Characterization and Caffeine Release Properties of N-isopropylacrylamide/Hydroxypropyl Methacrylate Copolymer Hydrogel Synthesized by Gamma Radiation

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Received 16 December 2009; accepted 20 April 2010
DOI 10.1002/app.32675
Published online 27 July 2010 in Wiley Online Library (wileyonlinelibrary.com).

ABSTRACT: Research efforts have been devoted to demonstrate that the temperature sensitivity characters of poly(N-isopropylacrylamide)(PNIPAAm) can be applied in the field of drug carriers. A copolymer hydrogel of N-isopropylacrylamide/hydroxypropyl methacrylate (NIPAAm/HPMA) was synthesized by gamma irradiation. The nature of bonding was characterized by FTIR spectroscopy, whereas the thermal stability was characterized by thermogravimetric analysis (TGA). The influence of NIPAAm/HPMA composition on the swelling properties in water, at different temperatures and different pH values was studied. The release characters of caffeine drug from NIPAAm/HPMA hydrogels were also investigated. The gel fraction of NIPAAm/HPMA was found to increase slightly by increasing the ratio of HPMA in the initial solution. The IR spectra indicate the formation of copolymer hydrogels, whereas the TGA study showed that the NIPAAm/HPMA copolymer hydrogels displayed higher thermal stability than NIPAAm hydrogel. PNIPAAm hydrogel showed higher swelling in water than NIPAAm/HPMA hydrogels. Based on Fick's law, it was demonstrated that the diffusion of water into NIPAAm/HPMA is controlled. It was found that the main parameters affecting the drug release behavior from the hydrogels are composition and pH. J Appl Polym Sci 119: 577–585, 2011

Key words: thermosensitivity; N-isopropylacrylamide copolymer hydrogels; gamma radiation; drug release characters

INTRODUCTION

Extensive attention in recent years has been devoted to intelligent or smart hydrogels because of their rapid response to external environmental stimuli changes, high water content, and biocompatibility.[1–5] These hydrogels respond to external environmental change by swelling and deswelling. Intelligent polymers are soluble, surface coated, or cross-linked polymeric materials capable of undergoing sharp physical or chemical modifications in response to external stimuli such as temperature or pH. They have been widely used in applications such as controlled drug release because of their biocompatibility with the human body and also because they resemble natural living tissue more than any other class of synthetic biomaterial. This is because of their high water content and soft consistency that is similar to natural tissue.[6–10]

Thermosensitive hydrogels based on poly(N-isopropylacrylamide) (PNIPAAm) have been developed for drug delivery, because of its unique phase transition at a lower critical solution temperature (LCST) in water around 32°C, which is near the human body temperature.[11,12] The synthesis of drug delivery hydrogels based on PNIPAAm has been processed by chemical initiation and ionizing radiation. In the field of chemical initiation, a novel thermosensitive hydrogel was designed and synthesized by graft copolymerization of N-isopropylacrylamide (NIPAAm) with biodegradable carboxymethyl chitosan (CMCS).[13] In comparison with the conventional PNIPAAm hydrogels, the resulted hydrogels have improved thermosensitive properties, including enlarged water content at room temperature and faster deswelling/swelling rate upon heating. The strategy described presents a potential alternative to the traditional synthesis techniques for thermosensitive hydrogels. A series of thermo-responsive grafted membranes with controllable length and density of grafted polymer chains were prepared by grafting PNIPAAm chains in the pores of anodic aluminum oxide (AAO) porous membranes with atom-transfer radical polymerization method.[14] The results showed that thermo-responsive characteristics of the AAO-*g*-PNIPAAm membranes were heavily affected by both the length and density of grafted PNIPAAm chains in the membrane pores, and the effect of the length of grafted PNIPAAm chains is more significant than that of the density. Azide-modified

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cellulose and alkyne-modified poly(N-isopropylacrylamide-co-hydroxyethyl methacrylate) P(NIPAAm-co-HEMA) were synthesized.[15] The obtained data showed that the formed hydrogels exhibited favorable thermosensitive properties upon temperature changes. Synthesis and characterization of hydrogels based on gamma radiation synthesis of hydrogels based on NIPAAm were also reported.[16] Anticancer drug release from poly(N-isopropylacrylamide/itaconic acid) copolymer hydrogels were synthesized by gamma radiation.[17] 5-Fluorouracil (5-FU) was used as a model anticancer drug. Diffusion of 5-FU solution into the hydrogels was found to be the non-Fickian type. Poly(N-isopropylacrylamide/itaconic acid) copolymer hydrogels synthesized by gamma radiation was used for the drug release of Lidocaine.[18] *N*-isopropylacrylamide/maleic acid (MA) copolymeric hydrogels were also prepared by irradiating the ternary mixtures of NIPAAm/MA/Water by gamma rays at ambient temperature.[19] A copolymer of (NIPAAm) and chitosan was synthesized and was studied as a pH-sensitive carrier for specifically targeting drug tumors.[20] The results revealed that drug-loaded nanoparticles, which encapsulation and loading efficiencies were 85.7% and 9.6%, respectively, exhibited pH-sensitive responses to tumor pH. The cumulative release rate was significantly enhanced below pH 6.8 and decreased rapidly above pH 6.9 at 36.5 ± 0.5°C. New smart surface-modified polypropylene (PP) was prepared for improving the loading and the sustained delivery of vancomycin and, thus, reducing the risk of biofilm formation when used as component of biomedical devices.[21] Reversible on/off-switching of bovine serum albumin permeation through a thermo-responsive composite membrane with negligible permeation in the off-state was demonstrated.[22] In this work, UV-photo grafting of PNIPAAm onto a poly(ethylene terephthalate) microfiltration membrane results in a hydrogel graft layer on the irradiated side of the membrane only. Synthesis, characterization, and the rapid response property of the temperature responsive poly(N-vinyl pyrrolidone)–graft-poly(N-isopropylacrylamide (PVP-*g*-PNIPAM) hydrogel.[23] The results showed that the PVP-*g*-PNIPAM hydrogel exhibited rapid response to the change in environmental temperature, because of free and mobile graft chains compared with the P(VP-co-NIPAM) hydrogel, which was prepared by free radical copolymerization. Thermosensitive membranes were prepared by radiation-induced graft copolymerization of monomers on PET fabrics. A binary mixture of *N*-isopropyl acrylamide (NIPAAm) and acrylic acid (AA) was grafted on polyester fabric as a base material to introduce thermosensitive poly(N-isopropyl acrylamide) pendant chains having LCST slightly higher than 37°C in the membrane.[24] The immobilization of tetracycline hydrochloride as the model drug and its release characteristics at different temperatures was investigated. It has been reported that aqueous PNIPAAm water solutions and hydrogels exhibit a LCST at 32°C,[10,25–28] below phase transition temperature NIPAAm is extremely soluble in water, however as the temperature is increased above its LCST, it becomes hydrophobic and precipitates out from the aqueous solution.

Caffeine is a well-known and widely used psychoactive substance for central nervous system from the group of xanthine derivatives and can be used to impart a desired level of increased alertness.[29] Most of the caffeine consumed comes from dietary sources. Thus, it is safe as component of food at doses required to overcoming sleep deprivation and to enhance sport performance. Many researchers have been used caffeine in the field of drug release behavior for thermosensitive hydrogels. In this contest, the influence of various drugs, including caffeine on the drug release behavior in thermosensitive hydrogels based on NIPAAm and cationic monomers was investigated.[30] The delivery ability of a pressure-controlled colon delivery capsule containing caffeine as a test drug was evaluated after oral administration to healthy male human volunteers.[31]

Poly(2-hydroxyethyl methacrylate) P(HEMA), is a favorable biomaterial because of its excellent biocompatibility and physicochemical properties similar to those of living tissues.[32,33] It also exhibits good chemical and hydrolytic stability and good tolerance for entrapped cells. Because of these unique characteristics, P(HEMA) is one of the most extensively studied materials in tissue engineering and has also been widely used as the backbone for synthesizing stimuli-responsive hydrogels. Thus the purpose of this study is to develop a dual character temperature-sensitive and drug delivery hydrogel systems based on gamma radiation copolymerization of NIPAAm and 2-hydroxypropyl methacrylate (NIPAAm/HPMA). This based on HPMA resembles HEMA in properties. The nature of bonding and structure of formed hydrogels was characterized by infrared spectroscopy. The effect of comonomer ratio on gel fraction, thermal stability and equilibrium swelling was investigated. The uptake and release of caffeine as drug model by the HPMA/NIPAAm was also studied. Caffeine was selected as a model drug from the standpoint of safety and as a nonionic drug.

EXPERIMENTAL

Materials

The NIPAAm monomer used in this study was a laboratory grade chemicals purchased from Merck

Chemical (Whitehouse, N.J. USA), and used as received. Hydroxypropyl methacrylate (HPMA), laboratory grade, purchased from Aldrich (Milwaukee, WI). A laboratory grade of N, N′-methylenebisacrylamide (MBAAm) and was obtained from Aldrich Chemical (Milwaukee, WI). Caffeine drug used throughout this study was a laboratory grade chemicals purchased from Alexandria for drugs and Pharmaceutical Products (Alexandria, Egypt), and used as received.

Preparation of HPMA/NIPAAm hydrogels

The hydrogels were prepared by dissolving different weight fractions of NIPAAm (0.50, 0.46, 0.45, 0.42, and 0.40 g) and HPMA (0.04, 0.05, 0.08, and 0.1 mL) in 5 mL of distilled water, in the presence of N,N-methylenebisacrylamide (MBAAm). MBAAm was used as cross-linker enhancer and to reduce the irradiation dose. The solutions were stirred until complete miscibility was achieved. According to the density of HPMA (1.066), the NIPAAm/HPMA hydrogel compositions were expressed as weight fractions (%) to obtain 100/0, 92/8, 89/11, 83/17, and 79/21 wt % in the mixtures. The mixtures were then poured into test tubes and deoxygenated by purging nitrogen gas for 5 min at least and sealed. The tubes were then subjected to gamma irradiation. Gamma irradiation to the required doses was carried out at a dose rate of 8.86 kGy/h in the ^{60}Co gamma cell made in Russia.

Gel fraction determination

The contents were removed from the tubes, washed with hot water to get rid of the unreacted monomers. Samples of the prepared hydrogels were accurately weighed (W_o) and then extracted with water, using Soxhlet system, and then dried in vacuum oven at 80°C to a constant weight (W_1). The gel fraction (%) was calculated according to the following equation:

$$\text{Gel fraction } (\%) = (W_1/W_o) \times 100$$

It should be noted that the recorded value of gel fraction (%) is the average of two experiments and standard deviation is ±0.015–0.02%

IR spectroscopic analysis

The infrared spectra were performed using a FTIR spectrometer (model Mattson 5000) made by Unicam over the range 500–4000 cm^{-1}. A dry constant weight from each hydrogel was ground with 3 mg of KBr and pressed to form transparent discs. The samples for IR analysis were first dried in vacuum oven at 80°C for 24 h.

Thermogravimetric analysis (TGA)

The TGA thermograms were performed on a Shimadzu–50 instrument (Kyoto, Japan) at a heating rate of 10°C min^{-1} under flowing nitrogen (20 mL min^{-1}) from room temperature to 500°C. The primary TGA thermograms were used to determine the different kinetic parameters of thermal decomposition reaction.

Swelling studies

Swelling studies were conducted on HPMA/NIPAAm hydrogels as a function of time (0–24 h). A known dry weight of insoluble hydrogel (W_d) was immersed in water at 25°C and pH of 7 up to equilibrium. The samples were removed on time intervals and blotted on filter paper to remove excess water and weighed (w_s), in which the percentage swelling was calculated according to the following equation:

$$\text{Degree of swelling } (\%) = [(W_s - W_d)/W_d] \times 100$$

It should be noted that the recorded value of swelling (%) is the average of two experiments and the standard deviation was ±1.5–8.6%.

For studying the temperature sensitivity and pH responsive characters of NIPAAm/HPMA hydrogels, dry weight (W_d) of sample hydrogels were immersed in water at 25°C for 24 h to reach the equilibrium state. The equilibrated samples were then immersed in water at different temperatures (10–50°C) and different pH values (2 and 8) to the equilibrium state (24 h) and then weighed W_c and W_{pH}, respectively. These tests were carried out in a temperature controlled water bath. During the time from removing the sample out of the water to measure its weight, care was made to insure that the required temperature was attained before the next test. The degree of swelling in each case is calculated based on the change in swelling with respect to the weight of the equilibrated sample. It should be noted that the recorded value of swelling (%) in different environmental conditions is the average of two experiments and standard deviation was ±4.6–11.3%.

Preparation of caffeine loaded gel

Caffeine was used as a model drug for the drug release studies. Dry gels of NIPAAm/HPMA hydrogels were immersed in 0.48 g/L solution of caffeine at pH 7 for 30 min in water bath at 40°C, and left at room temperature for 72 h until saturation. The drug-loaded gels were dried at room temperature.

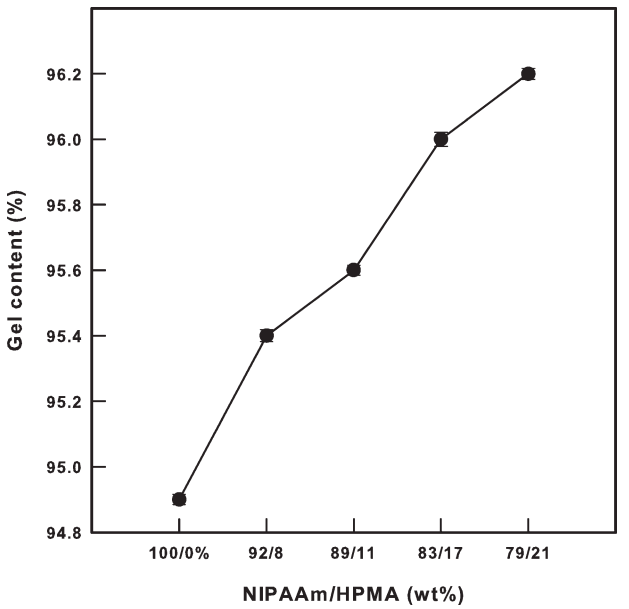

Figure 1 Effect of NIPAAm/HPMA ratio on gel fraction of hydrogels prepared at a dose of 20 kGy of gamma radiation.

Release of caffeine

NIPAAm/HPMA gels loaded with caffeine were allowed to swell in 20 mL buffer solutions of pH 2 and pH 8. At various time intervals, aliquots of 3 mL were drawn from the medium to follow the release of caffeine and returned into the vessel so that the solution volume is kept constant. Caffeine release was determined by a spectrophotometeric method using a Unicam 8625 UV/visible spectrophotometer at λ_{max} 272 nm. It should be noted that the recorded value of swelling (%) in different pH values is the average of two experiments and standard deviation was $\pm$86.4 mg/g gel.

RESULTS AND DISCUSSION

Effect on NIPAAm/HPMA comonomer ratio on gel content

NIPAAm and HPMA; both are soluble in water and have hydrophilic groups to form miscible solutions. Preliminary experiments were carried out to obtain homogenous hydrogels by changing adjusting the irradiation dose at 20 kGy in the presence of cross-linking agent to avoid using higher doses. It has been reported that the total absorption dose to attain complete gelation of NIPAAm is 48 kGy.[11] It was found that the appropriate dose to form homogenous hydrogels is 20 kGy of gamma radiation in the presence of 0.2 wt % of the cross-linking agent MBAAm.

Figure 1 shows the effect of NIPAAm/HPMA ratio, in the initial solution, on the gel content of the produced hydrogels. All hydrogels were prepared at a constant dose of 20 kGy of gamma radiation. It can be seen that the gel content of NIPAAm/HPMA hydrogels increases slightly with increasing the ratio of HPMA in the initial solutions. The gel content of NIPAAm was increased by $\sim$ 3% by using 21% of HPMA. The slight increase observed in the gel content of NIPAAm/HPMA hydrogels caused by increasing the ratio of HPMA is may be to the relatively higher sensitivity of HPMA toward gamma irradiation than NIPAAm monomer.

IR spectroscopic analysis of NIPAAm/HPMA hydrogels

IR spectroscopic analysis was used to illustrate the structure and nature of bonding of NIPAAm/HPMA copolymer hydrogels. Figure 2 shows the IR spectra of the hydrogels based on pure PNIPAAm and NIPAAm/HPMA copolymers of different weight ratios prepared at a constant dose of 20 kGy of gamma irradiation. The IR spectrum of PNIPAAm

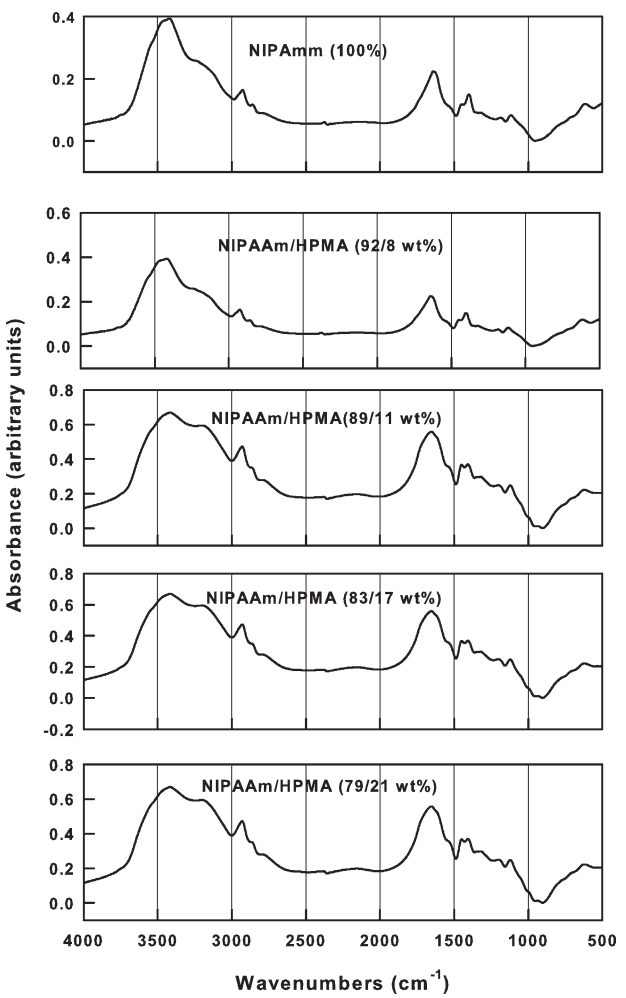

Figure 2 IR spectra of NIPAAm/HPMA hydrogels prepared at a dose of 20 kGy of gamma radiation.

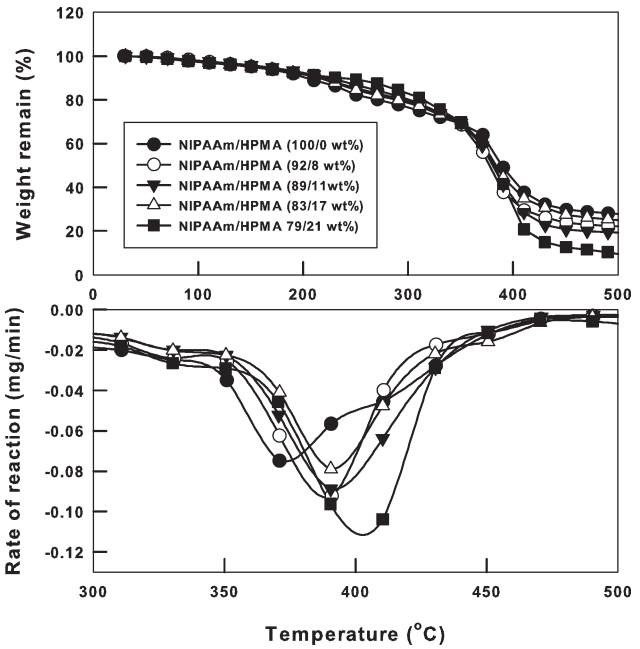

Figure 3 TGA thermograms of NIPAAm/HPMA hydrogels prepared at a dose of 20 kGy of gamma radiation.

hydrogel showed an absorption peak around 2950 cm^{-1} arising from C—H stretching. The characteristic absorption peaks, because of the C=O stretching of the amide groups can be seen at 1730 cm^{-1}. The presence of hydrogen bonding, which might be formed between the hydroxyl groups, can be confirmed by the wide absorption band at 3400 cm^{-1}. The IR spectrum of PNIPAAm, showed also characteristic bands at 1100 and 1340 cm^{-1} because of the bending vibration of C—O and C—H, respectively. The IR spectra of the hydrogels based on NIPAAm/HPMA copolymers showed different features from that of PNIPAAm, which indicates the formation of copolymers. The spectrum of NIPAAm/HPMA copolymers shows characteristic absorption peaks at 3410 cm^{-1}, 1700 cm^{-1}, and 1670 cm^{-1}, respectively, ascribed to the stretching vibrations of —OH (from HPMA), $-CONH_2$ (from PNIPAAm), and —C=O (from HPMA) groups.[34] Also, the intensity and broadness of the absorption bands increases with increasing the ratio of HPMA polymer in the initial solution.

Effect on NIPAAm/HPMA comonomer ratio on thermal stability

The dissociation energies of the covalent bonds C—H, C—C, C=O, C—O, and O—H were reported to be 414, 347, 741, 351, and 464 kJ mol^{-1}, respectively.[35] According to these values, the average complete dissociation energy for NIPAAm and HPMA monomers is calculated to be 407.1 and 416.6 kJ mol^{-1}, respectively. These values indicate that PHPMA have higher dissociation energy than PNIPAAm. Thus, it may be expected that the formation of copolymer hydrogels based on different ratios of NIPAAm and HPMA will eventually results in materials with higher thermal stability than pure NIPAAm component. Thermogravimetric analysis (TGA) was used to investigate experimentally the effect of incorporating HPMA on the thermal stability of the copolymer hydrogel. Figure 3 shows the initial TGA thermograms and the rate of thermal decomposition reaction curves. It should be noted that all the hydrogels were prepared at a constant dose of 20 kGy of gamma radiation. It can be seen that all the hydrogels undergo similar thermal decomposition behavior indicating the formation of copolymer hydrogels. However, the major thermal decomposition occurs within the temperature range 200–400°C, in which no significant difference between the thermal decomposition of neither the hydrogel based on 100% NIPAAm monomer or HPMA/NIPAAm copolymers. The derivative of the TGA thermograms (DTGA) curves for the hydrogels based on 100% NIPAAm and NIPAAm/HPMA copolymers is shown in Figure 3. The different thermal kinetics taken from these thermograms are presented in Table I. According to T_{onset}, T_{endset}, and T_{peak} temperatures, NIPAAm/HPMA copolymers possess higher thermal stability than the hydrogel based on 100% NIPAAm monomer in accordance with the theoretical calculations based on the average complete dissociation energies.

Effect of NIPAAm/HPMA comonomer ratio on equilibrium swelling

Figure 4 shows the swelling kinetics in water at 25°C for PNIPAAm and NIPAAm/HPMA hydrogels of different compositions formed at a constant dose of 20 kGy of gamma irradiation. It can be seen that the degree of swelling for all the hydrogels increases progressively within the initial time of swelling up to 6 h and after that the equilibrium state is reached. PNIPAAm hydrogel displayed higher degree of

TABLE I
Kinetic Parameters of the Thermal Decomposition Reaction of Hydrogels Based on Pure NIPAAm and NIPAAm/HPMA of Different Ratios Prepared at a Dose of 20 kGy of Gamma Irradiation

NIPAAm/HPMA Ratio (wt %)	T_{onset} (°C)	T_{endset} (°C)	T_{peak} (°C)
100/0	348	461	373
92/8	349	427	391
89/11	351	450	391
83/17	354	433	391
79/21	358	437	410

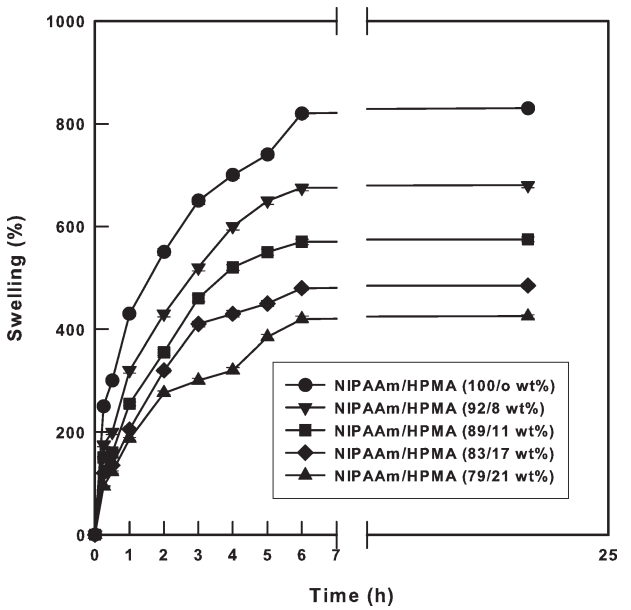

Figure 4 Swelling kinetics in water at 25°C and pH of 7 for NIPAAm/HPMA hydrogels prepared at a dose of 20 kGy of gamma radiation.

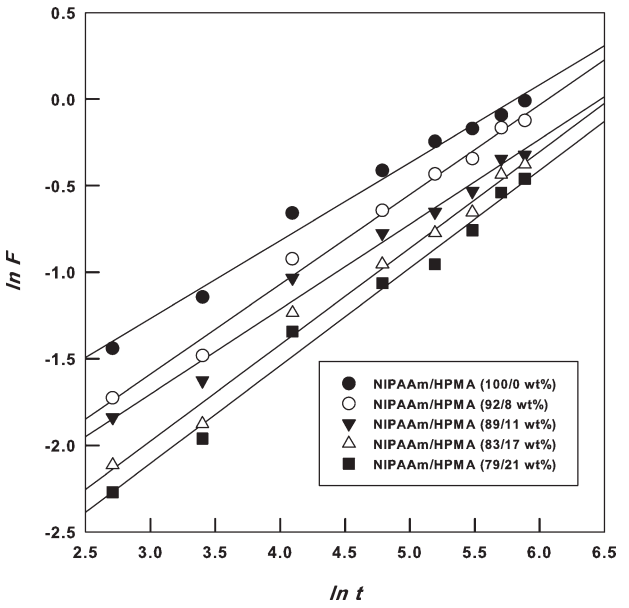

Figure 5 Linear dependence of $ln\ M_t/M_\infty$ on ln t of NIPAAm NIPAAm/HPMA hydrogels of different compositions prepared at a dose of 20 kGy of gamma radiation. The calculations were carried out for the swelling of hydrogels equilibrated at 25°C and pH of 7.

swelling than the hydrogels based on NIPAAm/HPMA. This is because of the higher hydrophilic character of PNIPAAm than HPMA. The degree of swelling of NIPAAm/HPMA hydrogels displayed a systematic trend in accordance with composition.

To obtain a more quantitative understanding of the nature of the sorption kinetic in NIPAAm/HPMA copolymeric hydrogels, the initial swelling data were fitted to the exponential Ficks equation.[36]

$$F = M_t/M_\infty = kt^n$$

Where F is the fractional sorption, M_t/M_∞; where M_t is the amount of solvent absorbed at time t, M_∞ is the maximum amount absorbed; k is a constant incorporating characteristic of macromolecular network system, n is the diffusion exponent, which is indicative of the transport mechanism. The exponents n and k values were calculated from the slope and intercept of the plots of $ln\ F$ versus $ln\ t$ for pure PNIPAAm and NIPAAm/HPMA copolymer hydrogels at different HPMA contents. For Fickian kinetics in which the rate of diffusion is rate limiting, $n = 0.5$, whereas a value of $0.5 < n < 1$ indicates an anomalous non-Fickian type diffusion and contributes to the water-sorption process Figure 5 shows linear dependence of $ln\ M_t/M_\infty$ on $ln\ t$ of NIPAAm NIPAAm/HPMA hydrogels of different compositions prepared at a dose of 20 kGy of gamma radiation. The results in Table II indicate that as the HPMA content increases the water fractional uptake at the same absorption time increases. It is clear from the analysis that as the HPMA content in the gel structure increases the diffusion release kinetic exponent n increases from 0.45 to 0.56 for NIPAAm/HPMA hydrogels. This evidence shows that the swelling transport mechanism was transferred from Fickian to non-Fickian transport with the increasing HPMA content in the gel structure.

Thermosensitive characters of NIPAAm/HPMA hydrogels

The PNIPAAm hydrogels are attracting more and more interest in biomedical applications because they exhibit a well-defined LCST in water around 31–34°C, which is close to the body temperature. Figure 6 shows the effect of temperature on the equilibrium swelling of PNIPAAm and NIPAAm/HPMA hydrogels. It can be seen that there is a transition change in the equilibrium swelling of NIPAAm/HPMA hydrogels over the temperature range 30–40°C. PNIPAAm is a model of temperature

TABLE II
Kinetic Parameters of Water Diffusion into NIPAAm/HPMA Hydrogels

NIPAAm/HPMA Ratio (wt %)	$k \times 100$	n
100/0	7.295	0.45
92/8	4.294	0.52
89/11	4.163	0.49
83/17	2.599	0.58
79/21	2.242	0.56

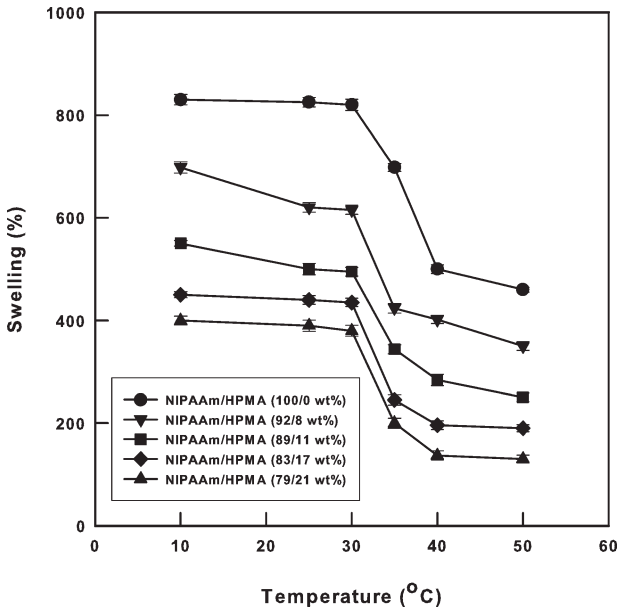

Figure 6 Effect of temperature on the equilibrium swelling at pH of 7 for NIPAAm/HPMA hydrogels prepared at a dose of 20 kGy of gamma radiation.

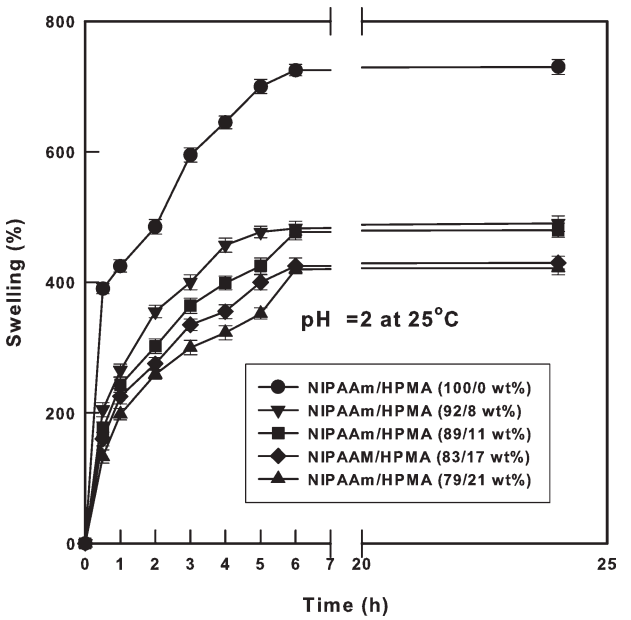

Figure 7 Equilibrium swelling at 25°C and pH of 2 of NIPAAm/HPMA hydrogels prepared at a dose of 20 kGy of gamma radiation.

responsive hydrophilic hydrogel segment. The transition change is probably because of the formation of copolymer network structures.

Effect of pH on equilibrium swelling of NIPAAm/HPMA hydrogels

The equilibrium swelling-time relationship at 25°C and different buffer solutions for the hydrogels based on PNIPAAm and NIPAAm/HPMA, prepared at a dose of 20 kGy of gamma irradiation, conducted is shown in Figures 7 and 8. It can be seen that all the hydrogels exhibit high water uptake in which the swelling increases with increasing the HPMA ratio in the initial solutions. However, an opposite situation is seen at low pH value, in which the equilibrium swelling decreases with increasing the HPMA ratio. PNIPAAm is a nonionic hydrogel and does not have any group that could be ionized in aqueous solutions.[37] Also, PHPMA is practically not pH-sensitive and does not have any group that could be ionized in aqueous solutions. In acidic solution, the NIPAAm/HPMA hydrogels were in collapsed state due to the formation of hydrogen bonding between the OH^- groups of the HPMA chains and the $CO{-}NH_2$ amide groups of NIPAAm.[3] In alkaline solution, the carbon of the carbonyl group of an ester may be attacked by a good nucleophile before protonation.[38] This is the same addition-elimination path as for nucleophilic attack on acid chlorides or anhydrides leading to ionized COO and also the hydrogen bonding formed between NIPAAm and HPMA at low pH values could be broken.

Upload and release of caffeine studies

First, a standard curve representing the UV absorbance of different concentrations of caffeine (at λ_{max}= 272 nm) was constructed. The relation correlating this curve can be written as: $y = 0.07731\ x + 0.0773$ or Absorbance = concentration (g L^{-1}) × 0.0773.

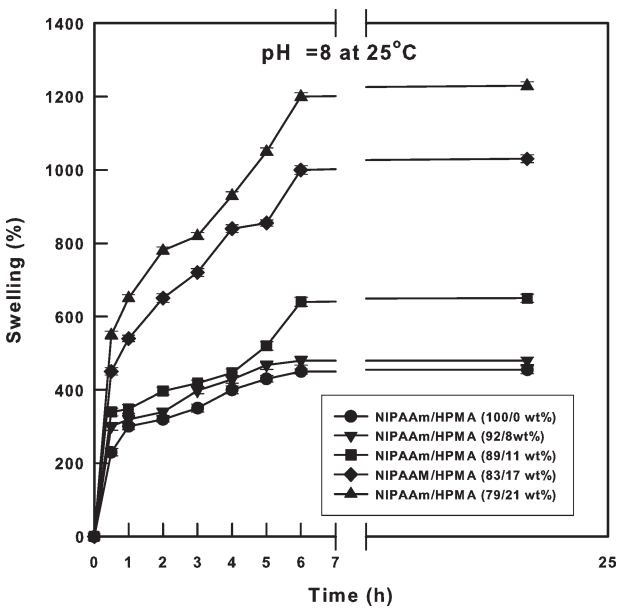

Figure 8 Equilibrium swelling at 25°C and pH of 8 of NIPAAm/HPMA hydrogels prepared at a dose of 20 kGy of gamma radiation.

From this relation the concentration of unknown sample can be determined. Before the release experiment, the amount of caffeine loaded in the hydrogels was measured. It was found that amount of caffeine loaded depends on hydrogel composition. Taking in consideration that the loading process was carried out in saturated solution of caffeine and at pH of 7, the amount measured for the different hydrogels was as follows:

PNIPAAm (100%) = 250 mg g^{-1} gel
NIPAAm/HPMA (92/8 wt %) = 235 mg g^{-1} gel
NIPAAm/HPMA (89/11 wt %) = 210 mg g^{-1} gel
NIPAAm/HPMA (83/17 wt %) = 155 mg g^{-1} gel
NIPAAm/HPMA (79/21 wt %) = 100 mg g^{-1} gel

It is clear that the upload ratio of caffeine into the hydrogels is largely related to the swelling ratio of the hydrogels as shown in Figure 4 rather than the functional groups of hydrogels.

The accumulated release (mg g^{-1} dry gel) profile of caffeine at different pH values as a function of time from NIPAAm/HPMA hydrogels, prepared by gamma irradiation at a dose of 20 kGy, was studied as shown in Figures 9 and 10. It can be seen that the release from the hydrogel increases with time to reach equilibrium after 6 h at pH 2 or pH 8, in which the release at pH 8 is $\sim$ 2.5 times at pH 2.

CONCLUSIONS

In this study, the preparation of the novel NIPAAm/HPMA hydrogels and their drug release behaviors have been investigated. For the characterization of these hydrogels, the effect of composition on gel fraction and thermal stability was studied. It has been found that the specific swelling capacity of hydrogels increases with increasing HPMA content in the gel structure. This has been explained because of the incorporation of more specific OH^- groups into the network and consequent higher swelling capacity of the gels. As the hydrogels prepared in this study can be considered as potential carriers for the drug delivery systems, their drug release behaviors were investigated at the physiological pH. The release studies showed that some of the basic parameters affecting the drug release behavior of NIPAAm/HPMA hydrogels are pH of the solution. In conclusion, the hydrogels prepared in this study may be used as especially local therapeutic application of cationic drugs such as caffeine under controlled pH.

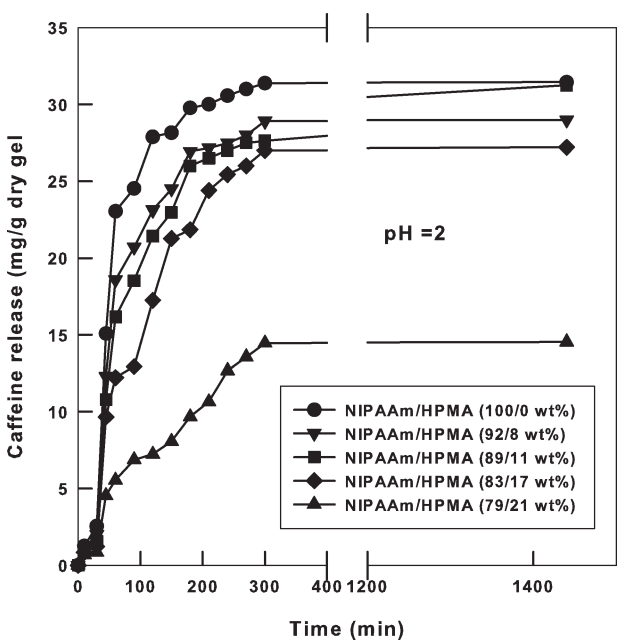

Figure 9 Release profile of caffeine drug at 25°C and pH of 2 from NIPAAm/HPMA hydrogels of different compositions, prepared at a dose of 20 kGy of gamma radiation, as a function of time.

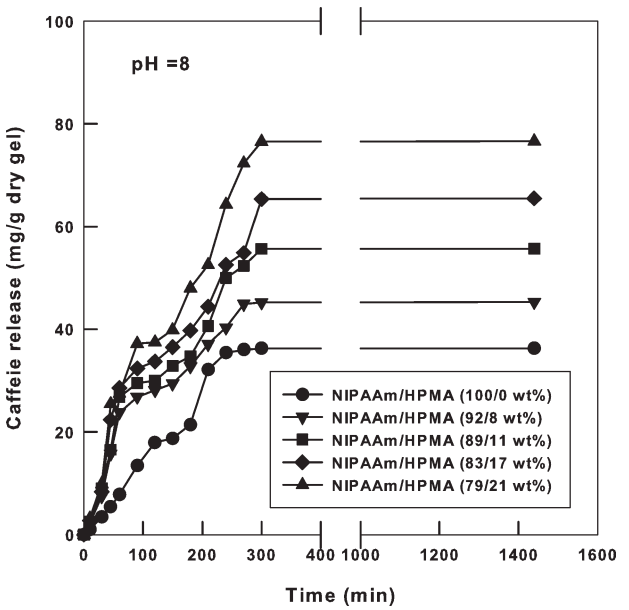

Figure 10 Release profile of caffeine drug at 25°C and pH of 8 from NIPAAm/HPMA hydrogels of different compositions, prepared at a dose of 20 kGy of gamma radiation, as a function of time.

References

1. Huang, X.; Nayak, B. R.; Lowe, T. L. J Polym Sci Part A: Polym Chem 2004, 42, 5054.
2. Langer, R.; Peppas, N. A. AIChE 2003, 49, 2990.
3. Huang, X.; Lowe, T. L. Biomacromolecules 2005, 6, 2131.
4. Zhang, J. T.; Huang, S. W.; Cheng, S. X.; Zhuo, R. X. J Polym Sci Part A: Polym Chem 2004, 42, 1249.
5. Zhang, X. Z.; Wu, D. Q.; Sun, G. M.; Chu, C. C. Macromol Biosci 2003, 3, 87.
6. Devine, D. M.; Higginbotham, C. L. Polymer 2003, 44, 7851.
7. Anseth, K. S.; Bowman, C. N.; Brannon-Peppas, L. Biomaterials 1996, 17, 1647.
8. Kishida, A.; Ikada, Y. In Polymeric Biomaterials, 2nd ed.; Dumitriu S, Ed.; 2002, p 133.

9. Ravichandran, P.; Shantha, K. L.; Panduranga Rao, K. Int J Pharm 1997, 154, 89.
10. Peppas, N. A.; Bures, P.; Leobandung, W.; Ichikawa, H. Eur J Pharm Biopharm 2000, 50, 27.
11. Guo, C. B.; Gao, Q. Y. Carbohydr Res 2007, 342, 2416.
12. Guilherme, M. R.; Silva, R.; Girotto, E. M.; Rubira, A. F.; Muniz, E. C. Polymer 2003, 44, 4213.
13. Hou-Feng, Z.; Hui, Z.; Li-li, Z.; Sai-Bo, C.; Yi-jiang, Z.; Yu-lan, Z. Carbohydr Polym 2009, 77, 785.
14. Li, P. F.; Xie, R.; Jiang, J. C.; Meng, T.; Yang, M.; Ju, X. J.; Yang, L.; Chu, L.-Y. J Membr Sci 2009, 337, 310.
15. Zhang, J.; Xu, X. D.; Wu, D. Q.; Zhang, X. Z.; Zhuo, R. X. Carbohydr Polym 2009, 77, 583.
16. Nizam El-Din, H. M. J Macromol Sci Pure Appl Chem 2007, 44, 1209.
17. Tasdelen, N.; Kayaman-Apohan; Güven, O.; Baysal, B.M. Radiat Phys Chem 2005, 73, 340.
18. Tasdelen, N.; Kayaman-Apohan; Güven, O.; Baysal, B.M. Radiat Phys Chem 2004, 69, 343.
19. Tasdelen, N.; Kayaman-Apohan; Güven, O.; Baysal, B.M. Radiat Phys Chem 2004, 69, 303.
20. Fan, L.; Wu, H.; Zhang, H.; Li, F.; Yang, T.-H.; Gu, C.-H.; Yang, Q. Carbohydr Polym 2008, 73, 390.
21. Ruiz, J.; Alvarez-Lorenzo, C.; Taboada, P.; Burillo, G.; Bucio, E.; Prijck, K.; Coenye, T.; Concheiro, A. Eur J Pharm Biopharm 2008, 70, 467.
22. Micky, A. M. E.; Vertommen, H. J. L.; Cornelissen, C. H. J. T.; Dietz, R. H.; Maartje F.; Kemmere, J. T. F.; Keurentjes. J Membr Sci 2008, 322, 243.
23. Shuping, J.; Mingzhu, L.; Shilan, C.; Chunmei, G. Eur Polym J 2008, 44, 2162.
24. Gupta, B.; Mishra, S.; Saxena, S. Radiat Phys Chem 2008, 77, 553.
25. Ju, H. K.; Kim, S. Y.; Kim, S. J.; Lee, Y. M. J Appl Polym Sci 2002, 83, 1128.
26. Kopecek, J. Eur J Pharm Sci 2003, 20, 1.
27. Deshmukh, M. V.; Vaidya, A. A.; Kulkarni, M. G.; Rajamohonan, P. R.; Ganapathy, S. Polymer 2000, 41, 7951.
28. Kim, S. J.; Lee, C. K.; Lee, Y. M.; Kim, S. I. J Appl Polym Sci 2003, 90, 3032.
29. McLellan, T. M.; Kamimori, G. H.; Voss, D. M.; Bell, D. G.; Cole, K. G.; Johnson, D. Aviat Space Environ Med 2005, 76, 647.
30. Lee, W. F.; Lee, R. J. C.; Chin, R. Mater Sci Eng C 2002, 20, 161.
31. Muraoka, M.; Hu, Z.; Shimokawa, T.; Sekino, S.; Kurogoshi, R.; Kuboi, Y.; Yoshikawa, Y.; Takada, K. J Controlled Release 1998, 52, 119.
32. Brahim, S.; Narinesingh, D.; Elie, A. G. Biomacromolecules 2003, 4, 497.
33. Lahooti, S.; Sefton, M. V. Tissue Eng 2000, 6, 139.
34. Ghanshyam, S.; Chauhan, S.; Sen, C. U.; Garg, D. Desalination 2009, 243, 95.
35. Whittin, K. W.; Gailelt, K. D. General Chemistry with Quantitative Analysis, Saunders College Publishing: Philadephia, 1981, p 372.
36. Peppas, N. A.; Franson, N. F. J Polym Sci Polym Phys Ed 1983, 21, 983.
37. Tasdelen, B.; Kayaman-Apohanb, N.; Olgun Güven, O.; Baysal, B. M. Int J Pharm 2004, 278, 343.
38. Ralph, J. F.; Joan, S. F. Organic Chemistry, Willard Grant Press, Philadelphia, USA, 1981; Chapter 13, p 627.