Design and Development of Temperature Sensitive Porous Poly(NIPAAm-AMPS) Hydrogels for Drug Release of Doxorubicin-a Cancer Chemotherapy Drug

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ABSTRACT: Temperature sensitive polymer network porous hydrogels were developed with N-Isopropylacrylamide (NIPAAm) and AMPS (2-acrylamido-2-methyl-1-propanesulfonicacid), as well as with sucrose as porogen by crosslinking with hydrophilic crosslinker N,N[1]-methylenebisacrylamide (MBA). The temperature responsive behaviour, the swelling/deswelling kinetics of the hydrogels were investigated. The structural and morphological characterizations of the developed hydrogels were obtained from FTIR spectroscopy and scanning electron microscopy (SEM). The increment in the lower critical solution temperature (LCST) of NIPAAm hydrogels can be done with the help of AMPS and it is confirmed with differential scanning calorimetry (DSC) as well as temperature dependent swelling curves. The model cancer chemotherapy drug Doxorubicin (Dox) was loaded into theses hydrogels and the release studies as well as the released profiles of the drug showed that more than 8–54% of the loaded drug was released in the first half-an-hour at a buffer solution of 7.4 and the rest of the drug was released slowly. © 2010 Wiley Periodicals, Inc. J Appl Polym Sci 116: 3593–3602, 2010

Key words: porous; swelling/deswelling kinetics; doxorubicin lower critical solution temperature

INTRODUCTION

Temperature sensitive hydrogels can absorb huge amount of water below their lower critical solution temperature(LCST) but hold less amount of water above their LCST.[1] These temperature-sensitive hydrogels have large potential activity in biomedical field such as controlled drug delivery systems, immobilized-enzyme reactors[2,3] and other biological applications.[4,5]

Poly(N-Isopropylacrylamide) (PNIPAAm) is one of the most popular well known temperature-sensitive hydrogel. These hydrogels are able to swell or deswell as a result of change in the temperature of the surrounding medium. Because of their unique properties these hydrogels are used in a number of applications.[6–8] Generally, in the case of temperature-sensitive hydrogels, LCST property plays an important role. This property can be analyzed on the basis of its chemical and physical properties[9–11] and also depends on the composition of the co-monomers.[12,13] If the composition of the hydrogel has a hydrophilic co-monomer, its LCST property increases, whereas the incorporation of hydrophobic co-monomer in the hydrogel leads to decrease in its LCST.[14,15]

2-Acrylamido-2-methyl-1-propanesulfonic acid is basically a strong acid[16,17] which can act as a good hydrophilic monomer. Therefore, its products have super swelling properties.[18–21] Depending on these properties they are used in a number of applications such as water absorbent[22] and contact lenses.[23]

This work involves the development of PNIPAAm porous hydrogels with higher LCST value by incorporating hydrophilic AMPS monomer(2-acrylamido-2-methyl-1-propanesulfonic acid) as well as sucrose as porogen in the hydrogel networks and crosslinking with another hydrophilic MBA(*N,N*[1]-methylenebisacrylamide) as a crosslinker. The effect of AMPS concentration on the swelling behaviour of hydrogel, equilibrium swelling ratio values in water as well as Doxorubicin drug loading and drug release profiles at different temperatures were also investigated.

EXPERIMENTAL

Materials

Analytical reagent grade samples of *N*-Isopropylacrylamide (NIPAAm), 2-acrylamido-2-methyl-1-propanesulfonic acid (AMPS) and Doxorubicin were

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TABLE I
Composition and Swelling Data of Poly(NIPAAm-AMPS) Hydrogels

Hydrogel Code	Concentration in the feed mixture of the hydrogel net works						Swelling ratio at equilibrium (S_{eq}) (g/g)	Equilibrium water content (EWC) (%)
	NIPAM m*M*	AMPS m*M*	Sucrose m*M*	MBA m*M*	APS m*M*	TEMAD m*M*		
B	8.837	–	–	0.648	2.191	0.172	4.383023	81.42308
NA1	8.837	0.2412	0.8764	0.648	2.191	0.172	11.69113	92.12048
NA2	8.837	0.4825	0.8764	0.648	2.191	0.172	13.59655	93.14907
NA3	8.837	0.9650	0.8764	0.648	2.191	0.172	32.83838	97.04478
NA4	8.837	1.4475	0.8764	0.648	2.191	0.172	52.41772	98.12796

purchased from Aldrich chemicals. Sucrose (SR), *N,N*[1]-methylenebisacrylamide (MBA), ammonium persulphate (APS), and *N,N,N*[1],*N*[1]-teramethlethylenediamine (TMEDA) were purchased from S.D fine chemicals. All the chemicals were used without further purification. Throughout the experiments double distilled water was used.

Synthesis of hydrogels

N-Isopropylacrylamide (8.83 m*M*) was dissolved in 2 mL of distilled water and taken in a 250 mL beaker. To this 0.2412 m*M* AMPS was added as a co-monomer. Then 0.8764 m*M* of SR a porogen, 0.0648 m*M* of MBA as a hydrophilic crosslinker and also 2.191 m*M* of APS, 0.172 m*M* of TMEDA as an initiating pair system were added. After the addition of the reactants the temperature of the system was raised to 50°C for 30 min. After the reaction has been completed, the hydrogel was immersed in distilled water at room temperature for 24 h to remove the unreacted materials present in the hydrogel network. Finally, the hydrogel was dried at room temperature for 2 days. Similarly, other hydrogels were prepared by the above procedure. The feed compositions of the hydrogels are presented in Table I.

Swelling measurements

The equilibrium swelling behaviour of the hydrogels was measured by gravimetric method. The hydrogels were made to swell with distilled water at room temperature until the swelling equilibrium was reached (almost 20 h) and were removed and blotted with filter paper to remove the overloaded water on the surface, and weighed. The immersion time and drying procedure were repeated until the weight of swollen samples was constant. The swelling ratio, equilibrium swelling ratio, and the swelling water content in percentage was defined as follows:

$$\text{Swelling ratio } (S_{g/g}) = [W_t - W_d/W_d]$$

$$\text{Equilibrium swelling ratio } (S_{eq}) = [W_s - W_d/W_s]$$

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

where W_t, W_s and W_d are the weights of the swollen state of the gels at time t, at equilibrium and dry gel, respectively.

Swelling and diffusion characteristics evaluation

To evaluate the mechanism of the swelling process of hydrogels, several kinetic models are used to test the experimental data. A simple kinetic analysis is the second order equation.[24,25]

$$d\,S/dt = k_s(S_{eq} - S)^2$$

where k_s, S_{eq}, and S refer to swelling rate constant, the equilibrium swelling(theoretical) and swelling at any time, respectively. The combination of the above equation over the limits $S = S_o$ at time $t = t_o$ and $S = S$ at equilibrium time $t = t$, gives the following equation.

$$t/S = A + Bt,$$

where $B = 1/\ S_{eq}$ is the converse of the maximum or equilibrium swelling, $A = (1/k_s S_{eq}^2)$ is the equal of the initial swelling rate of the hydrogel and k_s is the swelling rate constant. To observe the above kinetic model for these hydrogel, t/s versus t graphs were plotted and the initial rate of swelling (r_i), swelling rate constant (k_s), and theoretical equilibrium swelling (S_{eq}) values of hydrogels were calculated from the slope and intersection of the lines obtained in the graphs.[26] The dynamics of the water sorption process were investigated by monitoring the change in the amounts of water imbibed by the hydrogel at various intervals. In the present diffusion study also, the previous swelling results were utilized. For the kinetic analysis, the swelling results obtained were utilized only up to 60% of the swelling curves.[27,28]

$$F = W_s - W_d/W_d = k\,t^n$$

where F, W_s, and W_d denote the fraction swelling ratio at time t, the weight of the swollen hydrogel at t, and the weight of the dried hydrogel at time $t = 0$,

respectively, k is a swelling constant related to the structure of the network and n is the swelling exponent, which indicates the water transport mechanism. When $n = 0.5$, the release is Fickian in nature and diffusion controlled, whereas values of n between 0.5–1.0 indicate non-Fickian diffusion (anomalous diffusion). In anomalous diffusion, diffusion and relaxation are said to be isochronal effective.[27,28] If n value is exactly equal to unity, then the diffusion is designed as Case II diffusion. In very few cases, the n value is found to exceed unity and is called super Case II diffusion ($n > 1$). To estimate the swelling exponent (n) by using the above equation up to 60% of the swelling values, In S versus In t graphs were plotted to obtain straight lines. The swelling exponent was calculated from the slope of the lines of In S-In t plots.

The diffusion coefficient of theses hydrogels were calculated by using the short time approximation method.[29,30] This method is valid for the first 60% of the swelling results. The hydrogels diffusion coefficients were calculated using the following equation:

$$S = 4[D/\Pi r^2]^{1/2} t^{1/2}$$

where D, r, S, and t represent the diffusion coefficient of the hydrogel, the radius of the hydrogel, fractional swelling, and time, respectively. To investigate the diffusion coefficient of hydrogels, S versus $t^{1/2}$ plots were plotted and diffusion coefficients were calculated from the slopes of these lines.

Characterizations

FTIR spectrophotometer was used to identify the hydrogel formation. To record the FTIR spectra of hydrogel, the samples were completely dried in an oven (Baheti Enterprises, Hyderabad, India) at 40°C for 6 h. These samples were read between 600 and 4000 cm^{-1} on a Bruker IFS 66V FTIR spectrometer(Ettlingen, Germany) using the KBr disk method. UV-Vis absorption spectra of the samples were recorded on an ELICO SL 164 Model (The Elico co, Hyderabad, India). The drug loading efficiency and releasing profiles of Doxorubicin in the hydrogels samples were determined by UV-spectral measurement[31] at λ_{max} 491nm. Scanning Electron Microscopy, SEM, (JEOL JSM 840A, Tokyo, Japan) was employed to study the internal structure of hydrogels under dry conditions. The dry samples were coated with a thin layer of palladium gold alloy.

Determination of the phase-transition temperature (LCST)

The experiment was carried out in a thermostatic water bath equipped with systems of heating and cooling. The hydrogels were placed in distilled water at several temperatures, ranging from 20 to 80°C until the equilibrium swelling ratio of the samples was reached. Then, the excess water on the samples surface was removed as stated above, and the samples were weighed. The phase transition temperature associated with the LCST was determined as the inflexion point in the plot of swelling as a function of temperature, and also confirmed by differential scanning calorimetry (DSC), using a TA instruments Model 2010. NA4 sample were immersed in distilled water at ambient conditions and allowed to swell to reach equilibrium prior to DSC measurement. These swollen samples were placed inhermetically in sealed pans and the thermal analysis was performed at a heating rate of 2°C/min. The onset point of the endothermic peak was used to estimate the LCST.

Drug loading

In a typical Doxorubicin (Dox) drug loading process, 50 mg of dry hydrogel was allowed to equilibrium swelling in a drug solution (10 mg in 25 mL of distilled water) for 24 h at 25°C. Then the swollen hydrogel was transferred in to a disk and allowed to dry at 25°C for 2 days. The drug loading efficiency of Dox in the hydrogel sample was determined by UV-spectral measurement (The Elico.Co, Hyderabad, India) method at λ_{max} 491 nm. The results of percentage of encapsulation efficiency were calculated by using the eq. (1). The results are depicted in Table IV.

$$\% \text{ Encapsulation efficiency} = [\% \text{ Actual loading}/\% \text{Theoretical loading}] \times 100$$

In vitro drug release

The *in vitro* release studies of the Dox drug were carried out by placing the dried and Dox loaded hydrogel in definite volume (50 mL) of releasing medium(7.4 pH phosphate buffer) at various temperatures (20-50°C). Drug release kinetics were analyzed by using the percentage of cumulative release data[32] (Mt/Mo) versus time (where Mt is the amount of drug released at time t and Mo is the initial loaded drug amount), the amount of Dox release was measured spectrophotometrically in pH 7.4 buffer. The absorption of the solutions of Dox was measured at λ_{max} 491nm

RESULTS AND DISCUSSIONS

Effect of AMPS concentration on swelling and diffusion characteristics of hydrogels

The experiment results of swelling and diffusion kinetics of the hydrogels were evaluated at room

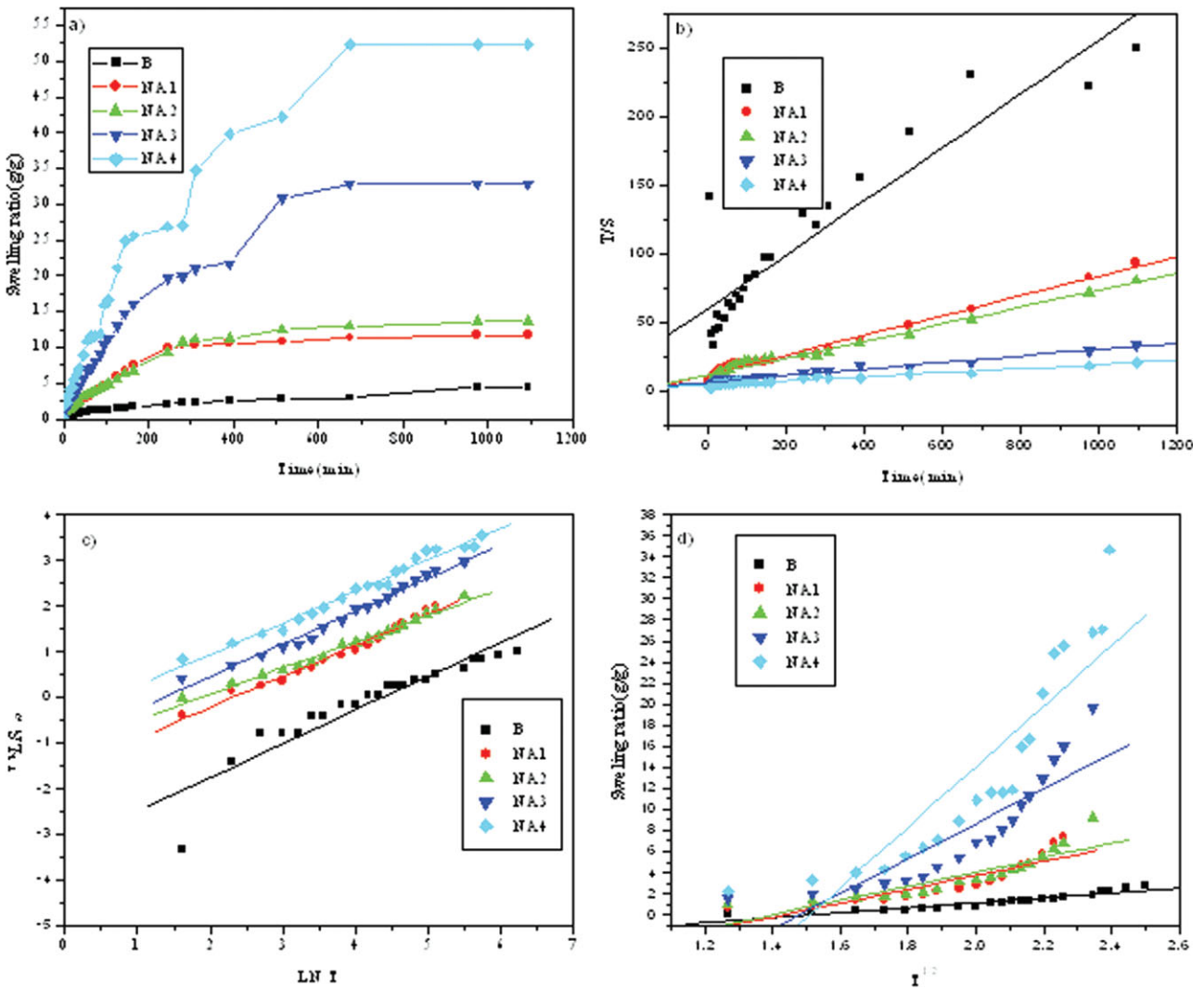

Figure 1 Influence of AMPS content on swelling behaviour of hydrogels (B, NA1, NA2, NA3, NA4) (a) Swelling isotherms, (b) T/S and T graph, (c) Ln S and Ln T graph, and (d) S and T^{1-2} graphs of hydrogels. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

temperature. The relationship between the AMPS concentration and water absorbency values was studied by varying the AMPS concentration from 0.2412 to 1.4475 m*M*. The results are presented in Figure 1(a) indicating that, the equilibrium swelling ratio increases from 4.3 to 52 g/g when the AMPS concentration increased from 0.2412 to 1.4475 m*M*. The increase in the water absorbency with an increase in the amount of AMPS concentration is due to the hydrophilic nature(acid groups) of the AMPS monomer, thereby more number of water molecules will be bound to the AMPS chains which inturn increases the swelling capacity.[32] But in the case of blank hydrogel the network does not have more hydrophilic groups, when compared with AMPS added hydrogels. Therefore, its swelling ratio has less value when compared with AMPS added hydrogels. Figure 2 shows the dry hydrogel, swollen and deswelled photographs of NA4 hydrogel.

The swelling and diffusion kinetic parameters, such as initial swelling rate (r_i, g water/g hydrogel/min) (0.01713–0.00627), swelling rate constant (k_s, g gel/g water/min) (248.22–0.0122), theoretical equilibrium swelling (T_{seq} g water/g hydrogel) (0.159118–4.341408) [Fig. 1(b)], swelling exponent(n) (0.73–0.57) [Fig. 1(c)] equilibrium water content (EWC%, 81.423–98.127), and diffusion coefficient ($cm^2\ s^{-1}$) (0.178–3.439) [Fig. 1(d)] were calculated from the dynamic swelling ratio values for the hydrogels prepared with different amounts of AMPS. The diffusion coefficient results indicate that the swelling transport mechanism is of non-Fickian in nature. These values are presented in Table II.

Effect of feed composition on thermoresponse

The swelling capacity as a function of monomer concentration with respect to temperature was

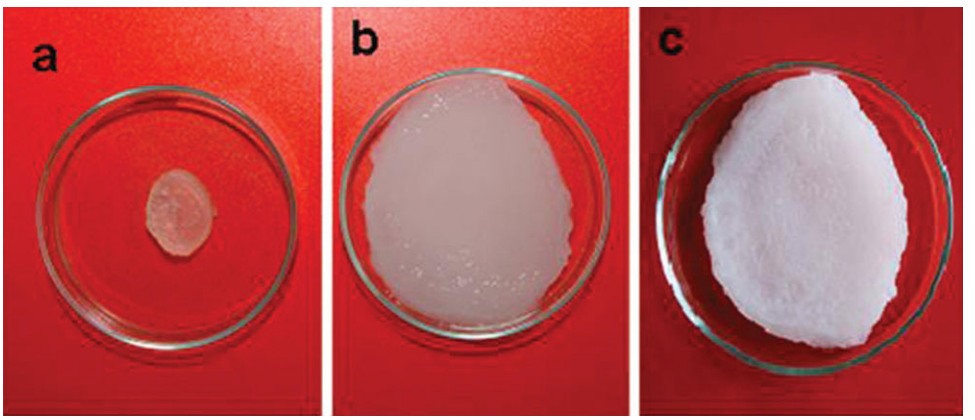

Figure 2 Poly (NIPAAm-AMPS) hydrogel (NA4) photographs (a) Dry hydrogel, (b) swollen hydrogel, and (c) deswollen hydrogel. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

investigated and the results are shown in Figure 3. The effect of feed composition on the swelling ratio was known from its LCST value. The LCST value can be calculated by a method[33] in which the swelling curve is divided into three parts and to this three tangents are drawn. The values of the connecting points of central tangent with other two tangents gives two values (T1,T2) of which the average gives LCST of hydrogesl. The LCST values of hydrogels with change of feed composition are given in Table III. The values indicate that when the AMPS concentration increases, both the swelling capacity and the LCST property of IPN hydrogels increase. This property is because of linkage of a hydrophilic AMPS monomer with PNIPAAm hydrogel networks thereby increasing the hydrophilicty of PNIPAAm networks. The LCST values of the Blank (B) and NA4 sample were confirmed by DSC [Fig. 4(a,b)]. From these values it is concluded that the LCST value has increased significantly in the AMPS added hydrogels, and this effect is more important in potential applications such as biomedical devices or in reversible systems.[34]

Spectral analysis

FTIR spectra

The AMPS added hydrogel(NA4) was characterized by FTIR spectroscopy. The IR (Fig. 5) spectra showed absorption peaks at 3461.1 cm^{-1}, because of the stretching frequency of the O—H groups present in poly (NIPAAm-AMPS) units,[35] at 2917.0 cm^{-1}, 2849.7 cm^{-1} representing the C—H stretching frequency of the hydrogel. The primary amide carbonyl group peaks of AMPS and NIPAAm units, and secondary amide N—H deformation peaks of hydrogel units are observed at 1627.6 and 1545.7 cm^{-1}, respectively. The peaks at 1465.3 cm^{-1} indicates C—H bending of CH_2 groups,[36] at 1384.5 cm^{-1} indicating the vibration of the isopropyl group,[35] at 1216.6 cm^{-1}, 1078.70 cm^{-1}, and 1016.3 cm^{-1} are indicating the asymmetric and symmetric stretching of S—O bond of SO_3^- groups.[37–39] The C—N stretching vibration occurs at 1183.3 cm^{-1}, 1148.5 cm^{-1}, 1113.8 cm^{-1} for the hydrogel unit.[36] The C—S stretching occurs at 628.3 cm^{-1} (AMPS Unit),[36] and NH wagging vibrations occur at 723.7 cm^{-1}, 764.0 cm^{-1}, 829.4 cm^{-1}, and 919.8 cm^{-1}, respectively. All the above peaks confirm the incorporation of NIPAAm and AMPS units in the hydrogel networks.

SEM images

The SEM (Fig. 6) images reveal the network structures of the porous hydrogels. The images show the differences between the drug loaded and the drug unloaded hydrogels. By taking advantage of the higher porosity and the hydrophilic nature of

TABLE II
Swelling Data of Poly(NIPAAm-AMPS) Hydrogels

Hydrogel code	Swelling exponent (n)	Diffusion coefficient (D) $cm^2\ s^{-1}$	Initial swelling rate (r_i) [(g water/ g hydrogel)/min]	Theoretical equilibrium swelling (T_{Seq}) [(g water/ g hydrogel)]	Swelling rate constant (k_s) [(g hydrogel/ g water)/min]
B	0.7375	0.17887	0.01713	0.159118	248.2225
NA1	0.6783	0.92485	0.00202	1.35084	0.405684
NA2	0.5744	0.90897	0.00199	1.376614	0.383322
NA3	0.7200	2.20833	0.00056099	3.183091	0.031006
NA4	0.6917	3.43953	0.0062760	4.341408	0.012221

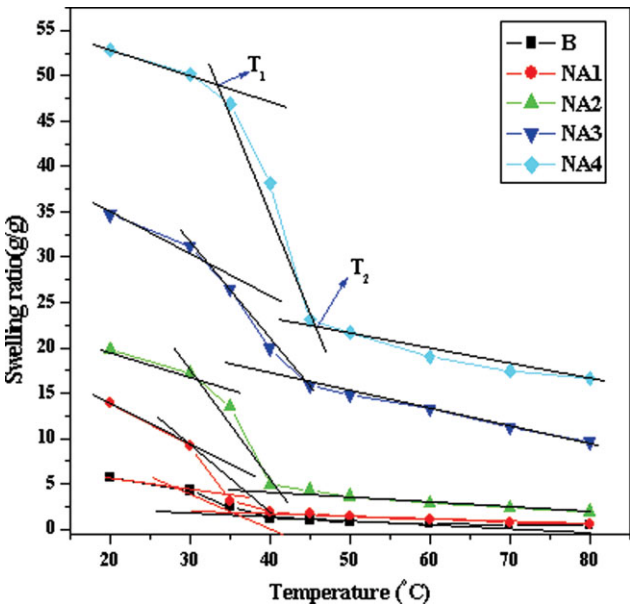

Figure 3 Temperature dependence of equilibrium swelling ratio of blank (B) and AMPS (NA1, NA2, NA3, and NA4) added hydrogels. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

hydrogels, it is possible to load higher amounts of drug. This has been indicated in the images and it clearly explains the distribution of Doxorubicin drug particles inside the hydrogels.

Drug releases studies

In this study Doxorubicin (Dox) was selected as a model drug. It is widely used in cancer chemotherapy.[39,40] Its chemical structure is shown in Figure 7. The percentage of cumulative release of Dox from the hydrogel was calculated using the following equation.[32]

$$\text{The \% of cumulative release} = \text{Mt/Mo} \times 100\% \quad (2)$$

where *Mt* is the amount of drug released at time *t* and *Mo* is the initial loaded drug amount. Figure 8 depicts the percentage of cumulative releases of Dox from the hydrogels at 7.4 pH at various temperatures. The release values are presented in Table IV.

TABLE III
LCST of AMPS Varied Hydrogels

Sample code	Tangent values		LCST (°C)
	T1	T2	
B	27.01	36.15	31.63
NA1	29.52	40.28	34.90
NA2	31.02	41.50	36.26
NA3	31.98	44.63	38.30
NA4	33.03	45.87	39.45

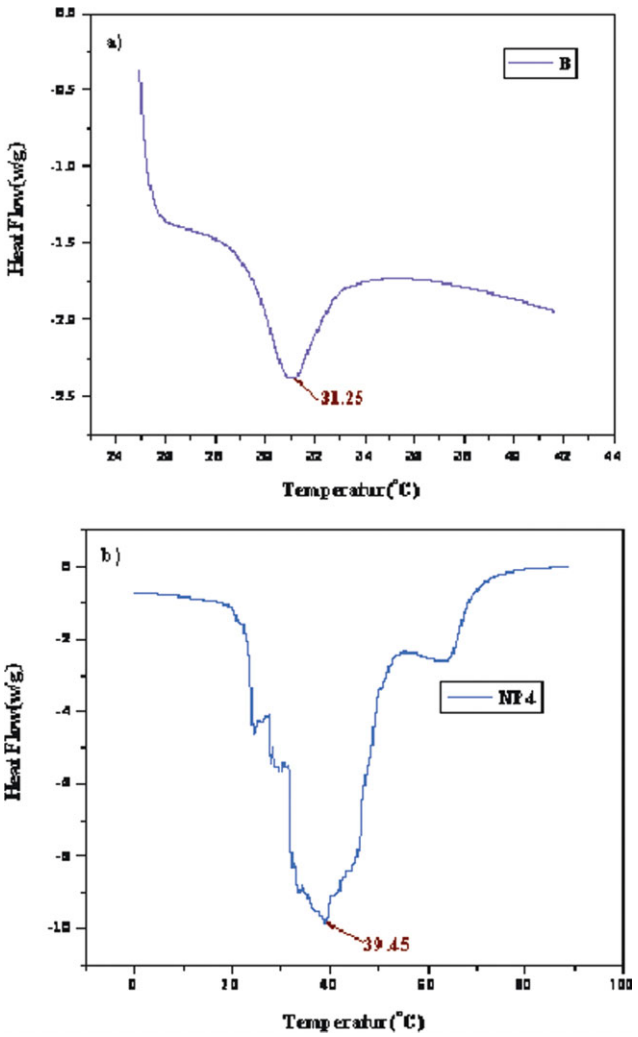

Figure 4 LCST determinated by DSC (a) blank hydrogel (B), (b) Poly (NIPAAm-AMPS) hydrogel (NA4). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Figure 8 shows that the drug release profiles are temperature dependent. The percaentage of cumulative release of Dox from the AMPS added hydrogels was higher at 50°C than that of other temperatures. The Figures indicate that when the temperature increases from 20 to 50°C the drug relesing rate increases. The reason for this behaviour is that at temperatures below LCST the PINPAAm chains are water solvated and randomly distributed but collapses near or above the LCST. Therefore, when the temperature increases from 25 to 50°C its releasing profile increases because PNIPAAm chains become more hydrophobic. So that the AMPS added hydrogel releases the drug much faster at higher temperature when compared with lowest temperature (See Fig. 9).

The blank hydrogel initially shows low releasing profile, but after increasing the temperature from 20 to 25°C it shows higher release rate, and further

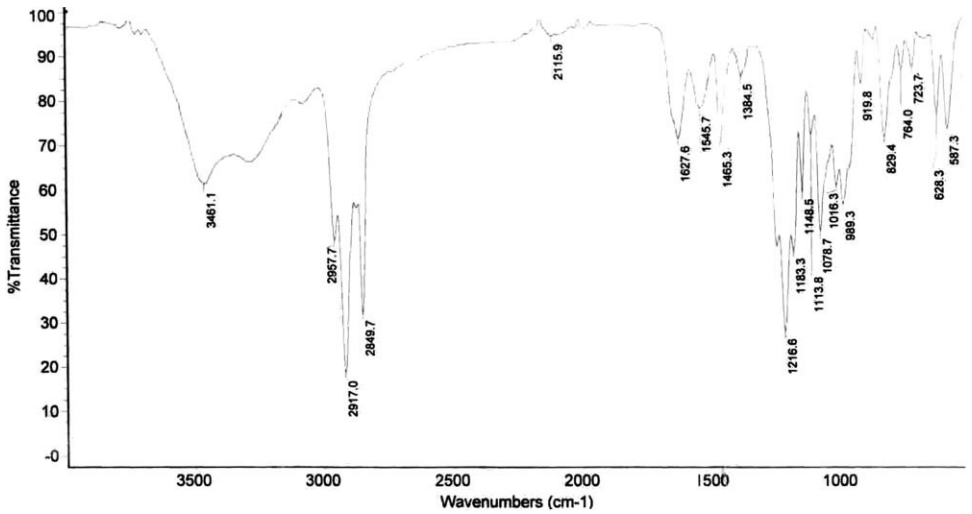

Figure 5 FTIR spectra of poly(NIPAAm-AMPS) hydrogel. (NA4 code).

increasing the temperature from 25 to 50°C we have observed low releasing profile. This is because initially its network structure has randomly distributed at lower temperature below LCST, but increasing the temperature the swollen capacity falls down. This is because of the hydrophobic nature of NIPAAm groups at higher temperatures. Therefore, when the temperature increases the hydrogel networks have more hydrophobic interactions. Because of this reason, the hydrogel chemical structure cannot allow more drugs particles when compared with other hydrogels.

But NA4 AMPS added hydrogel shows higher releasing profile, with increase of temperature within a short time interval. This is because of higher AMPS concentration with regard to NIPAAm thereby increasing the drug loading capacity. Therefore, it automatically increases the releasing of the drug at a faster rate with increase of temperature within a short time.

Interestigly, all our formulations have exhibited a prolonged release of Dox over an extended period of time. The prepared poly(NIPAAm-AMPS) hydrogels

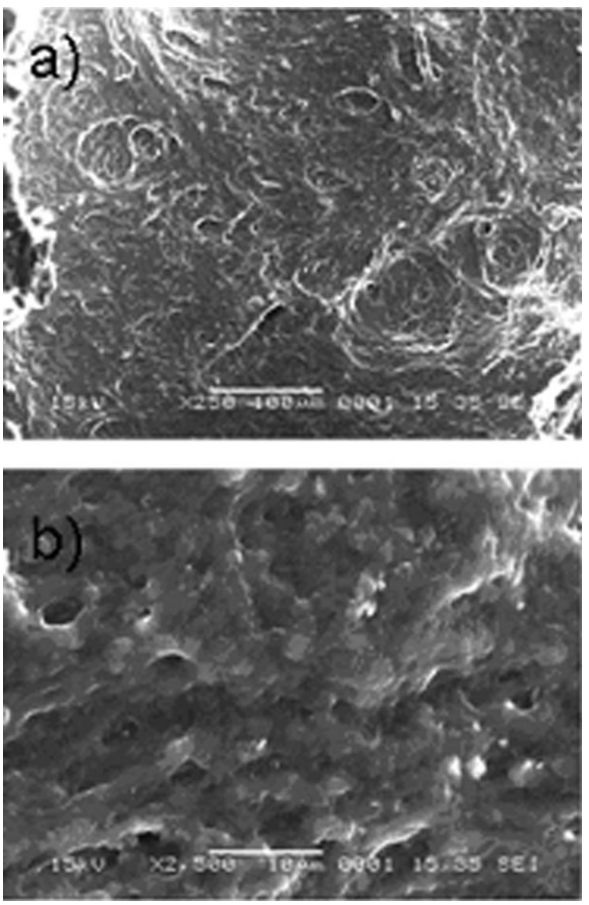

Figure 6 SEM micrographs (a) NA4 hydrogels and (b) NA4 drug loaded hydrogels.

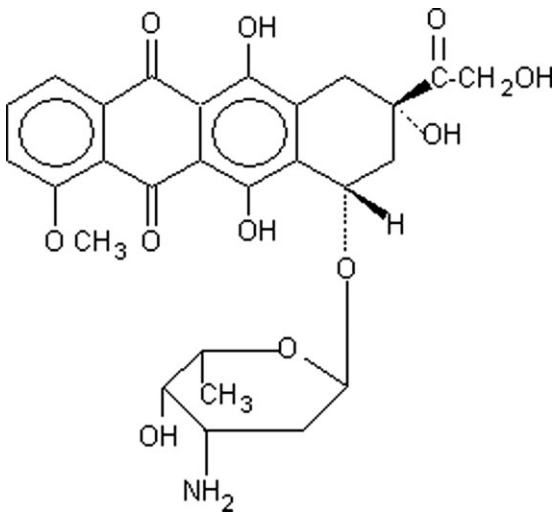

Figure 7 Doxorubicin chemical structure.

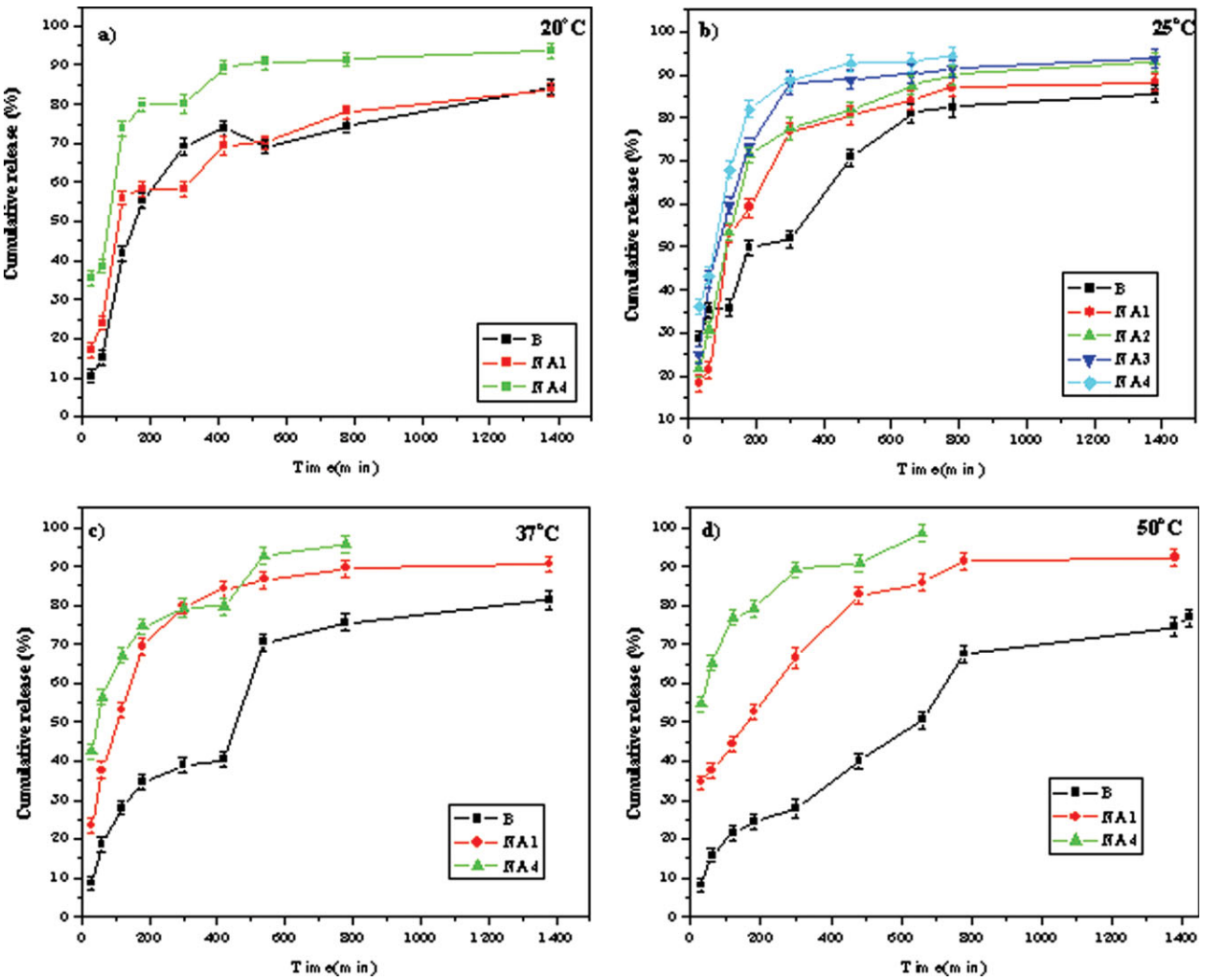

Figure 8 Drug releasing profile of poly(NIPAAm-AMPS) hydrogels at various temperatures (20, 25, 37, 50°C). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

have shown the thremoresponsive trends during *in vitro* release of dox when dissolution experiments were performed at 20,25,37, and 50°C. In contrast, NaAlg-NIPAM microspheres exhibited a release of 5-Flurouracil of about 90% for 12 h[41] and also poly(-vinyl alcohol)/poly(acrylamide-co-acrylamidoglycolic acid) hydrogels exhibited a release of 5-Flurouracil of about 100% for 12 h.[42] Whereas the poly(NIPAAm-AMPS) hydrogel formulations of ours show up to 98% cumulative release in 20 h.

Effect of AMPS content on Dox release

Figure 8 shows the effect of AMPS content on the Dox release behavior in the buffer solution (pH 7.4) at various temperatures (20, 25, 37, and 50°C). A

TABLE IV
Percentage of Encapsulation Efficiency and Percentage of Cumulative Releases of Blank and Poly(NIPAAm-AMPS) Hydrogels Data at Ph 7

Hydrogels code	Percentage of encapsulation efficiency	Percentage of cumulative releases at various temperatures with in the 30 min				Percentage of cumulative releases at various temperatures at there end time			
		20°C	25°C	37°C	50°C	20°C	25°C	37°C	50°C
B	7~ 8	10.46	28	8.6	8.139	84.30	85.64	81.29	76.74
NA1	8~11	11.13	18	23.49	34.50	83.73	88.16	90.46	92.31
NA2	22.4	–	21	–	–	–	92.92	–	–
NA3	23	–	24	–	–	–	93.62	–	–
NA4	43~46	35.43	36.2	42.5	54.67	93.55	94.40	95.65	98.44

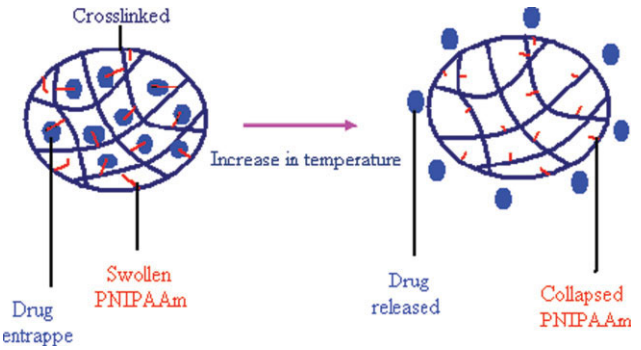

Figure 9 Doxorubicin drug releasing profile of AMPS added hydrogels at higher temperature. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

tendency for an increase of Dox release with increasing of AMPS content can be observed in all cases. However, the experiential results show there is a large difference in the percentage of cumulative release within 30 min at various temperatures. The difference in the percentage of cumulative release at the end time is not much at 20 and 25°C but we can able to see some difference at 37 and 50°C between NA1 and NA4 sample because of the increase in the concentration of AMPS. This can also be explained in terms of the swelling behaviour of hydrogel. It is found that the PNIPAAm hydrogels have minimum swelling ratio, but the swelling ratio increases with increase of AMPS content in the hydrogel networks (See Fig. 1). For the hydrogel delivery systems, the release of Dox is controlled by the swelling behaviour of the hydrogel. When the swelling of the carrier increases the aqueous solvent within the polymer matrix enables the Dox to diffuse though out the swollen network into the external environment. In this study, we have observed mainly this effect in the case of NA4 hydrogel. It releases very faster than that of other hydrogels within a short time. This is because of the presence of more acidic groups (hydrophilic groups) of AMPS. So that it can be swollen more readily and releases more effectively than other, hydrogel networks.

CONCLUSIONS

PNIPAAm hydrogels were prepared with AMPS as co-monomer as well as SR as a porogen in the hydrogel networks and crosslinking with another hydrophilic MBA as a crosslinker. The increment in the LCST of NIPAAm hydrogels can be done with the help of AMPS and it is confirmed with DSC as well as temperature dependent swelling curves. The swelling and deswelling kinetic parameters suggest that the hydrogels network is of non-Fickian in nature. The prepared poly(NIPAAm-AMPS) hydrogels have shown the thremoresponsive trends during invitro release of Dox when dissolution experiments were performed at 20,25,37, and 50°C. The hydrogels formulation shows up to 98% cumulative release in 20 h. Results of this study are useful in extending the life of Dox to an extended period of time lasting up to ˜20 h. The characterization by FTIR confirms the hydrogel formation and SEM analysis confirms the morphological changes in the hydrogels networks, such as porous nature and drug loading.

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