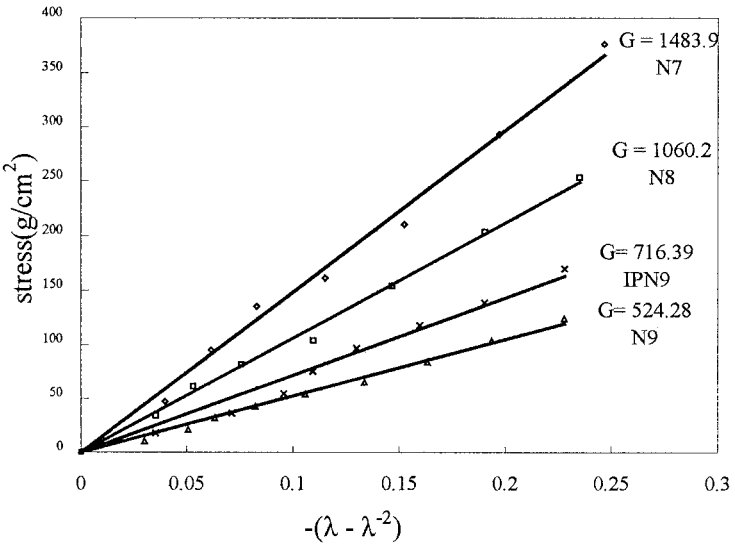

Figure 9 Stress–strain curves for poly(AA-*co*-NVP)/chitosan gels at 25°C.

Effect of crosslinked chitosan on gel strength and crosslinking densities for poly(AA-*co*-NVP)/chitosan hydrogels

The stress–strain curves for a series of poly(AA-*co*-NVP)/chitosan hydrogels, in the swollen state at 25°C, are shown in Figure 9. The slope of the straight line is the shear modulus (G), and the value represents the gel strength of a gel. The crosslinking densities of the hydrogels, calculated from eq. (3), are listed in Table IV. Figure 9 shows that IPN9 has a higher G value than that of the corresponding N9 gel. This is because the IPN gel has a larger crosslinking density and strengthens the gel. Figure 9 also shows that the G value is higher for the gels containing more NVP. This is because the complexation effect between PAA and PVP strengthens the gels.[38,39] Results in Table IV also indicate that the crosslinking densities of the hydrogels increase with increase in the shear modulus of the hydrogels.

CONCLUSIONS

The experimental results showed that the addition of crosslinked chitosan to the poly(AA-*co*-NVP) hydrogel caused the gel network to become denser. The swelling ratios of the present gels decreased with the addition of chitosan and also decreased with increase in NVP content, but increased with an increase of pH value of the buffer solutions under pH 9. The gel strength increased with increases in NVP content in the gel and chitosan addition in the gel compositions. In caffeine and vitamin B_{12} release experiments, results showed that the higher the swelling ratio of the gels, the higher the fractional release of the gels. In phenol red release experiments, the results showed that the greater the amount of AA in the gel, the stronger the ion repulsion, and the faster the drug release. In neutral red release experiments, the results showed that the cationic neutral red cannot be released from the anionic gel in deionized water, but can sustain release in physiological saline because of the ion exchange effect.

TABLE IV
Shear Moduli and Crosslinking Densities of the Present Hydrogels

Sample code	G (g/cm^2)	$\rho_x \times 10^5$ (mol/cm^3)
N7	1483.9	7.12
N8	1060.2	6.67
N9	524.3	5.25
IPN9	716.4	6.19

The authors thank Tatung University for financial support under Grant B91–1413-01.

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