Effect of Hydrotalcite on the Swelling and Mechanical Behaviors for the Hybrid Nanocomposite Hydrogels Based on Gelatin and Hydrotalcite

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ABSTRACT: A series of hybrid nanocomposite hydrogels, based on gelatin and intercalated hydrotalcite (IHT), crosslinked with glutaraldehyde, was prepared in this study. The microstructures of the IHT and sample gels were identified by X-ray diffraction (XRD). Swelling behaviors and physical properties of these hybrid gels were investigated. XRD results indicated that exfoliation of IHT was achieved in the hybrid nanocomposite gels. The results indicated that adding a small amount of IHT could effectively decrease the swelling ratio of the hybrid gels, but adding excess IHT could increase the swelling ratio of the nanocomposite hybrid gels. The crosslinking densities (ρ_x) of the present gels varied with IHT content and swelling ratio of the gels. The drug release behaviors of these gels were also investigated. © 2006 Wiley Periodicals, Inc. J Appl Polym Sci 100: 500–507, 2006

Key words: gelatin; hydrotalcite; nanocomposite hybrid gel

INTRODUCTION

Hydrogels are three-dimensional hydrophilic polymers, which swell but do not dissolve when brought into contact with water, and they sometimes undergo a volume phase change in response to a change in surrounding conditions, such as temperature,[1,2] pH,[3] ionic strength,[4] and electric field.[5,6]

Gelatin is usually obtained by thermal denaturation or physical and chemical denaturation of collagen, which is the most widespread protein in the body occurring in most connective tissues as skin, tendon, and bone.[7–9] Food, pharmaceutical, and photographic industries are the main users of gelatin, which has several other technical applications. Its most frequent uses in the biomedical field include hard and soft capsules, microspheres, wound dressing and adsorbent pad for surgical use; furthermore, it is much cheaper and easier to obtain in concentrate solutions.[7,8,10] At a temperature of about 40°C, gelatin solutions are in the sol state and change into gels when they are cooled down to room temperature, provided that their concentration is high enough.[11] The sol–gel transformation is due to a conformational disorder–order transition of the gelatin chains, which form thermoreversible networks by associating helices in junction zones stabilized by hydrogen bonds. The mechanism of gelation and the properties of gelatin gels have been extensively investigated.[11–13] On the other hand, gelatin exhibits poor mechanical properties, which limits its possible applications as a biomaterial. Therefore, reinforcing gelatin materials has been a challenge for researchers. Many attempts, such as gelatin-based composites filled with montmorillonite,[14] hydroxyapatite,[15] tricalcium phosphate,[16] and carbon fiber[17], have been made.

Hydrotalcite (HT), a type of layered doubled hydroxide (LDH), occurs as a natural mineral and can be synthesized by reacting dilute aqueous solutions of magnesium and aluminum chlorides with sodium carbonate.[18] The material consists of stacks of mixed hydroxide layers of Mg and Al, which are positively charged and requires the presence of interlayer anions to maintain overall charge neutrality.[19,20] The anion exchange capacity of such materials is controlled by the Mg^{2+}/Al^{3+} ratio. Their general composition can be represented as $[M^{II}_{1-X}M^{III}_{X}(OH)_2]^{X+} \cdot [A^{q-}_{x/q} \cdot nH_2O]$, where M^{II} and M^{III} are divalent and trivalent cations, respectively, and A^{q-} is an exchangeable anion.

In this study, at first, the hydrotalcite was intercalated by an intercalating agent AMPS. Then, a series of hydrogels based on gelatin and intercalated-HT (IHT) were prepared by crosslinking with

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glutaraldehyde. The effect of different contents of IHT in the hybrid nanocomposite gels on the swelling behavior and physical properties was investigated. In addition, the drug release behavior of these gels was also investigated.

EXPERIMENTAL

Materials

Gelatin from porcine skin, type A, 300 Bloom, isoelectric point (IEP) ranging from pH 7 to 9, corresponding to a molecular weight range of 50–100 kDa (SIGMA Chemical Co., St. Louis, MO) as a natural polymer was used as received. Glutaraldehyde (GA) (Wako Pure Chemical Co. Ltd., Osaka, Japan) as gelatin crosslinking agent was used as received. Hydrotalcite (HT) (Aldrich Chemical Co., Milwaukee, WI) had anion exchange capacity (AEC) of about 350 meq/100 g. 2-Acryloylamido-2-methyl propane sulfonic acid (AMPS) (Fluka Chemical Co., Buchs, Switzerland) as intercalating agent of hydrotalcite was used as received.

Intercalation of HT

The quantity of the intercalating agent required was calculated by following equation. It means that the equivalence of ion exchange of HT is equal to the equivalence of intercalating agent (AMPS).

$$AEC \times (W_{HT}/100) \times 10^{-3} - W_{IA}/M_{IA} \times 1/E_{IA} \quad (1)$$

$$W_{RIA} = W_{IA} \times \text{multiple}$$

where W_{HT} is the weight of HT (g), W_{IA} is the weight of intercalating agent (g), M_{IA} is the molecular weight of intercalating agent (mol/g), E_{IA} is the equivalence of intercalating agent, and W_{RIA} is the required weight of intercalating agent (g).

A suspension solution containing 5 g of HT and 3.62 g of AMPS was mixed in 500 mL of *N*,*N*-dimethyl acetamide (DMAc). The suspension solution was stirred at 70°C for 24 h. Then, the intercalated HT was separated by centrifugation and washed with a large volume of water to remove un-intercalated AMPS. The sample was dried in the vacuum oven at 40°C for 3 days.

Preparation of gelatin/IHT hybrid nanocomposite hydrogels

Gelatin powder (1 g) was soaked in 10 mL of deionized water (18.2 MΩ cm) and stirred at 60°C, a homogeneous solution was obtained (the pH of the gelatin was adjusted by a solution of NaOH to pH = 10, above the isoelectric point). The intercalated HT (IHT), with various weight ratios based on gelatin weight, was then poured in and mixed thoroughly at 60°C. Then, the mixture was immediately injected into the space between two glass plates. The gel membrane thickness was adjusted with a silicone spacer between the two glass plates. Physical crosslinking was carried out at 5°C for 2 h. After the gelation was completed, the gel membrane was further crosslinked with 20 mL of 1 wt % glutaraldehyde for 24 h at room temperature. After this crosslinking reaction was completed, the gel membrane was cut into disks, 10 mm in diameter, and then immersed in an excess of deionized water for 1 day to remove the residual unreacted glutaraldehyde. The hybrid gels were dried at 40°C for 3 days, and then further dried in a 25°C vacuum oven for 1 day.

X-ray diffraction analysis

Powder XRD analyses were performed by using a MAC Science X-ray powder diffractometer with Cu anode (model M21X, Osaka, Japan), running at 40 kV and 30 mA, scanning from 2° to 13° at 3°/min. The structure of the HT was determined at different stages of the nanocomposite synthesis. The HT powders were mounted on a sample holder with a large cavity and a smooth surface was obtained by pressing the powders with a glass plate. Analyses of the HT swollen in the gels were performed by spreading the mixture on a gel membrane disc (50-mm diameter, 2-mm thin) used as sample holder. It was designed so that a maximum surface could be irradiated at low angle, giving an optimum intensity to the XRD signal. The nanocomposite plates produced during the molding process had a fairly smooth surface.

FTIR analysis

Fourier transform infrared spectra were recorded from pressed KBr pellets containing about 1% of the HT and intercalated HT, respectively, using a Horiba FT/IR-720 spectrophotomer (Kyoto, Japan).

Zeta-potential analysis

The dried gel powder (30 mg) was immersed in 20 mL of deionized water. The zeta-potential of each sample was measured by a zeta-meter microscope 3.0+ (Staunton, USA).

Measurement of swelling ratio

The preweighed dried gels (W_d) were immersed in an excess amount of deionized water at 25°C until swelling equilibrium was attained. Each gel was then removed from the water bath, tapped with filter paper to remove excess surface water, and weighed as the wet weight (W_w). The swelling ratio (SR) was calculated from the following equation:

$$SR = \left(\frac{W_w - W_d}{W_d}\right) \tag{2}$$

Measurement of dynamic swelling

The dried gels were immersed in an excess amount of deionized water at 25°C. The swelling ratio was obtained by weighing the initial and swollen samples at various time intervals. The amount of water absorbed, W_t, was reported as a function of time, and the equilibrium absorption at infinitely long time was designated as W_∞. The eq. (3) was used to calculate the diffusion coefficient D for $W_t/W_\infty \leq 0.8$.[21]

$$\frac{W_t}{W_\infty} = \left(\frac{4}{\pi^{0.5}}\right)\left(\frac{Dt}{L^2}\right)^{0.5} \tag{3}$$

where t is the time and L is the initial thickness of the dried gel. To investigate the diffusion model of the gel, the initial swelling data were fitted to the exponential heuristic equation for W_t/W_∞ [leq] 0.6.[22,23]

$$\frac{W_t}{W_\infty} = Kt^n \tag{4}$$

where K is a characteristic constant of the gel and n is a characteristic exponent of the mode transport of the penetrate.

Measurement of physical properties

The gel strengths of these samples were measured by uniaxial compression experiments with universal a tester (LLOYD LRX). The eq. (5) was used to calculate the shear modulus:[24,25]

$$\tau = \mathrm{F/A} = \mathrm{G}(\lambda - \lambda^{-2}) \tag{5}$$

where τ is compression stress, F is compression load, A is cross-sectional area of swollen gels, and λ is compression strain (L/L_0). At low strains, a plot of shear stress versus $-(\lambda - \lambda^{-2})$ would yield a straight line whose slope is shear modulus (G). The effective

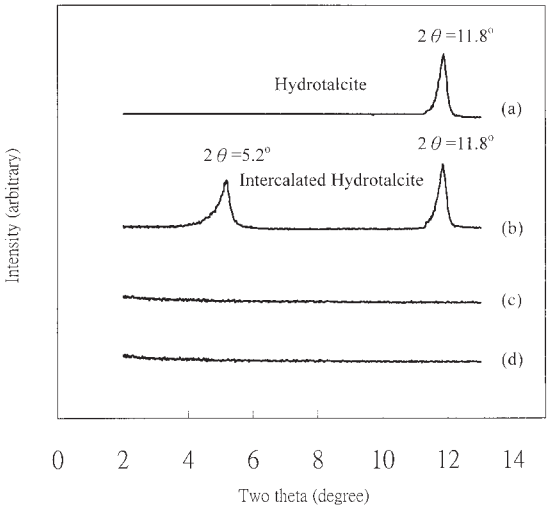

Figure 1 The XRD patterns of HT (a), Intercalated HT (b), GHT3 dried state (c) and swollen state (d).

crosslink density (ρ_x) can then be calculated from the shear modulus and polymer volume fraction (ν_2) as follows:

$$\rho_x = \mathrm{G}/\mathrm{v}_2^{1/3}\mathrm{RT} \tag{6}$$

where R is the gas constant (8.48×10^4 g cm/mol K) and T is the absolute temperature.

Drug release experiments

Phenol red (M_w = 354) and neutral red (M_w = 288), chosen as model drugs, were used in drug release experiments. The dry gels were equilibrated in drug solution at 25°C for 1 day to load drug into the gels. The drug release experiments were carried out by transferring previously incubated-drug gels into 10 mL 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 drugs were analyzed by an ultraviolet spectrophotometer (JASCO V530, Tokyo Japan) for phenol red at 430 nm, and for neutral red at 275 nm, respectively.

Morphology

Samples were equilibrated in deionized water for 2 days and the swollen gels were frozen to −80°C and then fractured and freeze-dried. The morphologies of the fractured specimens were examined using scanning electron microscopy (SEM; JEOL JXA8600, Tokyo, Japan) with an acceleration voltage of 15 kV. The specimens were coated with a gold metal layer to provide proper surface conduction.

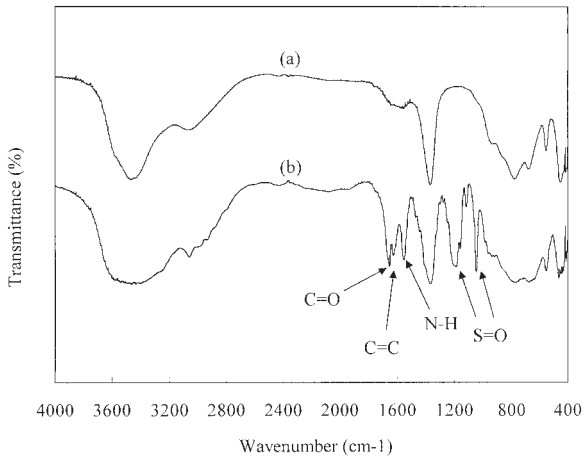

Figure 2 The FTIR spectra of (a) HT and (b) Intercalated HT.

RESULTS AND DISCUSSION

Identification of the hybrid nanocomposite hydrogels

The XRD patterns of various samples are plotted in Figure 1. A typical XRD pattern of HT, with a strong peak corresponding to a basal spacing of 7.49 Å, is shown in Figure 1. After treatment with AMPS, a new peak appeared, corresponding to basal spacing of 16.97 Å. This result shows that the AMPS is intercalated between the layers during the anion-exchange process adopting a lateral bilayer structure. For the AMPS-HT, two peaks are present at $2\theta = 5.2°$ and $2\theta = 11.8°$. This indicates that both AMPS and carbonate group are present in the interlayer galleries of the AMPS-HT. The result in Figure 1 shows that the carbonate group content is approximately equal to the AMPS content. Therefore, AMPS (having one charge) cannot exchange carbonate group (having two charges) completely. After the crosslinking reaction, both the xerogels and the swollen gels were also analyzed by XRD.

The XRD patterns for the representative GHT3 gel in dry and swollen state are also shown in Figure 1. GHT3 represents 3 wt % IHT dispersed in the gelatin hydrogel and crosslinked with 1 wt % glutaraldehyde. The results indicate that the diffraction peak disappears in all samples. This result demonstrates that the intercalated HT incorporated into the gels was completely exfoliated.

FTIR analysis

The FTIR spectra of the hydrotalcite and AMPS–hydrotalcite are shown in Figure 2, respectively. For AMPS–hydrotalcite, strong absorption peaks of asymmetric and symmetric $R—COO^-$ group appear at 1610 and 1375 cm^{-1}, respectively. The characteristic absorption peaks of C═O stretching, C═C stretching, N—H bending, asymmetric stretching S═O, and symmetric stretching S═O appear at 1658, 1630, 1558, 1205, and 1049 cm^{-1}, respectively. This result indicates that the AMPS was intercalated into the HT layer [Fig. 2(b)].

Effect of IHT content on equilibrium swelling ratio in deionized water

The effects of IHT content on equilibrium swelling ratio and zeta potential for the present gels are shown in Figure 3. The results show that the equilibrium swelling ratios decrease with increase in the content of IHT until 2 wt %, then the equilibrium-swelling ratio increases gradually. In other words, the greater the IHT content the lower is the swelling ratio, but adding excess IHT could increase swelling ratio for the present gels. This is because gelatin is an amphoteric polyelectrolyte with an isoelectric point ranging from pH 7 to 9, which abounds with $—NH_2$ and —COOH in its molecular chain. But, under higher pH (pH = 10), the carboxylic acid group in the gelatin would ionize into carboxylate group. This result lets the gel possess a net negative charge. Under this condition, an inter- or intramolecular bonding would occur between anionic gelatin gels and cationic IHT nanolayers. Hence, when the content of IHT is 2 wt %, there is a minimum swelling ratio and the net charge approaches to zero in the gels (see the zeta-potential values). That makes the gel network denser. According to Flory's swelling theory,[26] decreasing the fixed charge of the polymer network could decease the swelling ratios.

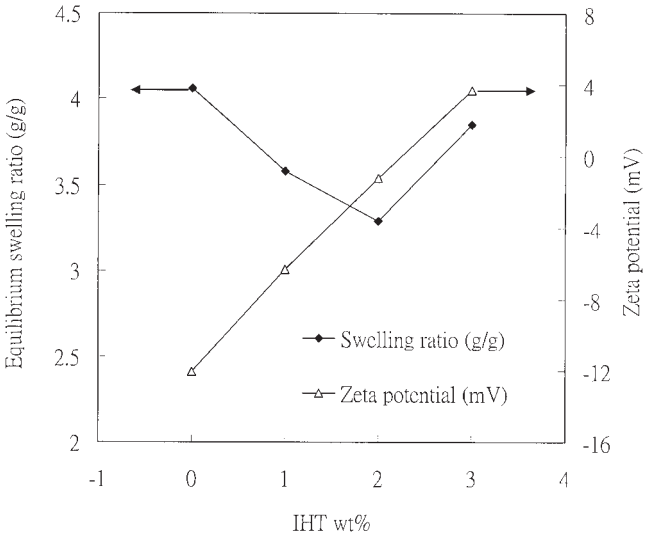

Figure 3 Effect of IHT content on equilibrium swelling ratio and zeta potential of gelatin/IHT nanocomposite hybrid gels.

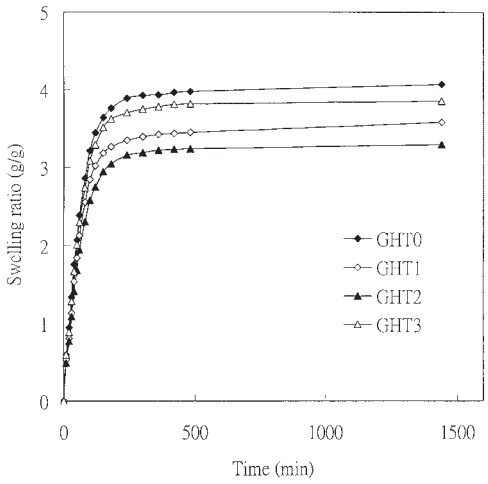

Figure 4 Swelling ratio as a function of time for the gelatin/IHT nanocomposite hybrid gels in deionized water at 25°C.

But when the content of IHT exceeds 2 wt %, the equilibrium-swelling ratio of the gel increases gradually. There are two effects of IHT on the swelling ratio of the present gel. On the one hand, the net charge of the present gel became positive (see the zeta-potential values). According to Flory's swelling theory,[26] increasing the identical charge of the polymer network could increase the swelling ratio. This is due to the charge repulsion of the polymer network in the present hybrid gel. On the other hand, addition of the hydrophilic monomer IHT into the hybrid gel can increase the affinity of the gel toward water, and the swelling ratio increases. The $[M^{II}_{1-X}M^{III}_{X}(OH)_2]^{X+}$ nanolayers were exfoliate and dispersed in the hybrid matrix, making the more $[M^{II}_{1-x}M^{III}_{X}(OH)_2]^{X+}$ nanolayers form and providing the stronger hydration ability of the OH group. This also leads to the nanocomposite hybrid gel becoming more hydrophilic. Hence, the swelling ratios increased with an increase of the content of IHT in the gels.

Swelling kinetics for the nanocomposite hybrid gels in deionized water

The swelling ratios as a function of time for the hybrid gels in deionized water at 25°C are shown in Figure 4. The results indicate that adding a small amount of IHT could effectively decrease swelling ratio of the hybrid gels, but adding excess IHT could increase swelling ratio of the hybrid gel. The n, K, and D values calculated from eqs. (3) and (4) are listed in Table I. The results show that the diffusion coefficients D for the present hybrid gels in deionized water are in the order of GHT3>GHT2>GHT1. These results show that the greater the content of IHT in the hybrid gels, the higher is the rate of water penetrating into the gel during the swelling process. At the same time, the results shown in Table I also indicate that the transport mechanisms for the hybrid gels with a low swelling ratio belong to Fickian transport ($n < 0.5$) according to the classification of diffusion type presented by Alfrey et al.[27]

TABLE I
Fundamental Properties of Gelatin/IHT Nanocomposite Hybrid Gels

Sample codes	Gelatin 10 wt % (mL)	IHT (g)	Equilibrium swelling ratio (g/g)	$D \times 10^7$ (cm^2/sec)	n	$K \times 10^2$
GHT0	10	0	4.06	1.80	0.38	2.58
GHT1	10	0.01	3.58	1.58	0.35	3.38
GHT2	10	0.02	3.29	1.67	0.34	3.73
GHT3	10	0.03	3.85	1.99	0.36	3.07

Effect of IHT content on gel strength and crosslinking densities

The gel strength (G) and crosslinking densities (ρ_x) for these gels, calculated from eqs. (5) and (6), are listed in Table II. The results show that addition of IHT could improve the mechanical properties of gelatin. The gel with only 1 wt % IHT content exhibits a shear modulus of 3070.4 N/cm^2 and a crosslinking density of 2.14×10^{-4} mol/cm^3, which were 1.2 times those of the original gelatin, respectively. When IHT content reaches 2 wt %, the shear modulus and crosslinking density are raised to 3442.5 N/cm^2 and 2.35×10^{-4} mol/cm^3, respectively. This substantial enhancement of the mechanical properties is ascribed to the uniform dispersion of IHT nanolayers in gelatin matrix and the strong interaction between gelatin and IHT, which results in the increased shear modulus and crosslinking densities. But, when the IHT content is over 2 wt %, the shear modulus and crosslinking density begin to decrease. This is because addition of excess hydrophilic IHT into the hybrid gels can increase the

TABLE II
Gel Strength and Crosslinking Density of the Gelatin/IHT Nanocomposite Hybrid Gels

Sample codes	G (N/cm^2)	ρ_x (10^{-4}) (mole/cm^3)
GHT0	2579.5 ± 6.21	1.75 ± 5.64
GHT1	3070.4 ± 7.65	2.14 ± 8.62
GHT2	3442.5 ± 6.23	2.35 ± 6.21
GHT3	2674.6 ± 6.55	1.80 ± 5.34

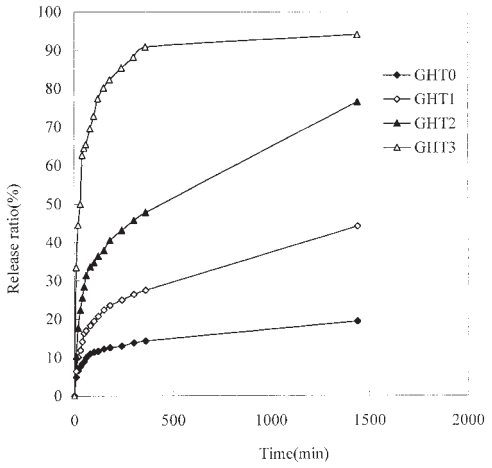

Figure 5 Neutral red release profile during loading at 25°C and releasing at 37°C for the hybrid gels in deionized water.

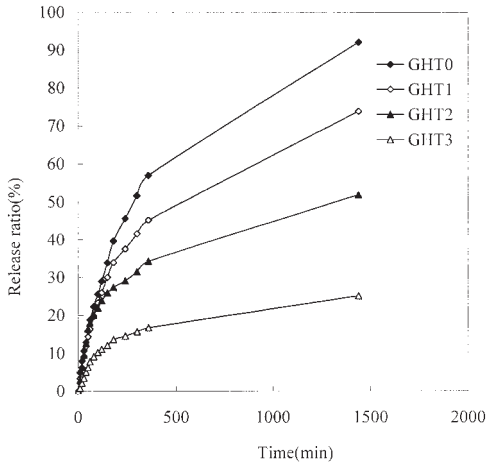

Figure 6 Phenol red release profile during loading at 25°C and releasing at 37°C for the hybrid gels in deionized water.

affinity of the gels for water and make the gel networks looser.

Charge effect of drug on the release behavior

The results of cationic neutral red solutes releasing from gelatin/IHT nanocomposite hybrid gels in deionized water at 37°C are shown in Figure 5. When the charges of the drug solute and the hybrid gel are opposite, attraction exists between them. Therefore, the neutral red solutes strongly bind in the anionic gels (GHT0, GHT1, and GHT2) and are difficult to release from the gel accompanied with unbound water. So the release ratios are lower, but increase with increase in IHT (cationic) content: the loading amounts are higher, but decrease with an increase of IHT content (see Table III). This is because addition of cationic IHT gradually decreases the negative charge of the anionic gels. For cationic GHT3 gel, the interactive force between neutral red and GHT3 gel are smaller than anionic gels, so the release ratio is the highest; the loading amount is the smallest and decreases sharply.

The results of anionic phenol red solutes being released from hybrid nanocomposite hydrogels are shown in Figure 6. Because the charges of phenol red and GHT0, GHT1, and GHT2 gels are the same, the drug release ratios for these gels are higher than those of GHT 3 gels. This is because charge repulsion exists between the phenol red and the gels (GHT0, GHT1, and GHT2): the solute is not easily loaded into the hydrogel but easily released from the gels. Hence, the release ratios are higher but decrease with increase in IHT content; the loading amounts are lower, but increase with increase in IHT content (see Table III). In addition, the interactive forces between phenol red and cationic GHT3 are larger than for anionic gels so the release ratio is the lowest hence the loading amount is the highest and increases sharply.

Based on the above results and description, the net charge of the present gels changes from negative (GHT0, GHT1, and GHT2) to positive (GHT3), which was proven by the zeta-potential experiment.

TABLE III
Drug-Loading Amount and Maximum Release Ratio of Gelatin/IHT Nanocomposite Hybrid Gels

	Neutral red (+) (M_w = 288)		Phenol red (−) (M_w = 354)	
Sample codes	Loading amount (ppm drug/g gel)	Max. release ratio (%)	Loading amount (ppm drug/g gel)	Max. release ratio (%)
GHT0	2020	19.3	462	92.1
GHT1	1864	44.2	479	73.8
GHT2	1483	76.5	576	51.8
GHT3	315	94.1	825	25.1

SEM observation

To understand the microstructure and morphology of the nanocomposite gels, the morphologies of the gels were taken by SEM. The results of the pore size in the nanocomposite hydrogels are shown in Figure 7. We found that the amount of pores increased with the content of IHT and the pore size decreased with increase of IHT and pore channels formed. These results can explain why the gel strength increased with increase in IHT. However, when the

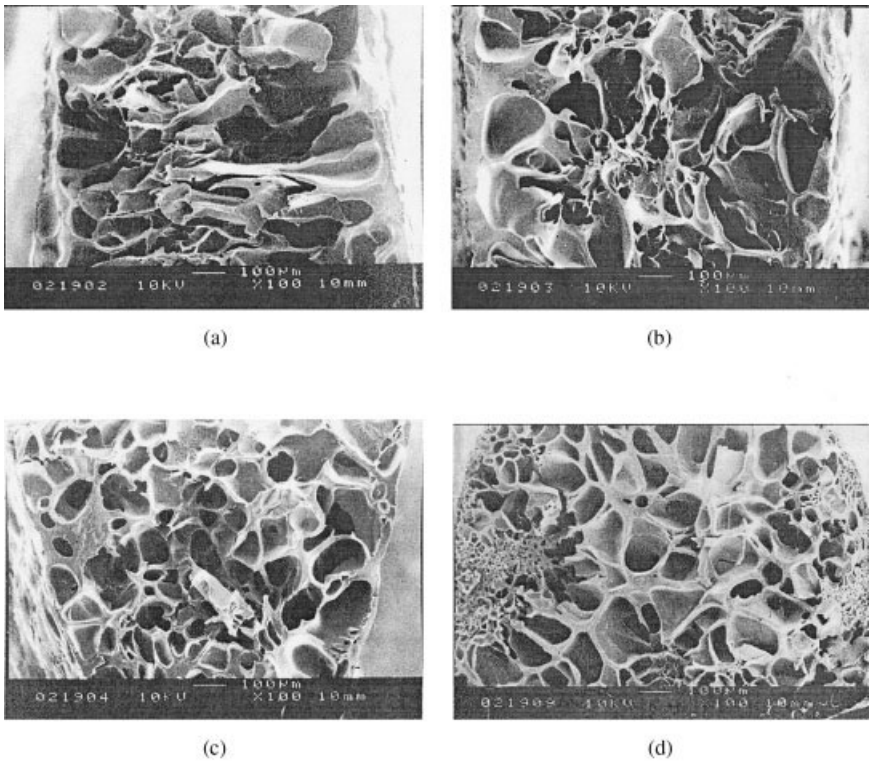

Figure 7 Scanning electron micrograph for the cross section of the gel magnified 100×: (a) GHT0; (b) GHT1; (c) GHT2; (d) GHT3.

IHT content was 3 wt %, the pore size became asymmetric to make the gel strength decrease.

CONCLUSIONS

The experimental results showed that nanocomposite hybrid gels were successfully prepared. The XRD patterns showed that, in the xerogels and the swollen hydrogels, the HT are intercalated and exfoliated. The results showed that adding a small amount of IHT could effectively decrease swelling ratio of the nanocomposite hybrid gels, but adding excess IHT could increase swelling ratio of the nanocomposite hybrid gels. In diffusion transport mechanism, the results indicate that the swelling exponents n for all hybrid gels at 25°C are in the range from 0.34 to 0.38. This implies that the swelling transport mechanism is a Fickian transport. The diffusion coefficients (D) for the gels increase with an increase of IHT content, so water molecules easily infiltrate into the hydrogels for the gels containing more IHT. In addition, the mechanical properties of composite have been improved significantly. The shear modulus and crosslinking density reach maxima when IHT content is 2 wt %. In drug release experiment, the charges of the drug solute also proved that the results of the zeta-potential experiment were correct.

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