

Synthesis and Swelling Properties of pH-Sensitive Hydrogels Based on Chitosan and Poly(methacrylic Acid) Semi-interpenetrating Polymer Network

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ABSTRACT: A novel semi-interpenetrating polymer network (semi-IPN) hydrogel composed of chitosan and poly(methacrylic acid) was synthesized using formaldehyde as a crosslinker. The amount of crosslinker was searched and optimized. The structure of the hydrogel was investigated by Fourier transform infrared (FTIR) spectroscopy. The spectrum shows that a structure of polyelectrolyte complex exists in the hydrogel. The effects of pH, ionic strength, and inorganic salt on the swelling behaviors of the hydrogel were studied. The results indicate the hydrogel has excellent pH sensitivity in the range of pH 1.40 to 4.50, pH reversible response between pH 1.80 and 6.80, and ionic strength re-

versible response between ionic strength 0.2 and 2.0M. The results also show that the hydrogel has a bit higher swelling capacity in a mix solution of calcium chloride (CaCl₂) and hydrochloric acid (HCl) solution than in a mix solution of sodium chloride (NaCl) and HCl. These results were further confirmed through morphological change measured by scanning electron microscope (SEM). © 2005 Wiley Periodicals, Inc. *J Appl Polym Sci* 98: 1720–1726, 2005

Key words: pH sensitivity; hydrogel; semi-interpenetrating polymer network (semi-IPN); chitosan; poly(methacrylic acid)

INTRODUCTION

Chitosan (CS) is prepared by partial deacetylate from chitin that is the second most abundant naturally occurring biopolymer after cellulose. CS and its derivatives are bioactive materials that can resist ulcer, keep moisture, and also have biodegradation and biocompatibility. Thus, they have shown many applications in medicine, cosmetics, agriculture, and biotechnology.^{1,2} A hydrogel obtained from CS as carrier drug systems can prevent or reduce the stimulation on stomach mucosa at low pH.³ It is well known that CS has been considered as a single basic polysaccharide in nature because of the presenting amino groups (-NH₂) in its backbone. So CS can form polyelectrolyte complexes with polyacid such as poly(acrylic acid), dextran sulfate, or carboxymethyl cellulose.^{4–6}

Poly(methacrylic acid) (PMAA) is a classic acidic polyelectrolyte. Its conformation intensely depends on the pH value of the medium in dilute solution. It can form polyelectrolyte complexes by electrostatic interactions with an oppositely charged polyelectrolyte in a

specific solution. It is well known that electrostatic interactions are much stronger than the most secondary bonding interactions, such as hydrophobic interactions, hydrogen bonding, or van der Waals forces. This would break the hydrogen bonding between amino groups and hydroxyl groups in CS, resulting in an amorphous structure of the polyelectrolyte complex.⁴ Particularly, the stability of the complexes formed by electrostatic interactions is dependent on many environmental factors: the temperature, pH, ionic strength, or the nature of the solvent, and so on.⁷ This means that the complexes have stimuli-response with the changing environment.

Hydrogels prepared from natural polymers are the best choice for pH-sensitive controlled release systems because of the swelling properties, biocompatibility, and the three-dimensional network structure that can encircle drugs. Swelling properties of hydrogels are important factors for each application.⁸ Correspondingly, changes in swelling behavior affect the releasing patterns of bioactive materials in controlled release systems. Moreover, a major disadvantage of common hydrogels (i.e., their relatively low mechanical strength) can be overcome either by crosslinking or by formation of an interpenetrating network.^{9,10} Yao et al.¹¹ reported a pH-sensitive semi-IPN hydrogel based on crosslinked CS and polyether, and they thought that this hydrogel was superior to chitosan gel in the reversible response of swelling and deswelling in acid

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and alkali, respectively. In recent years, most attention has been focused on pH-sensitive hydrogels prepared from naturally occurring polymers out of respect for environmental preservation and the notion of safety for the human body.

Polyelectrolyte complexes are directly or indirectly related to the delivery information of genes and the interaction of antigen-antibody. Thus, the complexes can be used as carriers for the release of drugs for their special properties and pH response.¹²

Based on these considerations, developing a new kind of smart polyelectrolyte hydrogel that has some reasonable biocompatibility is the purpose of this study. So, CS was chosen as a gel-forming material, and a semi-IPN hydrogel with pH-sensitivity was synthesized from CS and PMAA by using an optimum amount of formaldehyde (HCHO) solution as crosslinker. The swelling properties of the semi-IPN hydrogel prepared by this work were studied in various environmental solutions. The SEM was used to characterize the morphological change of the semi-IPN hydrogel swollen in different swelling solutions.

EXPERIMENTAL

Materials

Chitosan was kindly provided by Lanzhou Institute of Chemical Physics CAR. Its viscosity average weight is 6.0×10^5 , calculated by the Mark-Houwink equation. The N-deacetylation degree of chitosan was determined to be 90% by a method of acid and alkali titration. Methylacrylic acid (MAA) was distilled under vacuum before use. 2,2'-Azo-bisobutyronitrile (AIBN) was C.P. grade and was recrystallized with 95% ethanol. Acetic acid was analytical grade and used directly. Formaldehyde (HCHO) solution (37 wt %) was A.R. grade and was filtered prior to use. Other chemicals were A.P. grade and were used directly without further purification.

PMAA preparation

PMMA was synthesized by free radical polymerization with MAA by using AIBN as an initiator in methanol. AIBN (90 mg) was dissolved in a small amount of methanol and then added into the mixture solution of MAA and methanol. The system was protected by N_2 flow at 65 °C for 1.5 h. The mixture was cooled naturally and the excess solvent was evaporated under reduced pressure; then the thick mixture was precipitated in diethyl ether. The crude product was further purified three times by precipitation with diethyl ether from a methanol solution and then dried under vacuum at room temperature to constant weight. The viscosity average molecular weight was estimated to

be 8.99×10^4 through intrinsic viscosity of PMAA in methanol at a constant temperature of 26 ± 0.1 °C.

Preparation of semi-IPN hydrogel

CS powder (0.25 g) was dissolved by adding 5 wt % acetic acid and PMAA (0.1335 g) was dissolved in distilled water. The unit molar ratio between CS and PMAA was chosen to be 1 : 1 because the complex between two macromolecules was better at this ratio.¹³ This conclusion was a typical characterization of complex formation.¹⁴ The aqueous solution of PMAA was dropped into the acetic acid solution of CS with agitation. Meanwhile, a white gel-like precipitation was formed, meaning that a complex structure was formed between the amino ion groups ($-NH_3^+$) in CS and the carboxyl ion groups ($-COO^-$) in PMAA, and then excess acetic acid was added to dissolve the precipitation. When the precipitation was dissolved completely, the pH of the mixture was about 2.6, at which a complex transition state existed between CS and PMAA.¹⁵ Then, a given amount of HCHO solution was added to the mixture, and the crosslinking reaction was maintained at 25 °C for 9 h. A hydrogel was obtained and cut into small blocks (around $0.6 \times 0.6 \times 0.3$ cm) and then immersed into double-distilled water for 24 h. The water was changed during the period five times to remove any unreacted HCHO and residual acetic acid. Another purpose of this operation was to form a better complex of CS and PMAA. Residual solvent and water were eliminated under a vacuum. The hydrogel was dried to constant weight under vacuum and then a dried semi-IPN gel was obtained.

Characterization of the gel by FTIR

The dried semi-IPN gel was ground to a suitable size powder. The powder could be used for IR analysis. The IR spectrum of the sample was obtained with a Nicolet Nexus 670 FTIR spectrometer.

Measurement of the degree of swelling of the gel in various swelling solutions

Swelling experiments were conducted in specified buffer solutions with the ionic strength adjusted by the addition of NaCl, except for swelling in various inorganic salt solutions. The dried gel (approximately 0.03 g) was immersed into the specified solutions (approximately 20 mL) at 37 °C. The pH of all solutions was measured on a pH-3B Model pH Meter. The weight of the swollen samples was measured after the excess surface solution was removed by filter paper. The degree of swelling was calculated by the following expression: W'/W_0 . Here W' and W_0 are the weights of the swollen and dried gel, respectively. An

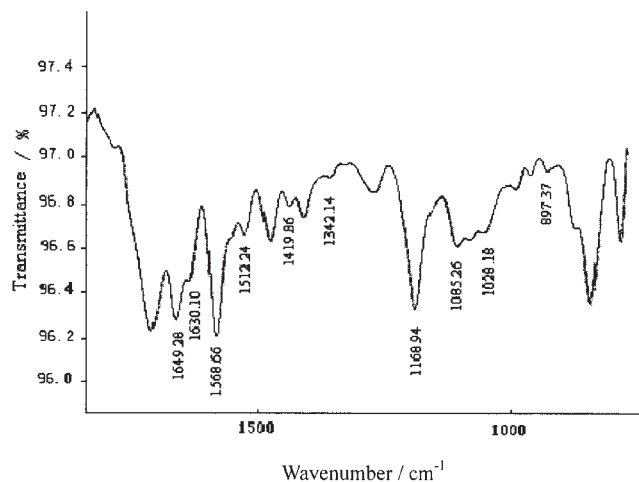


Figure 1 FTIR spectrum of the semi-IPN gel.

operation of swelling experiments in various inorganic salt solutions was similar to the former.

Measurement of the surface structure of the gel

The dried semi-IPN gel was swollen in the buffer solutions of NaCl-HCl (pH 1.80, $I = 0.2M$), NaCl-HCl (pH 1.80, $I = 2.0M$) and $CaCl_2$ -HCl (pH 1.80, $I = 2.0M$), respectively. All samples were swollen at 37 °C for 3 h and then freeze-dried for 15 h with Labconco Freeze Dry System and their surface structures were investigated with a JSM-5600LV SEM from Japan.

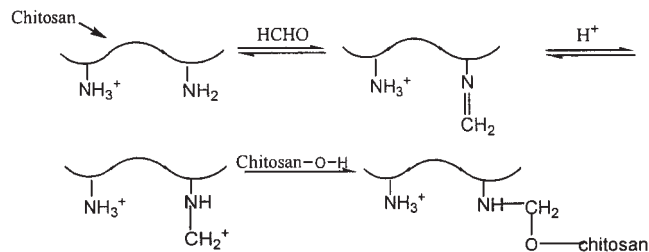
RESULTS AND DISCUSSION

IR spectrum analysis

Figure 1 shows the IR spectrum of the semi-IPN gel composed of crosslinked CS and PMAA. The IR spectrum shows peaks assigned to the saccharide structure at 1169 and 897 cm^{-1} . The absorption peaks at 1649 and 1342 cm^{-1} have been reported to be the amide I and III bands, respectively.¹⁶ Two absorption peaks at 1630 and 1512 cm^{-1} can confirm the $-NH_3^+$ formation¹¹ in the semi-IPN gel. The peaks at 1569 and 1420 cm^{-1} are attributed to the $-COO^-$ asymmetrical and symmetrical deformation modes, respectively. All these peaks can prove the presence of a polyelectrolyte complex. The absorption peaks at 1085 and 1028 cm^{-1} have been assigned to C-N-C and C-O-C flexible deformation modes,¹⁷ respectively. Thus, a crosslinking reaction took place between $-NH_2$ in CS crosslinking by HCHO.

Effect of the amount of crosslinker on the properties of the gel

The crosslinking mechanism of CS using HCHO as crosslinker was deduced by other authors.¹⁷ It was



Scheme 1 The crosslinking mechanism of CS.

analyzed through combining Schiff's base reaction mechanism with IR spectra and then the structure of crosslinked CS was achieved. The crosslinking process is shown in Scheme 1.

The number of $-NH_2$ as nucleophilic reagent in CS is small because a part of $-NH_2$ in CS is protonated in the reaction system at pH about 2.6; thus, attacking carbonyl in HCHO is difficult for $-NH_2$ in CS. Therefore, excess HCHO was added to the reaction system when the semi-IPN hydrogel was synthesized.

The ratio of the volume of crosslinker to the weight of CS is expressed by r . Table I displays the physical properties of the hydrogel obtained with different amount of crosslinker (HCHO). It can be seen that the physical properties of the hydrogel obtained when r is 6.4×10^{-3} mL/mg are the best. Table I also shows the relationship between the degree of swelling of the gel and the amount of crosslinker. When r is less than 7.2×10^{-3} mL/mg, the number of effective net chains in the hydrogel increases with increase of r . However, when r is greater than 7.2×10^{-3} mL/mg, the number of net holes increases continually, which would lead to excess compact structure. For these reasons, the de-

TABLE I
Effect of the Amount of Crosslinker (HCHO) on Physical Properties of the Hydrogel and the Degree of Swelling of the Gel (pH 3.00, $I = 0.2M$, 37 °C)

Sample	$r \times 10^3$ (mL/mg)	Physical properties of the hydrogel	Degree of swelling of the gel
1	4.0	A soft-hydrogel without fixed shape	26.95
2	4.8	A soft-hydrogel with fixed shape	38.80
3	5.6	A fixed-shape hydrogel, but its surface is damp	44.67
4	6.4	A fixed-shape hydrogel with more flexibility and toughness, and its surface is not damp	64.00
5	7.2	Similar to sample 4, but the hydrogel is crisp	73.73
6	8.0	Similar to sample 4, the hydrogel is much crisper	48.99

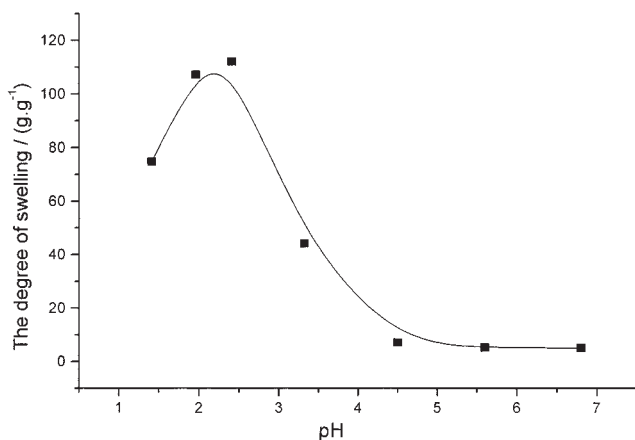


Figure 2 Effect of pH on the degree of swelling of the gel (ionic strength $I = 0.2M$, $37\text{ }^{\circ}C$).

gree of swelling increases from the beginning and then decreases. According to the results shown in Table I, an optimum value of r was determined to be 6.4×10^{-3} mL/mg.

pH dependence of the degree of swelling of the gel

To investigate the influence of pH on the degree of swelling of the gel, the ionic strength of buffers is kept constant ($I = 0.2M$) by adding NaCl. The swelling data of the gel are shown in Figure 2. Figure 2 shows four viewpoints. (1) The highest swelling capacity is at about pH 2.30. (2) With decreased buffer solution pH from 2.30 to 1.40, the swelling capacity decreases because the carboxyl ($-COOH$) in PMAA hardly exists as $-COO^-$ at lower pH, which leads to the dissociation of the major ionic bond in the network. That is to say, the number of effective net chains decreases. So the degree of swelling is lower at lower pH. (3) With increased swelling solution pH from 2.30 to 4.50, the degree of swelling decreases gradually because the

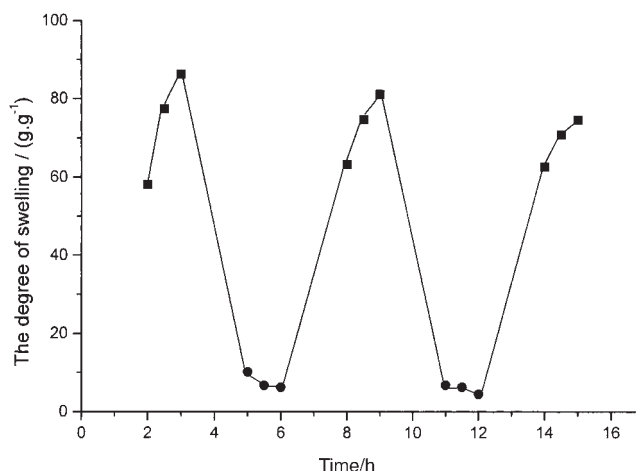
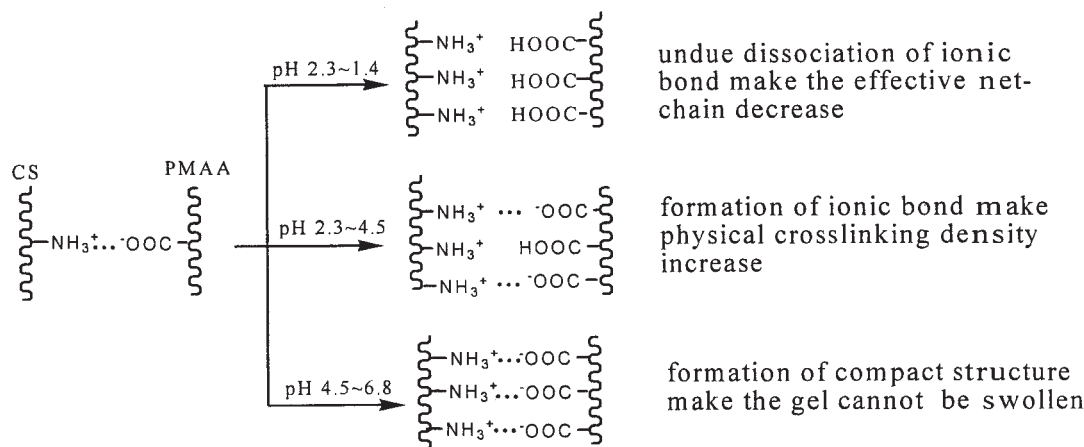


Figure 3 Reversible swelling of the gel in buffers of pH between 1.80 and 6.80 (■: pH 1.80; ●: pH 6.80; $I = 0.2M$, $37\text{ }^{\circ}C$).

semi-IPN hydrogel would form more ionic bonds between $-NH_3^+$ in CS and $-COO^-$ in PMAA, which results in the relative increased crosslinking density of the hydrogel. (4) When the pH of the buffer is higher than 4.50, the volume change of the gel is almost constant because of the compact structure, which can be explained by the level of complex between CS and PMAA. There is full complex between CS and PMAA in the pH range from 4.0 to 9.0.¹⁵ On the basis of the results obtained above, this mechanism of swelling can be deduced and illustrated in Scheme 2.

The semi-IPN gel shows excellent pH sensitivity in the pH range from 1.40 to 4.50 and it would be used for carrier drug systems for humans because of the acidic degree in the stomach. There is an excess, normal, and lower gastric acid at $pH < 1.60$, $1.60 < pH < 2.00$, and $pH > 2.00$, respectively.¹⁸

The above results of (3) and (4) can be used to explain the appearance of gel-like precipitate due to



Scheme 2 Structure change of polyelectrolyte complex in various pH solutions.

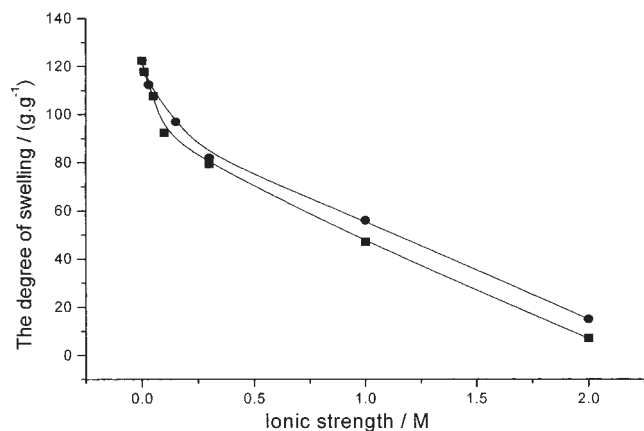


Figure 4 Effect of ionic strength and inorganic salt on the degree of swelling of the gel (■: NaCl-HCl; ●: CaCl₂-HCl; pH 1.80, 37 °C).

the formation of a complex between CS and PMAA. The addition of excess acetic acid reduced the pH value of the mixture, which resulted in the dissociation of the complex. So the gel-like precipitate can be dissolved.

The swelling process of the gel may be that the swelling solution makes the ionic bond dissociation into the surface of the gel and then permeates the gel slowly. In addition, the permeation of the solution results in the net chain extending to three-dimensional space. The network will shrink because it is subject to stress and produces flexible shrink energy. When the two opposite tendencies trend to be equal, the swelling of the gel reaches equilibrium. But, the gel would not be swollen at pH > 4.50 because the environmental solution cannot make the ionic bond into dissociation and permeate the gel for a better complex between CS and PMAA at these pH.

Reversible response of the gel in various pH solutions

It is obvious that there is a difference in the degree of swelling between pH 1.80 and 6.80 for the gel. Thus, the pH reversible response was studied at the two pH. The gel was placed into NaCl-HCl solution (pH 1.80) for 3 h at first and then transferred to KH₂PO₄-NaOH solution (pH 6.80). This operation was repeated to observe an abrupt reversible swelling. Figure 3 shows the reversible behavior of the gel swollen in acid medium (pH 1.80) and deswollen in neutral medium (pH 6.80). The reason for this phenomenon is the dissociation and formation of an ionic bond between -NH₃⁺ in CS and -COO⁻ in PMAA in acid and neutral media, respectively. The reversible phase transition with change of environmental pH is a desirable characteristic for drug delivery systems because of the acidic degree of the stomach (pH about 1.80) and intestines (pH about 6.80).

Ionic strength and inorganic salt dependence of the degree of swelling of the gel

The influences of different ionic strength and inorganic salt on volume change were studied and are shown in Figure 4. There is the same decreasing tendency for the degree of swelling of the polyelectrolyte gel in NaCl-HCl and CaCl₂-HCl solutions with ionic strength increase. The explanation for this phenomenon has been mentioned above. Another phenomenon that can be seen from Figure 4 is a bit higher swelling capacity for the gel swollen in CaCl₂-HCl solution than in NaCl-HCl solution at the same ionic strength. As we know, CS cannot chelate with alkali and alkaline earth-metal ions such as Na⁺ and Ca²⁺. The bond capacity between PMAA and metallic ions became stronger with the increase of ionic valence. Therefore,

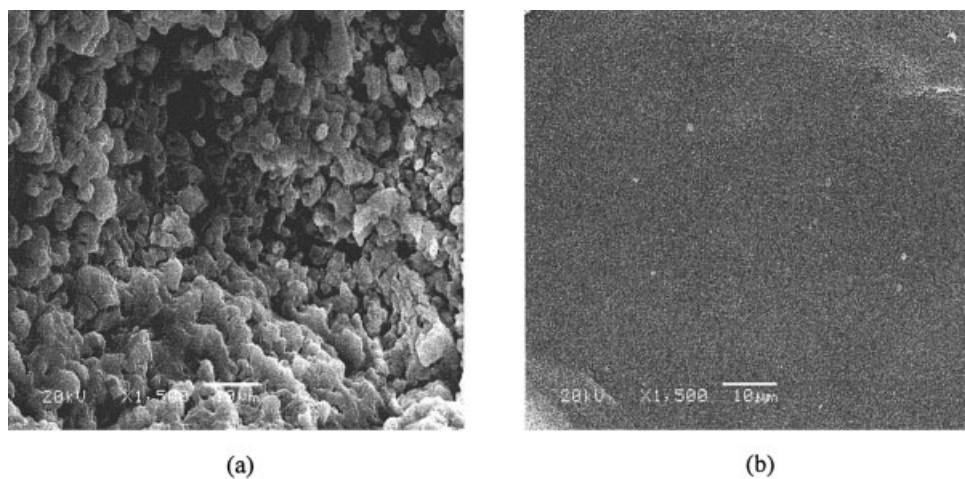


Figure 5 Effect of inorganic salt on the morphological change of the gel. [(a) CaCl₂-HCl; (b) NaCl-HCl; I = 2.0M, 37 °C].

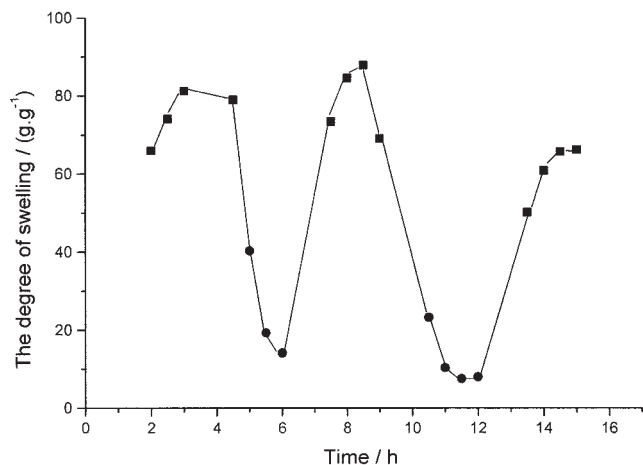


Figure 6 Reversible swelling of the gel between $I = 0.2$ and $2.0M$ (■, $I = 0.2M$; ●, $I = 2.0M$; pH 1.80, 37 °C).

it is easier to bond with Ca^{2+} than Na^+ for PMAA, which brings about a greater dissociation level of ionic bond between $-NH_3^+$ in CS and $-COO^-$ in PMAA. This result is similar to the result of Wang et al.¹⁹

To prove the higher swelling capacity of the gel swollen in $CaCl_2$ -HCl solution ($I = 2.0M$) than in $NaCl$ -HCl solution ($I = 2.0M$), SEM photos were obtained and are displayed in Figure 5. Figure 5(a) shows a loose structure, but Figure 5(b) shows a compact structure. This phenomenon indicates that the gel was slightly swollen in $CaCl_2$ -HCl solution, while it was hardly swollen in $NaCl$ -HCl solution at $I = 2.0M$. The result shows no difference from that achieved above.

Reversible response of the gel in various ionic strength solutions

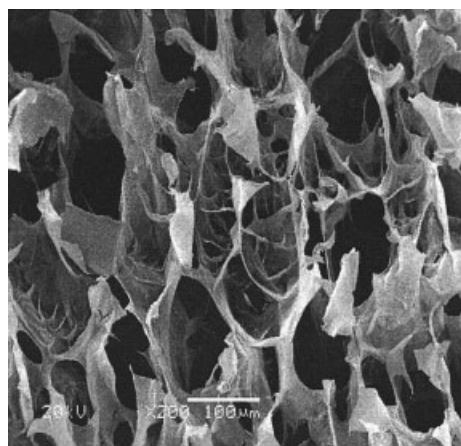
Based on the same consideration with reversible response of the gel at different pH, the reversible swell-

ing behavior for the gel in various ionic strength solutions was studied. Figure 6 shows an abrupt volume change in $I = 0.2M$ and $2.0M$ swelling solutions. The gel swollen in the solution of $I = 0.2M$ can be deswollen in the solution of $I = 2.0M$ and swollen again when environmental solution was changed back. Thus, it is not difficult to think about this phenomenon as similar to a cell that would undergo phase transition in two types of ionic strength solutions, and a part of Schiff's base structure that exists in the semi-IPN gel makes it have special bioactive properties. Accordingly, the obtained result is desirable and may strengthen the application foreground of the semi-IPN hydrogel.

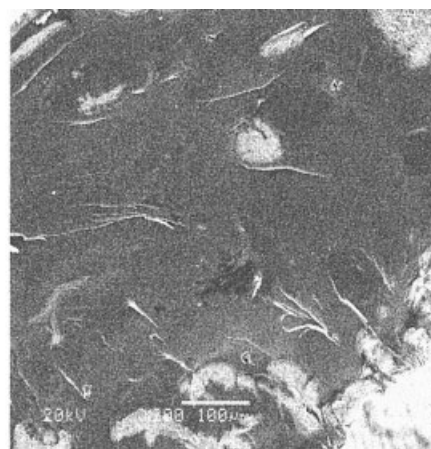
In attempting to understand the different swelling capacity of the gel in two types of ionic strength solutions, the SEM photographs of the gel swollen in the solution of $I = 0.2M$ or $2.0M$ at pH 1.80 were obtained and are shown in Figure 7. Figure 7(a) shows that the gel swollen in the solution of $I = 0.2M$ has larger three-dimensional net hole, while Figure 7(b) shows that the gel swollen in the solution of $I = 2.0M$ has a compact structure. This result shows that the semi-IPN gel has outstanding ionic strength sensitivity. Figure 7(a) also shows that there is a greater swelling capacity for the gel swollen in acidic medium.

CONCLUSIONS

A pH-sensitive semi-IPN hydrogel was obtained from crosslinked CS and PMAA. To obtain a hydrogel with better properties, an optimum amount of crosslinker (HCHO) was chosen. With changing pH of the swelling solutions, the swelling capacity of the gel reaches a maximum at pH about 2.30 and is restricted at pH ≥ 4.50 and the gel exhibits sensitive reversible response between pH 1.80 and 6.80. The reason of swelling and deswelling is the dissociation and formation



(a)



(b)

Figure 7 Effect of ionic strength on the morphological change of the gel immersed in $NaCl$ -HCl solutions [(a) $I = 0.2M$; (b) $I = 2.0M$; pH 1.80, 37 °C].

of ionic bond between -NH_3^+ in CS and -COO^- in PMAA. The study of the swelling behaviors of the gel in various ionic strength solutions indicates that the gel has ionic strength response because of the change in osmotic pressure of the ambient solution. Furthermore, a bit higher swelling capacity for the gel swollen in $\text{CaCl}_2\text{-HCl}$ solution than in NaCl-HCl solution is due to the bond capacity of PMAA and metallic ions and is testified through the morphological change measured by SEM. Other results achieved from SEM also show that the hydrogel has excellent pH and ionic strength sensitivity. All results show that the semi-IPN hydrogel we prepared would be a better application foreground in drug delivery systems.

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