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Polymer 46 (2005) 7695–7700
polymer
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pH switching on-off semi-IPN hydrogel based on cross-linked poly(acrylamide-*co*-acrylic acid) and linear polyallyamine

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Received 1 March 2005; received in revised form 29 April 2005; accepted 27 May 2005
Available online 5 July 2005

Abstract

pH sensitive hydrogels with semi-interpenetrating networks (semi-IPN) composed of cross-linked copolymer of acrylamide/acrylic acid (P(AM-*co*-AA)) and linear polyallylammonium chloride(PAAC) were synthesized by template copolymerization in the presence of *N*,*N*′-methylene bisacrylamide (MBAM) as a cross-linking agent. The networks contained both covalent bonds and ionic bonds. The covalent bonds retained the three-dimensional structure of hydrogel and the ionic bonds brought the hydrogel with much higher mechanical strength and pH stimuli responsive reversibility. The effect of the molar fraction of PAAC (based on monomeric units) on the swelling/deswelling transition pH and reversibility behavior of hydrogel was investigated by equilibrium swelling and oscillatory swelling techniques. The results showed that the semi-IPN hydrogels exhibited ampholytic and reversible pH-stimuli responsive characteristics. The swelling/deswelling transition pH value could be varied in a great range by modulating the PAAC contents at the molar fraction of AA (f_{AA}) fixed or varied. The drug loading and release of the semi-IPN hydrogels were also studied using theophylline as a model drug. The perfect reversibility and rapidly on-off switching properties of the hydrogels make them to be potential materials in the field of medicine, pharmacy and biotechnology.

Keywords: Semi-IPN hydrogels; Cross-linked poly(AM-*co*-AA)/PAAC; pH Response

1. Introduction

In recent years considerable research attention has been focused on the intelligent polymer materials, especially hydrogels that contain functional groups and are able to alter their volume or other properties in response to environmental stimuli, such as pH [1–16], temperature [17–20] and electric field [21]. Hydrogels could be interpolymer complex [5,11,14,22], lightly cross-linked networks of polymers [1,23,24], inter or semi- interpenetrating networks of polymers [15,25,26] and core-shell microspheres [27]. Hydrogels are promising materials for pharmacological applications. They provide the time-independent, sustained release of bioactive agents. Among the stimuli responsive polymers, pH-sensitive hydrogels are the most investigated ones. Different hydrogels containing weakly acidic or basic groups in the polymer backbone have been reported by several research groups. Cationic copolymers based on poly(dimethylaminoethyl methacrylate) (PDMAEMA) and poly(diethylaminoethyl methacrylate) (PDEAEMA) have been characterized and investigated for controlled release of protein and peptide drugs [2,3,7]. The pH-modulated swelling and release characteristics of anionic hydrogels based on polymethacylic acid (PMAA) copolymerized with hydroxyethyl methacrylate (P(MAA-*co*-HEMA)) was studied, it was concluded that the diffusion of non-ionizde drugs in the hydrogel was controlled only by the volume swelling ratio of the polymer [28]. Interpolymer complexes of poly(acrylic acid) with polyoxyethylene or poly(vinyl pyrrolidone) [5,11] and interpenetrating networks of chitosan with poly(ethylene oxide) have also been proposed as drug carriers because of their pH-dependent swelling behavior [12].

The objectives of this work were to develop one kind of ampholytic hydrogels containing both acidic and basic groups in polymer chains, which made hydrogels change their swelling/deswelling transition pH in a wide range of pH value by varying acid or base mole ratio. Previously we

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doi:10.1016/j.polymer.2005.05.121

have reported template copolymerization of acrylamide and acrylic acid with polyallyammonium chloride as a matrix [29,30]. The resulting copolymer exhibited multi-block structure with long AM and AA sequence length. The molar ratio of PAAC (based on monomeric units) to AA has strong influence on the microstructure of the products. On the basis of obtained results, the ampholytic hydrogels having semi-interpenetrating networks (semi-IPN) was proposed and synthesized by template copolymerization of acrylamide and acrylic acid in the present of polyallylammonium chloride as a matrix and *N*,*N*-methylene bisacrylamide as a cross-linking agent. The swelling behaviors and release rates of theophylline, a model drug, were evaluated.

2. Material and methods

2.1. Sample preparation

Semi-IPN hydrogels of acrylamide (AM, Jiangxi Changjiu Biochemical Engineering Corporation and used as received) and acrylic acid (AA, Tianjin Chemical Reagent Research Institute and distilled under vacuum over copper turnings) were synthesized by template copolymerization in the presence of poly(allylammonium chloride) as a matrix (PAAC, synthesized in our laboratory M_w 10,000), *N*,*N*′-methylene bisacrylamide (MBAM, Tianjin Chemical Reagent Research Institute) as a cross-linking agent. AM was mixed with an appropriate amount of AA to form mixtures containing 30, 35, 40 or 50 mol% AA, the total monomer concentration was 5 wt%, and PAAC was added to the mixture at 0, 87.5, 93.8 or 100 mol% (based on monomeric units) of AA.

2,2′-Azo-bi-(2-amidinopropane) dichloride (AIBA) was added at 0.3 wt% of total monomer as initiator, and MBAM was used as a cross-linking agent at 1.5 wt% of total monomer. Copolymerization was carried out in a constant temperature water bath at 55 °C for 12 h, then cooled to room temperature. The polymers obtained were cut and washed in pure water for 48 h to remove the residual monomer, then dried at 60 °C for 48 h. The final sample was about 5 mm in diameter and 3 mm in height.

2.2. Swelling measurements

The dry gels were immersed in 0.01 M $NaNO_3$ solution at 25 °C. Swelling equilibrium was measured by weighing the swelled hydrogels repeatedly until no weight change was detected. The pH of the solution was adjusted by dilute HCl or NaOH solutions. The weight swelling ratios of hydrogels (SR) in water were calculated as Eq. (1):

$$\mathrm{SR} = \frac{(m_t - m_0)}{m_0} \quad (1)$$

where m_t is the mass of swelled gel at time t, and m_0 is the initial mass of the dry gel.

2.3. TEM

The hydrogels used for TEM measurements were frozen at their swollen state and cut to slice, then negatively stained with uranyl acetate.

2.4. Drug loading

Hydrogels were loaded with theophylline by soaking them in an aqueous solution of various drug concentrations (2–100 mg/l). The solution also contained 0.01 M $NaNO_3$. The pH was adjusted with HCl or NaOH solution. The solution was gently stirred for 48 h at 25 °C. The equilibrium theophylline concentration in the medium was measured by a UV spectrophotometer ($\lambda = 271$ nm). The amount of theophylline loaded by the hydrogels was evaluated as the difference between the initial and the final quantities in the medium.

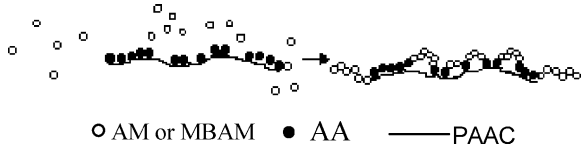
2.5. Release studies

Dried loaded hydrogels (about 0.2 g) in 100 ml 0.01 M $NaNO_3$ solution at 37 °C and pH 7.4 were measured as a function of time. The amount of theophylline released was measured using a UV spectrophotometer ($\lambda = 271$ nm) at predetermined time intervals.

3. Results and discussion

In this template copolymerization system, ionic monomer AA was preadsorbed by template PAAC through strong intermolecular electrostatic interaction. While neutral monomer AM and MBAM without interaction with PAAC dissolved in the bulk solution. As previously reported [29] the copolymerization was processed according to type I template copolymerization mechanism. The obtained products have longer sequences distribution of AM and AA along the copolymer chains and higher pK_a of AA than those of the corresponding conventional copolymers without the presence of PAAC [30]. The polymerization process could be illustrated by the following schematic representation Scheme 1.

The resulting polymeric hydrogels were composed of cross-linked poly(AM-*co*-AA) and linear PAAC, which interpenetrate each other to form semi-interpenetrating



Scheme 1. Schematic representation of template copolymerization (type I).

network (semi-IPN). The network contained both covalent bonds and ionic bonds. The covalent bonds retained the three-dimensional structure of hydrogel and the ionic bonds brought the hydrogel with much higher mechanical strength and pH stimuli responsive reversibility. The electrostatic repulsion was the main swelling driving force for the hydrogels. Fig. 1 illustrated the semi-IPN structure.

3.1. Swelling behavior

3.1.1. pH Response

Equilibrium swelling studies indicated that the semi-IPN hydrogels were sensitive to environmental pH. Figs. 2 and 3 showed the swelling behavior of the semi-IPN hydrogels in a pH range from 2.0 to 11.0. It was found that these swelling curves exhibited a sharp transition at a certain pH value. As pH exceeded this value the SR abruptly increased several tens of times and then level off. Interestingly the swelling/deswelling transition pH value of semi-IPN hydrogels was depended on the mole ratio of PAAC (based on monomeric units) to AA (PAAC/AA) and/or molar fraction of PAAC in hydrogels. When PAAC/AA varied from 0 to 1.0 with a fixed value of f_{AA}(=0.4) the transition pH value increased from 3.0 to 8.0 (Fig. 2). Similarly as PAAC (based on monomeric units) increased from 0.3 to 0.5 when PAAC/AA (=1) was fixed the transition pH value shifted from 6 to 9 (Fig. 3). While the transition pH value for conventional poly (AM-*co*-AA) without PAAC was located at lower pH value (~3.0) and was almost invariable with the change of f_{AA}.

For conventional hydrogel without PAAC, at lower pH conditions the hydrogel was at the deswollen state due to the hydrogen bonds between AM and AA. As pH increased the hydrogel began to swell due to the electrostatic repulsion between ionized carboxyl groups. But as to hydrogel with PAAC things was a bit difference. At lower pH conditions hydrogen bonds between AM and AA along with electrostatic repulsion between ionized amine groups coexisted, the hydrogel was at the swollen or deswollen state was depended on which force was dominant. In this experiment condition, the hydrogel was at the deswollen state, which indicated that the hydrogen bonds were

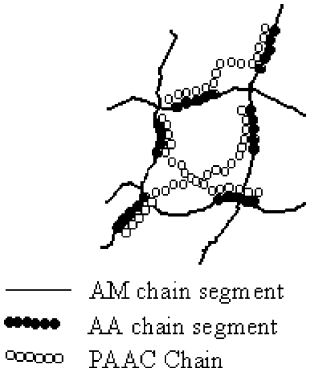


Fig. 1. The schematic representation of semi-IPN structure.

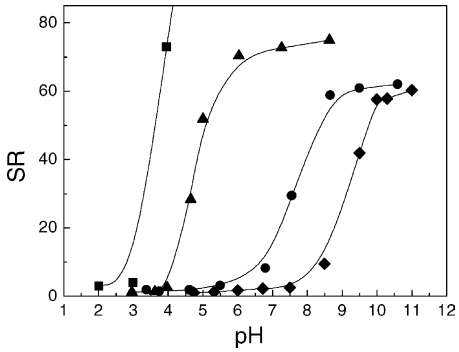


Fig. 2. Effect of PAAC/AA on the swelling behavior of semi-IPN hydrogels. [0 (■), 0.87 (▲), 0.93 (●), 1 (♦)] at f_{AA}=0.4.

dominant at lower pH conditions. As pH increased ionic bonds network between ionized carboxyl groups and ionized amine groups was formed the hydrogel was also at the deswollen state. To make the hydrogel swell pH should be increased to a value higher than that of the conventional hydrogel without PAAC at which the electrostatic repulsion between ionized carboxyl groups was higher than the ionic bonds attraction between carboxyl and amine groups. Meanwhile as PAAC in hydrogel increased whether f_{AA} was fixed or not (as illustrated in Figs. 2 and 3) the transition pH increased too. So the presence of PAAC increased the swelling/deswelling transition pH and made the swelling behavior of the semi-IPN more abundant.

3.1.2. Salt effect

The semi-IPN hydrogels are ionizable hydrogels that their swelling behavior also depends on the saline concentration of the medium. The swelling degree of the semi-IPN hydrogels in saline solutions was appreciably decreased as compared with the values measured in deionized water. This well-known phenomenon commonly observed in the swelling of ionizable hydrogels [31] was often attributed to the charge screening effect of the addition cations. Fig. 4 showed the relationship between swelling ratio and saline concentration at pH 7.4. It showed that initially the equilibrium swelling ratio (SR) dropped down

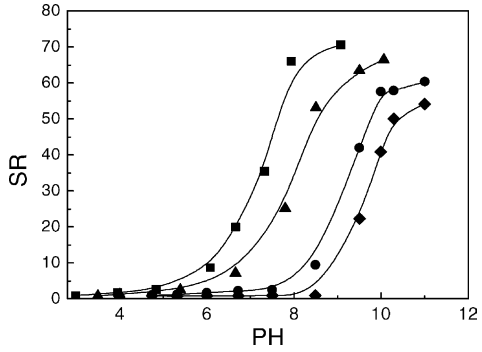


Fig. 3. Effect of PAAC on the swelling behavior of semi-IPN hydrogels [0.3 (■), 0.35 (▲), 0.4 (●), 0.5 (♦)] at PAAC/AA=1.

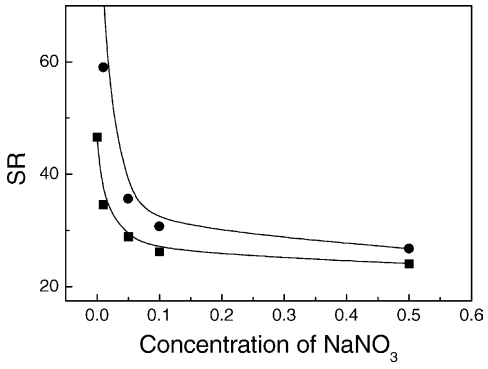


Fig. 4. Effect of ionic strength on equilibrium swelling ratio (SR), PAAC = 0.3, PAAC/AA = 1 (■), f_{AA} = 0.4, PAAC/AA = 0.875 (●) at pH 7.4.

quickly as $NaNO_3$ added, then flattened out after $NaNO_3$ concentration exceeded ~0.1 mol/l.

3.1.3. Swelling kinetics

Fig. 5 represented the dynamic swelling behavior of the semi-IPN samples in saline solution ($NaNO_3$ 0.01 mol/l) at pH 7.4. Initially the rates of swelling sharply increased and then level off. The equilibrium swelling was achieved after 10 h. Power law behaviors were obvious from Fig. 5. The initial swelling rate can be calculated using Voigt-based equation (Eq. (2)) [32].

$$S_t = S_e(1 - e^{-t/\tau}) \quad (2)$$

where S_t is swelling ratio at time t (g/g), S_e is equilibrium swelling ratio ('power parameter', g/g), t is time (s) for swelling S_t, and τ stands for the 'rate parameter'. From kinetic curves the rate parameters (τ) for different samples were obtained to be 25.2 (1), 21 (2), 15 (3), 10.2 (4), respectively. It could be found that when PAAC/AA kept constant the higher the PAAC content the higher the value of τ was and the lower the rate of swelling was. The phenomenon could be attributed to the fact that when PAAC/AA (=1) was fixed the increase of PAAC in hydrogel led to form more interpenetrating networks in

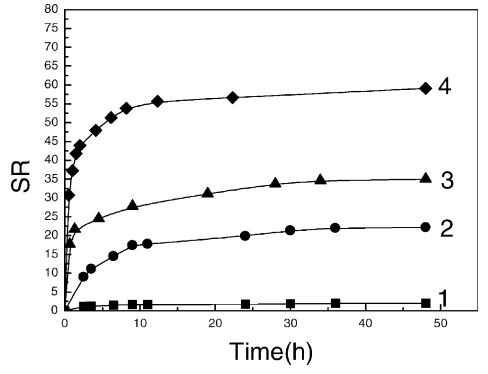


Fig. 5. Effect of molar fraction of PAAC or PAAC/AA on the swelling rate of semi-IPN hydrogels. [PAAC = 0.4, PAAC/AA = 1 (■), PAAC = 0.35, PAAC/AA = 1 (●), PAAC = 0.3, PAAC/AA = 1 (▲), PAAC = 0.4, PAAC/AA = 0.87 (♦)] at pH 7.4.

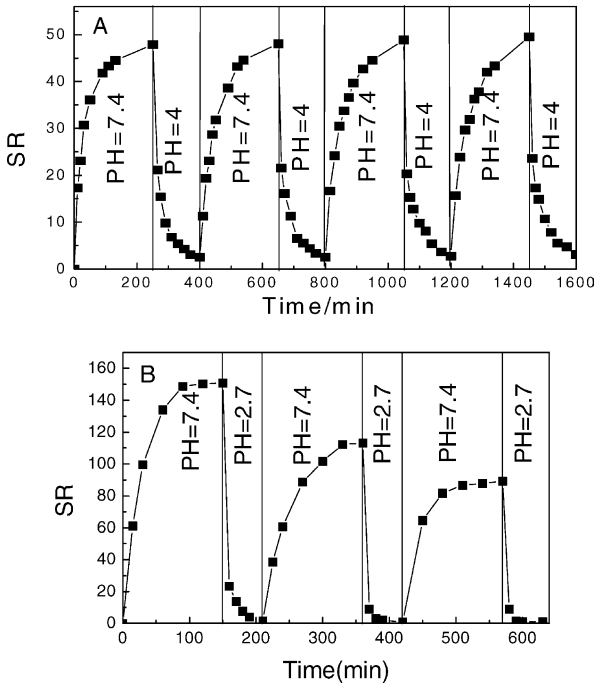


Fig. 6. Oscillatory swelling behavior as a function of time and pH at PAAC = 0.4, PAAC/AA = 0 (A) and PAAC = 0.4, PAAC/AA = 0.87 (B).

hydrogels, thus the swelling of hydrogel in water solution was restrained. Similar results were also appeared when varying the ratio of PAAC/AA as f_{AA} fixed.

3.1.4. Oscillatory swelling

The oscillatory swelling experiments were also conducted to investigate the resistance of the semi-IPN hydrogels to swelling–deswelling transition. Fig. 6 represented the oscillatory swelling behaviors of two samples A and B prepared by template polymerization in the presence of PAAC and conventional polymerization without the presence of PAAC respectively in 0.01 mol/l $NaNO_3$ solution at room temperature. The pH value of the solution was oscillatory from 4 to 7.4 (for sample A) or from 2.7 to 7.4 (for sample B).

As illustrated in Fig. 6 the semi-IPN sample exhibited an excellent reversibility. The swelling rate and swelling capacity was almost no losing even after many times of

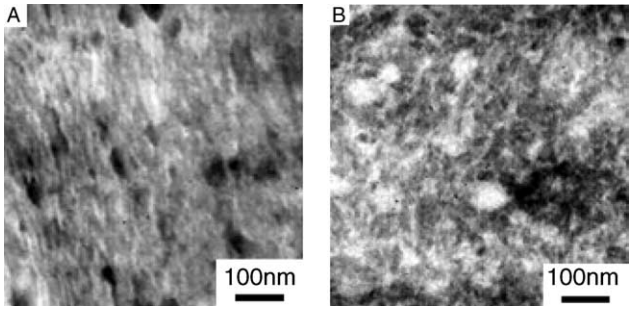


Fig. 7. TEM images of template copolymerization hydrogel (A) and conventional copolymerization hydrogel (B).

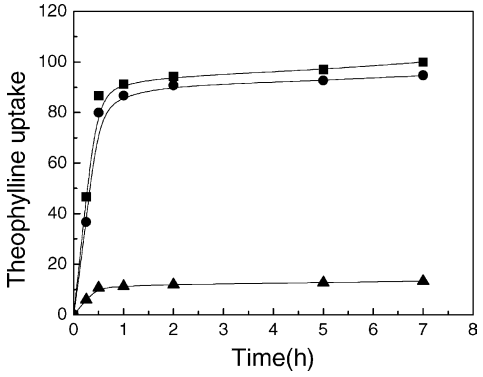


Fig. 8. Effect of pH (4.2 (▲), 5.2 (●), 7.4 (■)) on the theophylline uptake by semi-IPN hydrogel (PAAC = 0.4, PAAC/AA = 0.87) as compared to the maximum uptake quantity of pH 7.4.

oscillation. However the reversibility of reference sample B was not so good as that of sample A, after three times of pH oscillation the swelling ratio almost dropped 50% of the initial value. This difference indicated that the presence of template PAAC in the semi-IPN hydrogels played a great role in the enhancement of physical strength of the semi-IPN hydrogels due to the obvious increase of the interpenetrating density.

3.2. Micro-morphology

Fig. 7 showed the TEM images of sample A and B (identical samples with Section 3.1.4), which revealed a striking difference in the microscopic morphology. Sample A (semi-IPN hydrogel) exhibited more uniform structure with a smaller size pore compared with that of the sample B (obtained by conventional copolymerization), which indicated that the presence of PAAC greatly altered the microstructures of the semi-IPN hydrogels.

3.3. Drug loading and release

Based on the above results that the semi-IPN hydrogels was sensitive to environmental pH value may be considered as an excellent candidate for the design of a novel drug

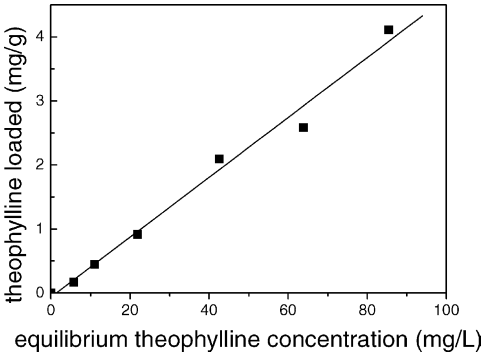


Fig. 9. Theophylline uptake by semi-IPN hydrogel (PAAC = 0.4, PAAC/AA = 0.87) from 0.01 M $NaNO_3$ solution at pH 7.4.

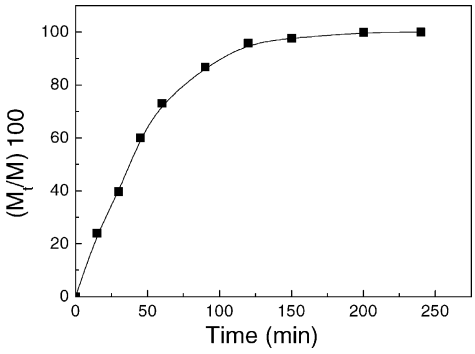


Fig. 10. Release profiles of theophylline from semi-IPN hydrogel (PAAC = 0.4, PAAC/AA = 0.87) at 37 °C and pH 7.4.

delivery systems. The preliminary experiments were conducted in $NaNO_3$ solution using theophylline as model drug.

3.3.1. Loading process

The uptake processes of theophylline by semi-IPN hydrogels at pH value varied from 4.2 to 7.4 were shown in Fig. 8.

At pH 5.2 and 7.4 the loading curves exhibited similar pattern, initially the loading quantity of theophylline remarkably increased and then level off. The loading capacity was found to less depend on the pH values as pH > 4.5, while at pH < 4.5 the uptake almost negligible due to that the hydrogels were kept in the deswollen state. The drug uptake by semi-IPN hydrogels was a fast absorption process, which reached to the maximum loading capacity within 1–1.5 h. As shown in Fig. 9 the relationship of uptake quantity and the equilibrium concentration of theophylline obeys the formula: $\sigma = kC$, σ is the uptake quantity of theophylline by hydrogel, k is a constant and C is the equilibrium concentration of theophylline, which indicated that the uptake of theophylline well followed the simplest model of Langmuir isotherm.

3.3.2. Release behavior

Fig. 10 illustrated a very fast release rate of theophylline from the semi-IPN hydrogels; almost 100% of the loaded theophylline was released from the semi-IPN hydrogels within 150 min. The following simple semi-empirical equation (Eq. (3)) [6] was used to calculate the transport exponent (n) of the theophylline released from the hydrogel, which characterized the release mechanism of the drug.

$$\frac{M_t}{M_\infty} = kt^n \tag{3}$$

where M_t/M_∞ is the fractional solute release, M_t is the concentration of solute released in time t, M is the concentration of solute released at equilibrium, k refers to the rate constant characteristic of the system. By plotting log (M_t/M_∞) versus log(t), k and n can be obtained directly from the linear portion of the slope. Based on the above

method, the transparent exponent (n) was obtained to be 0.8, which indicated that the release of theophylline from loaded hydrogels followed non-Fickian mechanism, the process of release partially controlled by viscoelastic relaxation of the matrix during water penetration.

4. Conclusion

A novel pH switching hydrogel consisted of covalent bond cross-linking networks and ionic interpenetrating networks between poly (AM-*co*-AA) and PAAC chains was synthesized by template copolymerization of acrylamide and acrylic acid in the presence of polyallylammonium chloride. The swelling of the semi-IPN hydrogels exhibited high sensitivity and reversibility to external pH stimuli. The swelling/deswelling transition pH value could be modulated in a great range by varying the molar fraction of PAAC at f_{AA} fixed or varied. TEM imagine indicated that the semi-IPN hydrogels exhibited more uniform structure with a smaller size pore compared with that of the hydrogel obtained by conventional process. The drug loading and release of the semi-IPN hydrogels were also studied using theophylline as a model drug, which indicated that drug uptake process followed the simplest model of Langmuir isotherm. While the release behavior of theophylline is a non-Fickian mechanism. The intelligent semi-IPN hydrogels are desirable to design novel drug delivery systems.

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