Radiation Polymerization and Controlled Drug Release of Polymer Hydrogels with NIPA and NVP

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ABSTRACTS: P(NIPA–NVP) and P(NIPA)/PVP interpenetrating polymer network hydrogels were synthesized by radiation polymerization in this article. Acetylsalicylic acid proved a model drug of salt resistance. Drug-controlled release of these hydrogels containing acetylsalicylic acid was investigated. Influences of radiation dose, feed composition on the lower critical solution temperature (LCST), swelling behavior, salt dissolubility, and controlled release effect were discussed. The preferable preparation conditions for the titled aim were dose rate of 1 KGy/h, total dose of 30 KGy, feed monomer ratio of NIPA:NVP between 1:1 and 4:1, and total monomer concentration of 10%. As NVP content of the hydrogel increased, LCST rose, swelling ratios increased, salt resistance improved, and both swelling and deswelling rates slowed. Due to the ability of forming association complex, these hydrogels had the function of solubilization that made the drug release of difficult dissoluble medicine effective. These hydrogels had a higher drug release at physiological environment. The experimental results showed that these hydrogels were promising materials for causing solubilization and developing a long-term controlled release system. © 2003 Wiley Periodicals, Inc. J Appl Polym Sci 88: 724–729, 2003

Key words: radiation polymerization; hydrogels; drug delivery system; N-isopropylacrylamide; N-vinylpyrrolidone

INTRODUCTION

Thermoresponsive hydrogels have recently become more attractive in the biomedical field; its use included controlled drug delivery,[1,2] immobilized-enzyme reactors,[3–5] and separation processes.[6–9] Poly(N-isopropylacrylamide) (PNIPA) is a typical one. This hydrogel swells in water or aqueous solution below the lower critical solution temperature (LCST) and shrinks above LCST.[10–15] Its copolymer hydrogels are often used in drug delivery and medicine concentration. But the drug release of difficult dissoluble medicine is not so effective. Linear P(N-vinylpyrrolidone) (PVP) has good physiological inertia and compatibility. PVP has the ability to bind reversibly to various molecules (dyes, metals, and some polymers) by forming association complexes.[16–19] Therefore, by introducing a 1-vinyl-2-pyrrolidone (NVP)-based structure into a polymer hydrogel, which is thermoresponsive in a proper temperature range, the reversible binding ability of PVP may be used together with the thermoresponsive behavior to control the interaction of various biological molecules with the derivative hydrogels.

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There are three methods for synthesis of the hydrogels involving N-isopropylacrylamide (NIPA): chemical initiation polymerization, ultraviolet irradiation polymerization, and radiation polymerization. In chemical initiation polymerization, the initiators commonly used are redox systems, ammonium persulphate or hydrogen peroxide as oxidizer, ferrous salt or tetramethylethylenediamine as reducers, and methylenebisacrylamide or glycol dimethylacrylate as crosslinkers. This method is studied more thoroughly. In ultraviolet irradiation polymerization, mercury-arc lamp with high voltage is often adopted. Photosensitizer is often added to improve photosensitivity. As irradiation time increases, the system temperature increases as well. Radiation sources for radiation polymerization could be ^{60}Co and electron beam accelerator. γ-ray produced by ^{60}Co has high penetrating power into the objective substance. However, electron beam brought out from the accelerator is only applied to the surface of the carrier. Syntheses of relative hydrogels involving NIPA by ^{60}Co radiation polymerization were less studied due to the restricted equipment.[14,20] In this simple method, crosslink degree may be controlled by feed composition, dose rate, and total dose of radiation without any additive. The product obtained is pure, not contaminated. The polymerization has nothing to do with the temperature and may be conducted at lower temperature. Thus, the containers, especially the enzyme and protein harbored, are not easy to lose their activities. Research on these hydrogels and their use are very important in both theory and application.

In this article, P(NIPA–NVP) and P(NIPA)/PVP interpenetrating polymer network (IPN) hydrogels were synthesized by radiation polymerization. Acetylsalicylic acid proved a model drug of salt resistance. Drug-controlled release of these hydrogels containing acetylsalicylic acid was investigated. Influences of radiation dose, feed composition on LCST, swelling behavior, salt dissolubility, and controlled release effect are discussed. The experimental results showed these hydrogels to be promising materials for causing solubilization and developing a long-term controlled release system.

EXPERIMENTAL

Materials

N-isopropylacrylamide was prepared by acrylonitrile and isopropanol,[21] then recrystallized with mixed solvent of hexane and benzene. NVP was obtained from Kaiyuan Fine Chemical Plant (Henan Province, China), dried over anhydrous $MgSO_4$, and vacuum-distilled in the presence of hydroquinone. Acetylsalicylic acid was obtained from Tianjin Nankai Chemical Plant. Phosphate buffer (pH = 7.4; I = 0.1), sodium chloride, potassium chloride, sodium sulfate, iron chloride, and manganese sulfate were analytically pure and used as received. Distilled water was used in all the polymerization. The radiation source was provided by Isotope Institute of Henan Province.

Synthesis of hydrogels

Preparation of NIPA homopolymers and copolymers

Aqueous solutions of monomers were mixed thoroughly and injected into clean glass plates separated by a 2 mm thick O-ring polytetrafluoroethylene. The plates were irradiated by γ-ray at room temperature with a fixed dose rate of 1 KGy/h and polymerized. After complete gelation, the hydrogel sheets were removed from the molds and punched with a borer of 1 cm diameter. The disks were immersed in excess distilled water, which was replaced daily for a week, dried at room temperature for 3 days, then under vacuum.

Preparation of P(NIPA)/PVP IPN

NIPA was added into aqueous solution of 5% PVP K30 (NIPA/PVP = 1) and mixed thoroughly. The samples were irradiated by γ-ray at 1 KGy/h dose rate and 30 KGy dose. The other procedure adopted was the same as that for the copolymers.

Measurement methods

Swelling ratios

Dried hydrogel disks were immersed and equilibrated in water or aqueous solution in glass vials, which were set in a constant temperature water bath. Each sample was taken from its respective vial, tapped with an experimental towel to remove excess surface water, and weighed directly. Swelling ratios (*SR*) were calculated as

$$SR = \frac{W_s - W_d}{W_d}$$

where W_s and W_d are the weights of swollen gel and dried gel, respectively. Relative swelling ratio was the quotient, the swelling ratio of the hydrogel measured in aqueous salt solution divided by that measured in pure water.

Drug release of hydrogels

Standard curve of acetylsalicylic acid.[22] Acetylsalicylic acid was weighed accurately, dissolved in absolute ethanol to make 100 ml solution. Distilled water was added into part of that solution, then boiled. After cooling, 0.01 mol/L $FeCl_3$ solution was added. The absorbance of a series standard solution with different concentration at 520 nm was determined by Shimadzu UV-3000 Ultraviolet Spectrophotometer. The standard curve of acetylsalicylic acid measured was $C = 172.4A - 9.65$ ($R = 0.998$).

Preparation of drug-loaded disks. Dried hydrogel disks were immersed and equilibrated in 10% acetylsalicylic acid–ethanol solution, dried at room temperature, placed in the drier, then weighed. Contents of acetylsalicylic acid were calculated.

Drug release of hydrogels. The drug-loaded disks were placed in phosphate buffer solution. Part buffer solution was taken at every set interval; 0.01 mol/L $FeCl_3$ solution was added. The absorbance at 520 nm was determined.

Scanning electron microscopy

The structural morphology of synthesized networks in the swollen state was evaluated using scanning electron microscopy (SEM). Polymer disks were swollen to equilibrium in isotonic phosphate-buffered saline at 25°C and subsequently free-dried at 25°C. Samples were coated with gold and palladium. Cross-sectional surfaces were examined with a KYKY-1000B model scanning electron microscope.

RESULTS AND DISCUSSION

Effect of radiation dose rate and total dose on polymerization

Preliminary experiments were conducted with PNIPA hydrogels. At radiation dose rate of 4 KGy/h and total dose below 40 KGy, PNIPA hydrogels synthesized were soft and elastic, while at total dose over 40 KGy, PNIPA hydrogels prepared were hard and broken into white powders under pressure. At radiation dose rate of 1 KGy/h and total dose below 40 KGy, the PNIPA hydrogels produced had thermoresponse; equilibrium swelling ratios of the hydrogels were all more than 10. While at total dose over 50 KGy, the swelling ratios of PNIPA hydrogels obtained dropped, and only little water were lost at LCST. At total dose above 70 KGy, the PNIPA hydrogels resulted did not have thermoresponse and were easily broken. The effect of temperature on equilibrium swelling ratio of PNIPA hydrogel prepared at different radiation dose was shown in Figure 1. At 10 KGy, crosslink degrees of PNIPA hydrogel networks were lower, and the hydrogels were soft. At 40 KGy, swelling ratios of the hydrogels below LCSTs dropped greatly. Within 20 and 30 KGy, crosslink degrees of PNIPA hydrogel networks were adequate, so the hydrophobic groups could act very effectively.

At radiation dose rate of 1 KGy/h, various total doses of 10 and up to 50 KGy were used to irradiate the copolymerization of NIPA and NVP with different monomer ratio. To a set composition, with the radiation dose increased, the copolymer hydrogel strengths were enhanced, the swelling ratios decreased a little, and LCSTs were similar. In this work, 30–40 KGy of radiation dose was preferable to P(NIPA–NVP) hydrogel.

Effect of feed composition on thermoresponse

With different monomer concentration and radiation dose, the swelling behavior of PNIPA hydrogels were determined. LCSTs of PNIPA hydrogels were all 33 ± 1°C. Equilibrium swelling ratios of PNIPA hydrogels at 25°C were measured. Hydrogels synthesized with 7% NIPA and radiation dose up to 40 KGy had certain strengths. PNIPA hydrogels prepared with 10% NIPA had optimum swelling ratios.

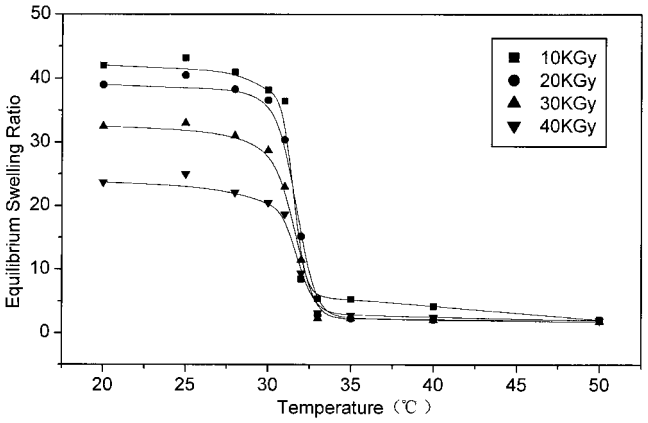

Figure 1 Effect of temperature for PNIPA hydrogels. Feed monomer of 10% NIPA.

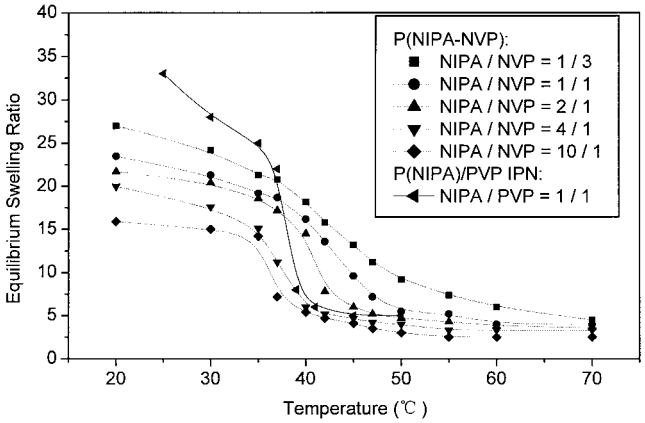

Figure 2 Effect of temperature for hydrogels. P(NIPA–PVP): feed composition of 10% (NIPA + NVP); P(NIPA)/PVP: feed composition of 5% NIPA and 5% PVP.

At 30 KGy radiation dose, with NVP content increased, the swelling ratio of copolymer hydrogel resulted was enhanced and the LCST was raised (Fig. 2). When the monomer ratio of NIPA:NVP was between 1:1 and 4:1, the LCST of P(NIPA–NVP) copolymer hydrogel was about 37°C, corresponding to physiological temperature.

By adding PVP, the LCST of IPN hydrogel of P(NIPA)/PVP was raised and was about 37°C, too. In this IPN hydrogel, PNIPA was in networks structure and joined with partial linear PVP, thus the hydrophilicity of PNIPA networks was enhanced. Scanning electron microscopy of this IPN hydrogel was shown in Figure 3.

Effect of electrolyte on relative swelling ratios

Effects of electrolytes on relative swelling ratios for P(NIPA–NVP) copolymer hydrogels and P(NIPA)/PVP IPN hydrogels were shown in Figure 4. As the ion strengths of electrolyte solutions increased, the relative swelling ratios of these hydrogels decreased, especially in more than 2 M electrolyte solutions, in the order of NaCl (KCl), Na_2SO_4, $MnSO_4$, and $FeCl_3$ solutions. However, relative swelling ratios of these hydrogels in 0.5–2 M NaCl solution dropped less. With NVP content increased, the swelling ratio of the copolymer hydrogel in aqueous salt solution was enhanced (Fig. 5). Therefore, compared with PNIPA hydrogels, P(NIPA–NVP) copolymer hydrogels and P(NIPA)/PVP IPN hydrogels improved salt resistance and had certain salt resistance as medicine carrier, considering the ionic strength of physiological envi-

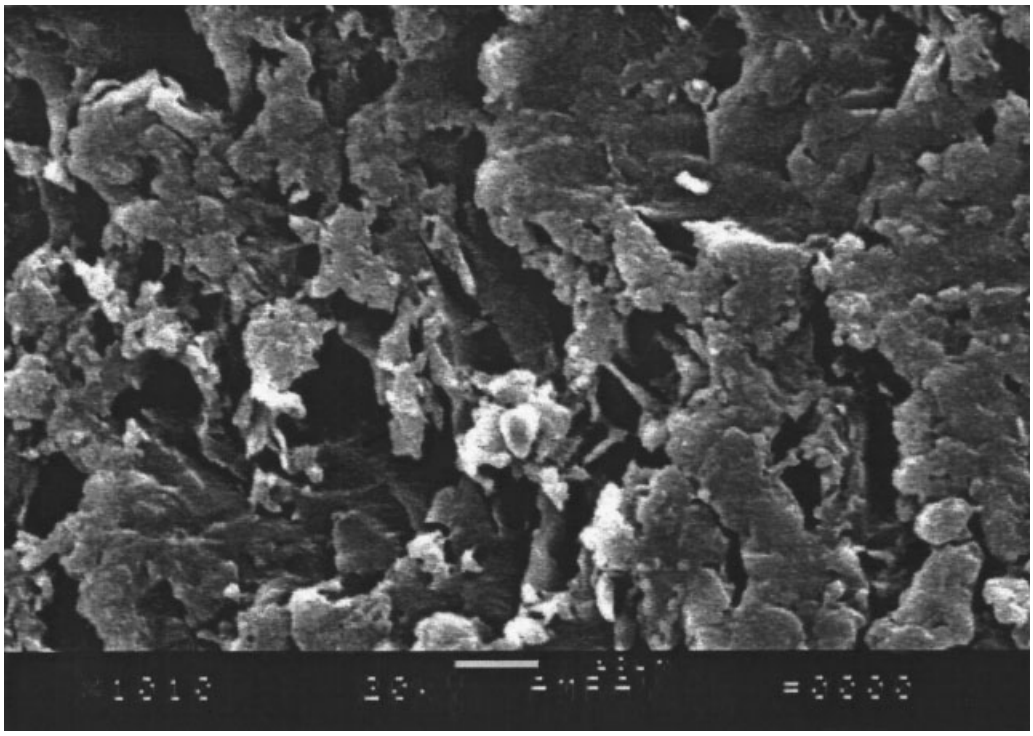

Figure 3 SEM micrograph of P(NIPA)/PVP IPN hydrogel.

ronment was about 0.1 M, less than 0.5 M. Furthermore, P(NIPA)/PVP IPN hydrogels had more salt resistance than P(NIPA–NVP) copolymer hydrogels in this work.

Swelling and deswelling kinetics

Swelling and deswelling kinetics of PNIPA, P(NIPA–NVP), and P(NIPA)/PVP IPN hydrogels prepared at 30 KGy dose were monitored at 25 and 45°C, respectively (Figs. 6 and 7). Here times to reach 80% of equilibrium swelling ratios were used as criterion of judging swelling rate. As NVP content increased, both swelling and deswelling rates slowed.

Drug release behavior

The samples of copolymer hydrogels were prepared at radiation dose of 3 KGy, feed monomer ratio NIPA/NVP of 4. The model drug release behavior of copolymer hydrogel were observed at 25°C and compared with that of PNIPA hydrogel (Fig. 8). The concentration of acetylsalicylic acid measured in complete drug release was 100 g/mL. In homopolymer hydrogel, the

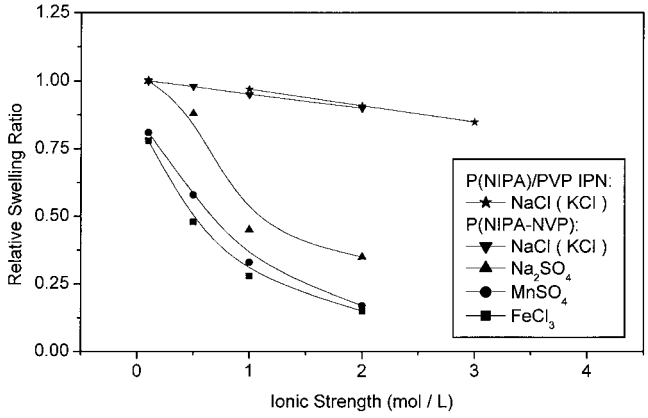

Figure 4 Effect of electrolyte for hydrogels at 25°C. P(NIPA–NVP): feed composition of 10% (NIPA + NVP); NIPA/NVP = 2.

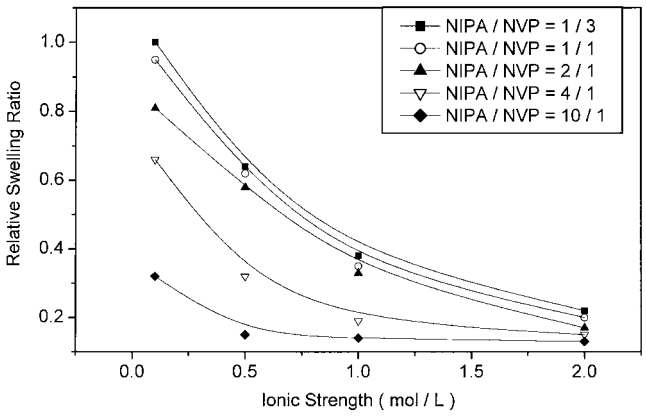

Figure 5 Effect of monomer ratio for P(NIPA–NVP) hydrogels in $MnSO_4$ solution at 25°C. Feed composition of 10% (NIPA + NVP).

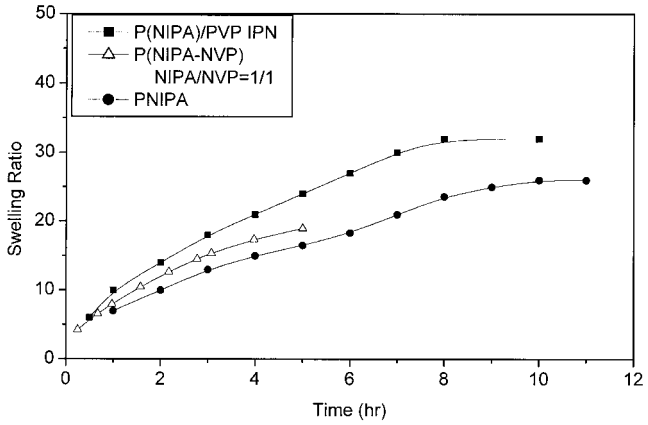

Figure 6 Swelling kinetics of hydrogels at 25°C. PNIPA: feed monomer of 10% NIPA; P(NIPA–NVP): feed composition of 10% (NIPA + NVP).

amount of drug release in the first 6 h was less than 20% of complete release, then acetylsalicylic acid was released quickly. While in copolymer hydrogel, acetylsalicylic acid was released easily, except during the first hour. The release velocity in copolymer hydrogel was obviously rapid compared with homopolymer hydrogel. Therefore, by introducing an NVP-based structure into the polymer hydrogels, PVP has the ability to improve solubility of acetylsalicylic acid by forming association complexes. (The solubility of acetylsalicylic acid was only 1/300.)

The release of acetylsalicylic acid in the same copolymer hydrogel was observed at 37°C. LCST of the copolymer hydrogel was about 37°C. At this physiological temperature, the copolymer hydrogel began to shrink, PNIPA was in contracted state, and NVP was swollen slowly. The drug release was approximately uniform during 24 h; the release time was prolonged greatly, thus the aim of long-term release was achieved.

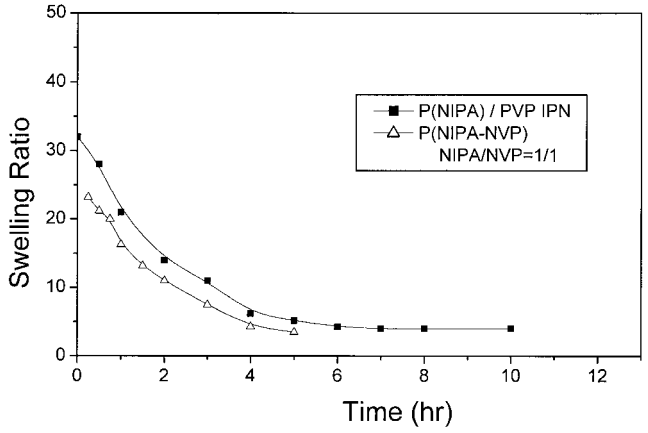

Figure 7 Deswelling kinetics of hydrogels at 45°C. P(NIPA–MVP): feed composition of 10% (NIPA + NVP).

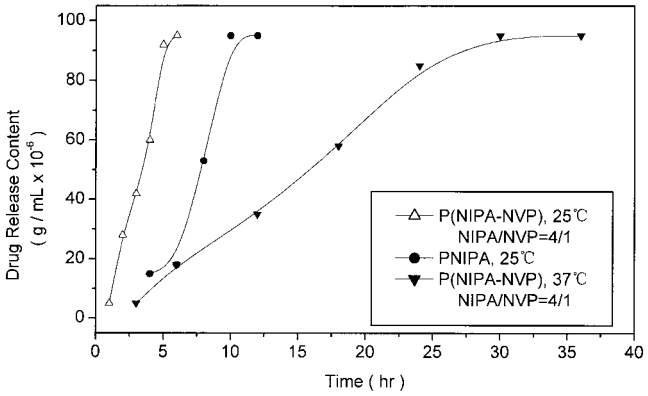

Figure 8 Drug release content for hydrogels. PNIPA: feed monomer of 10% NIPA; P(NIPA–NVP): feed composition of 10% (NIPA + NVP); NIPA/NVP = 4/1.

The release of acetylsalicylic acid measured with P(NIPA)/PVP IPN hydrogel at 37°C was shown in Figure 9. Comparing with P(NIPA–NVP) hydrogel, P(NIPA)/PVP IPN hydrogel had the same drug release behavior.

CONCLUSIONS

Polymer hydrogels were synthesized by radiation polymerization from NIPA and NVP or PVP in the form of copolymer or INP. The preferable preparation conditions for the titled aim were dose rate of 1 KGy/h, total dose of 30 KGy, feed monomer ratio of NIPA: NVP between 1:1 and 4:1, and total monomer concentration of 10%.

As NVP content of the hydrogel increased, the LCST was raised, the swelling ratios were enhanced, salt resistance improved, and both swelling and deswelling velocities slowed. Due to the ability of forming association complex, these hydrogels had the function of solubilization that made the drug release of difficult dissoluble medicine effective. These hydrogels had a higher drug release at physiological environment;

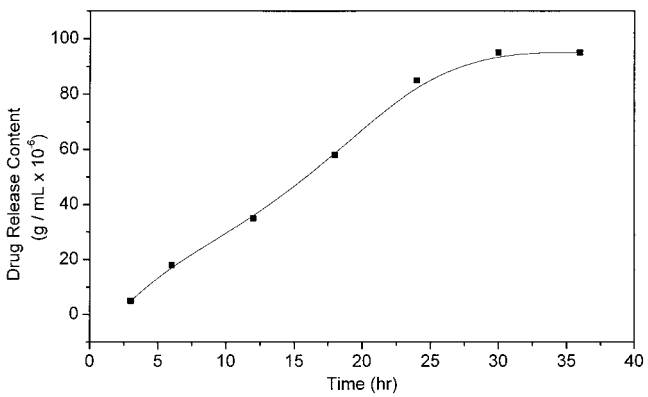

Figure 9 Drug release content for P(NIPA)/PVP IPN hydrogel at 37°C.

they are promising materials for causing solubilization and developing a long-term controlled release system.

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