Poly(*N*-isopropylacrylamide) Hydrogel: Effect of Hydrophilicity on Controlled Release of Ibuprofen at Different pH

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ABSTRACT: Stimuli-sensitive drug delivery systems (DDSs) have attracted considerable attention in medical and pharmaceutical fields; thermo-sensitive DDS dealing with poly(*N*-isopropylacrylamide) (PNIPAM) have been widely studied. Hydrogels composed of temperature-sensitive NIPAM and biocompatible and pH-sensitive maleic acid (MAc) were synthesized by sedimentation polymerization. Experiments on drug release from the crosslinked NIPAM-*co*-MAc hydrogel loaded with ibuprofen into different pH buffer solutions were successfully carried out at temperature swing between 25 and 40°C. The *in vitro* release studies have showed that the release rate depended on acidity or basicity (polarity) of the medium and the gel and swelling ratio of the gel network as a function of the environmental pH and temperature. The SEM image of the dry bead gave more insight into the surface architecture and the thermal studies shine light on the decomposition pattern and glass transition temperature of the gel. The mechanism of the drug release was discussed in relation to the diffusion rate and the abrupt change in the pH of the medium. © 2011 Wiley Periodicals, Inc. J Appl Polym Sci 124: 5079–5088, 2012

Key words: stimuli-sensitive polymers; drug delivery systems; hydrogels; biological applications of polymers; swelling

INTRODUCTION

The application of synthetic hydrogels started in the late 1950s' when for the first time contact lenses were made.[1,2] Hydrogels are crosslinked polymeric "swell gels,"[3] they swell in aqueous solutions without dissolving in them. When a hydrogel is in a dry state, the density of polymer chains are high, allowing little room for molecular diffusion. As the hydrogel swells and attains an equilibrium swelling value, the swelling pressure on the chains is counteracted by the force holding the chains together, namely, the force of crosslinking. At this equilibrium value, the molecular diffusion reaches its peak values.[4–15]

Controlled release of drug molecules from hydrogel is a technique well reported in the literature.[6–15] Temperature is a commonly used triggering signal for modulating drug release because of physiological relevance.[16–18] There are large numbers of polymeric materials investigated for this purpose. However, one polymer, poly(*N*-isopropylacrylamide) (PNIPAM), stands out particularly due to its volume phase transition temperature (VPTT or LCST) near the body temperature.[19–22] In addition, the LCST of PNIPAM can be suitably tuned by incorporating hydrophilic/hydrophobic comonomers.[23–29]

Polymers containing pendant carboxylic groups are typical acidic pH-responsive polymers.[30] Hydrogels containing carboxylic groups exhibit pH-sensitive swelling-deswelling behaviors and are widely used in controlled drug delivery systems.[14,31–33] The combination of pH and temperature response is particularly useful to optimize the control of drug release and a variety of hydrogels being sensitive to both pH and temperature have been synthesized. Most of these double-responsive hydrogels are IPN or semi-IPN being composed of pH-responsive part and temperature-responsive part.[34,35]

Vasile et al. were able to demonstrate nonphase separable PNIPAM-graft-poly(MAc-*alt*-vinyl acetate) for thermothickening behavior in semi-dilute aqueous solution.[36] Maleic acid (Mac)-based NIPAM

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copolymer gels were mainly studied for their swelling characteristics.[37] Here, they used MAc as comonomer with NIPAM mainly to improve the hydrophilicity and ion content of the hydrogel. In another communication, the copolymerization of NIPAM and MAc and it is different copolymer composition showed that after a certain pH, increasing the ion content only increased the swelling without impacting the LCST.[38] Comparing the properties of gels prepared from NIPAM-*co*-Acrylic acid (NIPAM-*co*-AAc) and NIPAM-*co*-Maleic acid (NIPAM-*co*-MAc), NIPAM-*co*-AAc was found to increase the LCST of the copolymer above physiologically relevant temperatures for relevant pH values, which places constraints on the degree of swelling.[38] So, it is desirable to develop a material in which swelling properties can be improved independent of the LCST. MAc is a diprotic acid and it gives additional benefits over NIPAM-*co*-AAc for application in pH-sensitive drug delivery. In the same year, Tasdelen et al. reported the influence of pH and temperature of the swelling media on the equilibrium swelling properties of NIPAM-*co*-MAc copolymer.[39] The swelling degree of hydrogels depends not only on the nature of hydrogel and swelling medium but also on the crosslink density.[40] A new class of partially biodegradable multisensitive hydrogels was designed and fabricated from thermo-sensitive NIPAM and pH-sensitive dextran-MAc precursors by Sun Chih-Chang Chu et al.[41] The hydrophilic drug, doxorubicin release data in this study suggested that the newly synthesized partially degradable PNIPAAm/Dex-MAc hybrid hydrogels could improve the therapeutic index of the drug when compared with other polymeric hydrogels.

Ibuprofen (2-(4-isobutylphenyl)-propionic acid) (IBU), a hydrophobic drug, is widely used for acute relief of pain and for treatment of chronic diseases such as rheumatoid arthritis and other rheumatoid conditions. In the past, the effect of various polymers on the controlled release of ibuprofen has been studied.[42–51] The release rate from hydrogel depended on many factors such as crosslink density, pH, nature of gel, diffusion medium, etc.[48–50] The release characteristics of ibuprofen loaded in PNIPAM microgel across silicone and human skin membrane was studied by Snowden and coworkers in 2004.[52] Fom the results obtained, they concluded that the more hydrophobic the gel matrix is stronger is the interaction between the hydrophobic drug and the microgel. In all these cases, authors observed a controlled release within the first 10–20 h. There are no reports in the literature which study slow release of IBU over days. Additionally, the synthesis of NIPAM-*co*-MAc spherical hydrogel was not reported in the literature. In addition, the drug release behavior of this hydrogel was not studied by any research group. Interestingly, it was reported that the swelling property of NIPAM can be improved with MAc without affecting the LCST.[38]

This article explains the synthesis, characterization and drug release behavior of NIPAM-*co*-MAc hydrogel.[53] We choose the IBU as a model drug because of its well-characterized skin permeation properties. Through the channels in the expanded gel matrix the IBU molecules can easily penetrate to obtain drug entrapment and since the IBU is hydrophobic, its interaction with the gel matrix consisting of hydrophilic segments is poor. This leads to the easy release of the IBU molecule to the solution. Here, the drug release study was extended to acidic and basic conditions because of the fact that pH varies from acidic to basic when stomach and intestine are considered.[30,54–56]

MATERIALS AND METHODS

N-isopropylacrylamide (NIPAM) from Sigma-Aldrich, ethylene glycol dimethacrylate (EGDMA) from Merck and AR grade *N*,*N*,*N*,′*N*′-tetramethyl Ethylenediamine (TMEDA) from s.d.fine, India were used as such. Ibuprofen tablet available locally was purified by reported procedures. Commercial silicone oil (Loba chemie, India) was used as purchased. Hexane (Merk) and MAc (Himedia) were purified before use. Buffer solutions were prepared using acetic acid : sodium acetate (pH 4), disodium hydrogen phosphate : HCl (pH 7), and borax : sodium hydroxide (pH 9) as per procedures reported elsewhere. All other reagents used were purified by common methods.

FTIR spectra were taken on Bruker FTIR system having ZnSe optics. SEM images were recorded on JEOL JSM-7400F Field Emission Scanning Electron Microscope and TGA, DSC, and DTA on LABSYS evo (TGA with simultaneous DTA or DSC), SETARAM Instrumentation.

Synthesis of hydrogel

Preparation of beads was carried out in DMF : water medium.[57,58] The procedure was as follows. The reactants, MAc (5.68 mg; 0.049 mmol; 8%), NIPAM (58.2 mg; 0.0582 mmol; 87 %), AIBN (2 mg), TMEDA (20 μL), and EGDMA (40 μL) were added in this order to 80% weight aqueous DMF solution. Nitrogen gas was purged for 15 min. Silicone oil was charged in a beaker and the temperature was maintained at 90°C. The monomer solution was injected as tiny drops into the silicone oil via a syringe with a thin needle. The reaction was continued for 2.5 h. The resulting beads were washed with acetone and after that with distilled water four times by swelling-deswelling using temperature swing between 20

and 80°C. It was then placed in water and stored in a refrigerator. The average diameter of swollen and dried gel in water was found to be 5 and 1 mm, respectively.

The acid number of the carboxy hydrogel was determined by reported method using standard KOH. The average mass of swollen bead at temperature 15°C (in water) was 100 mg and that of deswelled gel bead was 28 mg. The dependence of swelling ratio (SR) of the gel beads as a function of temperature over the range from 15 to 50°C was noted.

The SR of the gel beads in water were calculated using the eq. (1),[26,59,60]

$$\mathrm{SR} = (W_2 - W_1)/W_1 \quad (1)$$

where W_2 is the weight of the swollen hydrogel at a specific temperature and W_1 is the weight of the dried hydrogel.

Water Retention of the hydrogel was calculated using the following eq. (2),[26,59,60]

$$\text{Water Retention} = [(W_t - W_d)/W_s] \times 100 \quad (2)$$

where W_t = weight of hydrogel at a given time during swelling, W_d = weight of dried hydrogel, and W_s = weight of swollen hydrogel at temperature, 15°C.

The phase transition temperature (LCST) was recorded by taking the mean of heating and cooling analysis.[25] For this, five beads of almost same mass were added to pH 7 buffer solution and this was cooled/heated between temperature 20 and 50°C, during which the beads underwent swelling-deswelling process; the LCST was calculated by taking the average of the phase change during swelling-deswelling process. The temperature at which this reversible phase change occurred was measured with the help of a sensitive thermometer. The average of these two values gave the phase transition temperature (LCST) and was found to be 32°C (pH 4), 35°C (pH 7), and 38°C (pH 9).

Procedure for drug loading/release

Saturated solution of IBU was made by adding excess of powdered IBU to 10 mL buffer solution at pH 7. The solution was stirred at room temperature (28°C) for one day. The solution was filtered and this saturated solution of IBU was tested for its concentration by noting the λ_{max} at 264 nm. Dried gel beads (4 beads = 17 mg) were added to this solution by keeping it at saturated condition for maximum loading. This was stirred for 24 h and the drug loaded hydrogels were placed in fresh pH 7 buffer solution at room temperature. After 24 h, the UV–vis spectrum of the solution was taken at 264 nm and the absorbance value was noted. The beads were then transferred to another 10 mL of fresh pH 7 solution and stirred for another 24 h. And again UV value was determined. The process was repeated till there was no release from the gel beads. The same procedure was repeated in pH 7 buffer solution at 40°C and in pH 4 and 9 buffer solutions at room temperature and at 40°C, respectively. The data points are the average of 10 independent release studies in each case.

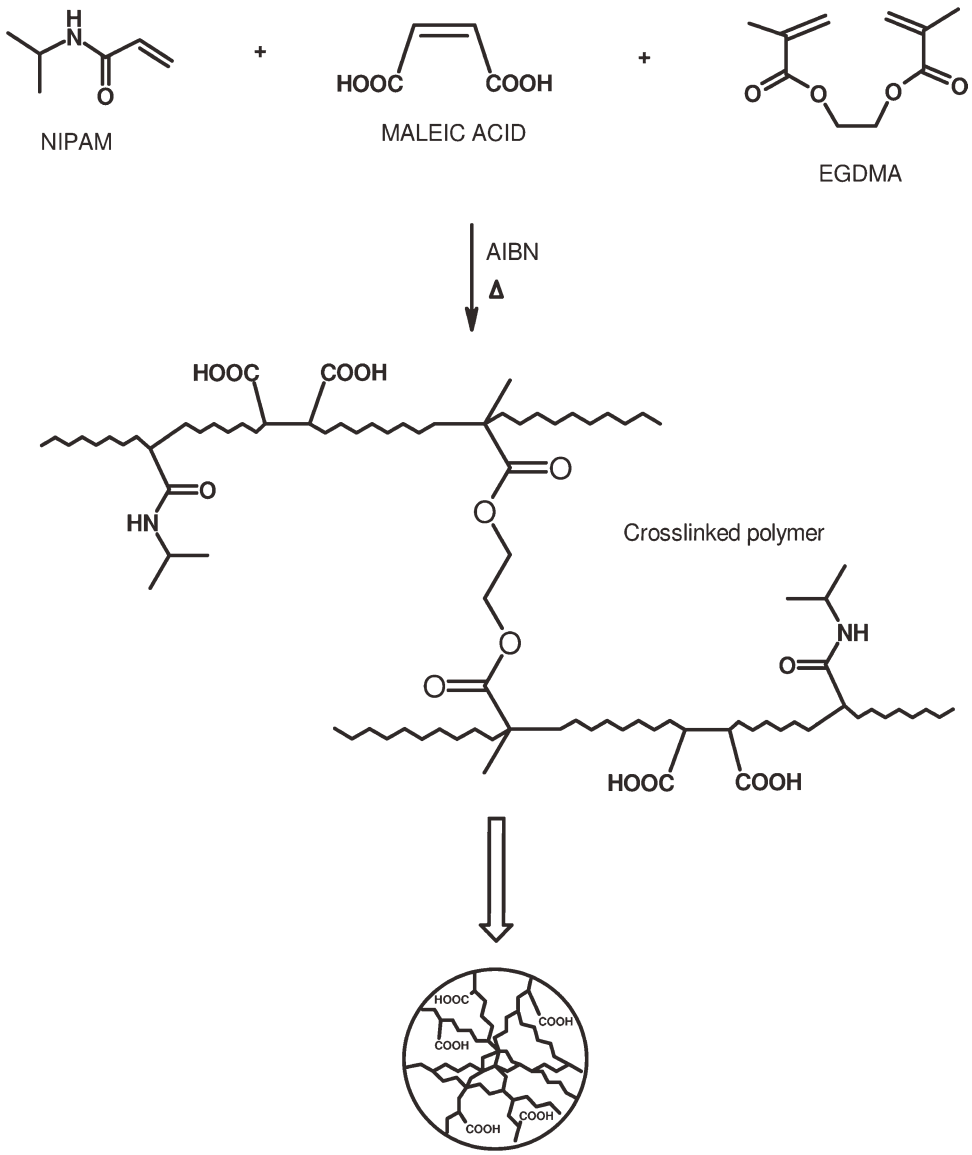
RESULTS AND DISCUSSION

Synthesis of PNIPAM gel beads

The sedimentation polymerization was carried out using a long cylindrical reactor containing silicone oil as heat medium. The polymerization took place smoothly when monomer in aqueous DMF solution was mixed with TMEDA and EGDMA. The mechanism of polymerization is shown in Scheme 1. As the crosslinking reaction took place inside the tiny droplet, the final hydrogel was obtained as fine beads. The sedimentation time for a 3-mm-diameter droplet in this apparatus was about 150 min at 90°C. The gels were washed in acetone followed by in water by swinging between above and below the LCST. The FTIR data of the gel confirmed the incorporation of MAc units in the crosslinked gel network. The hydroxyl groups in MAc appeared as a broad peak at 3450 cm^{-1}. The acid number of the bead was found to be 40 mg and this value was theoretically equal to 50% of the initial loading of MAc.

The optical photograph of these gel beads is shown in Figure 1(a), where both dried and swollen beads are given. These beads retained their spherical shape during the entire course of analysis. From the figure, it is evident that there is approximately twofold increase in the diameter of the gel after swelling in water. The comparative swelling of this gel in pH 4, 7, and 9 is presented in Figure 1(b). Here, the average diameter of swollen beads measured using screw gauge decreased in the order pH 9 > 7 > 4. This is represented as bead diameter in Table I.

The SR of all beads was higher at low temperature because both NIPAM and MAc are swellable and hydrophilic at temperature below the LCST. The SR of the gels decreased quickly as the temperature increased to above the LCST. SR at room temperature was measured five times to obtain the average value. The value was found to be 24 in water. The SR at various pH values is given in Table II. This data shows that SR is higher than hydrogels prepared using NIPAM with same amount of crosslinking agent.[40] The SR presented in Table II also shows that maximum swelling is in pH 9.[38] This is



Scheme 1 Synthesis of NIPAM-*co*-MAc Hydrogel.

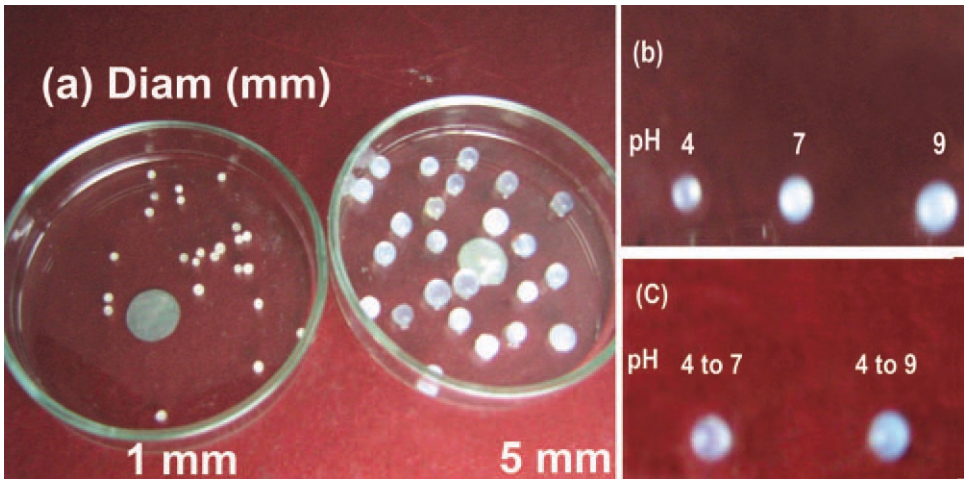


Figure 1 (a) Dried and Swollen bead (pH 9); (b) Maximum swelling in pH 4, 7, and 9; (c) Change in swelling with pH. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE I
Diameter of Gel Beads Below and Above LCST

pH	Below LCST Diam (mm)	Above LCST Diam (mm)
4	2.23	1.38
7	3.38	2.24
9	4.86	2.67

expected because of the presence of carboxylic acid units in the gel. The carboxylate ions thus generated induce repulsion within the gel. The water retention of this gel was found to be close to 29, which is slightly higher than the value reported in the literature.[26,59,60]

Additionally, we observed a change in swelling when the pH was changed. A graphical representation of this variation is presented in Figure 2, which is generated after 24 h. In this figure, the orange color columns show the variation in swelling when the beads having IBU, loaded at three different pH conditions, were allowed to release the drug in pH 4. Correspondingly, the release at pH 7 (violet) and pH 9 (magenta) are also recorded. On comparing Table I and Figure 2, it can be seen that the bead size is not reaching the maximum value when the pH is changed. For instance, the gel loaded with IBU at pH 4 when placed in pH 9 gave a bead size of only 3.5 mm (magenta, Fig. 2), which was very much lower than the maximum value, 4.86 mm in pH 9 (Table I). This may be partly because the interior pH of the gel bead was not appreciably changed.

The high-resolution optical photograph presented in Figure 3 gave some more information regarding the microstructure of the gel. It shows a shell-like structure with a big channel at the center. This architecture was similar to the one observed by other authors under similar polymerization conditions.[57,58,61] Since the polymerization took place above the LCST, it was expected that the chains collapsed within the gel or on their periphery.[58] This could be one of the reasons for the heterogeneous polymerization from the surface of the droplet leading to the formation of open nutshell structure. However, this architecture disappeared under swollen condition.

The beads swelled in water at room temperature and deswelled when heated above the LCST, showing a clear transition point around 35°C. The swelling-deswelling was found to be reversible. The

TABLE II
Swelling Ratio of PNIPAM Gel Beads

pH	Swelling Ratio
4	6.2
7	15.8
9	28.7

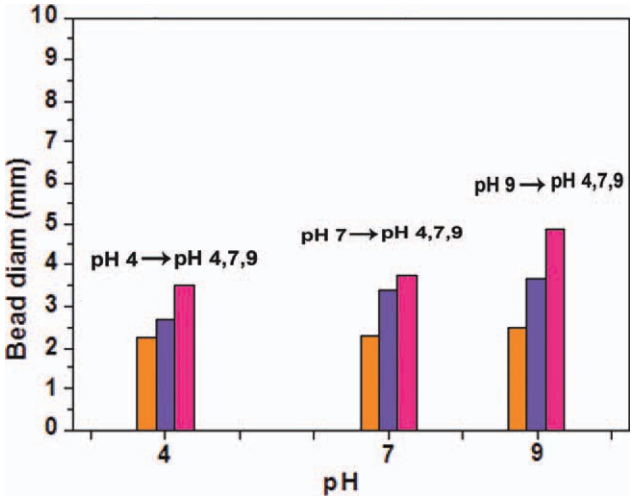


Figure 2 Variation in swelling when the bead was loaded with IBU at pH 4 and placed in pH 4 (orange), 7 (violet), and 9 (majenta) separately at r.t. Same is repeated for pH 7 and 9 loading. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

LCST value increased with increase in pH and the beads also possessed the same fine spherical shape and narrow particle dispersity in all cases. The phase transition temperature (LCST) was found to be 32°C (pH 4), 35°C (pH 7), and 38°C (pH 9).

The SEM image of the dried gel is shown in Figure 4. A very highly porous periphery and a bulk rigid structure can be seen. This rigidity in the dried state limited our attempt to image the base of the gel. The big channel at the center is clearly visible in the SEM image as well. This porous network is

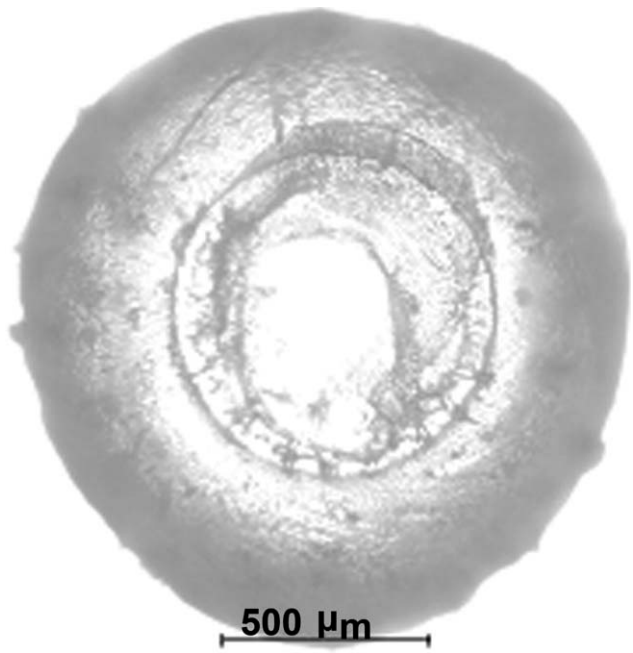


Figure 3 High resolution optical photograph of a dried bead.

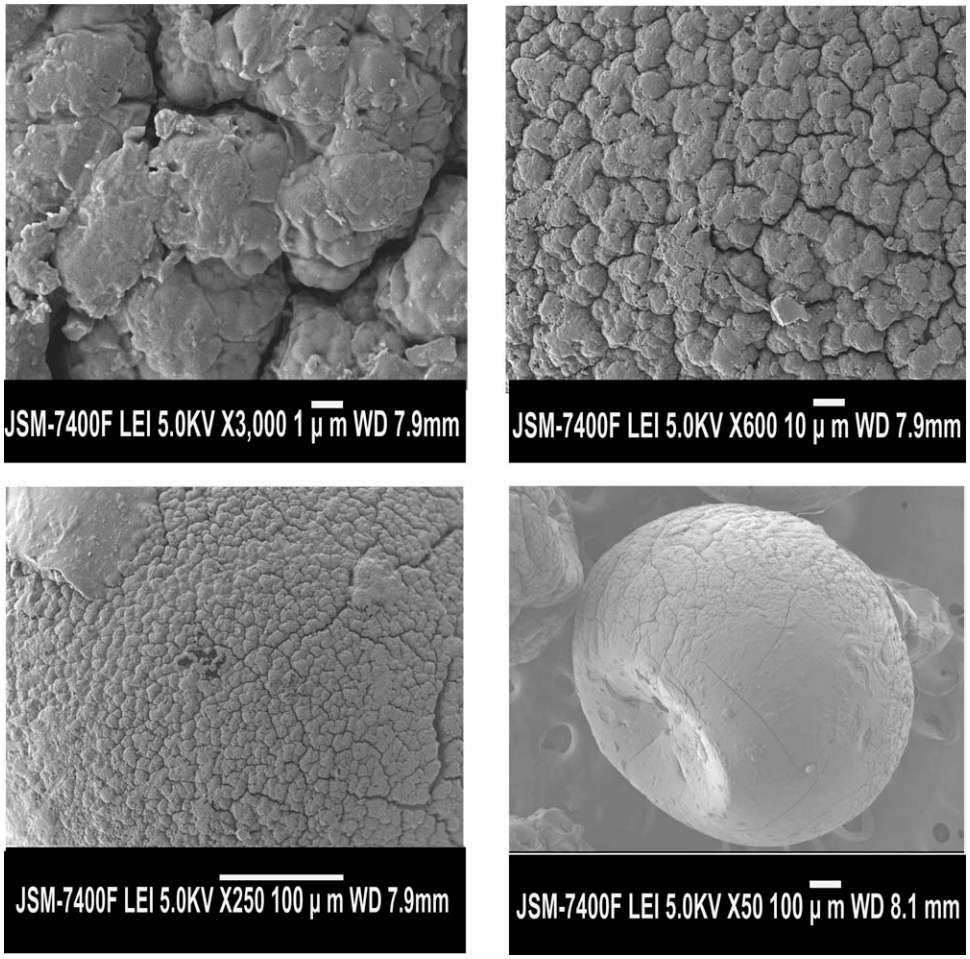


Figure 4 SEM images of dried sample of hydrogel.

responsible for the fast swelling in water and pH solutions.

The TGA (green), DSC (blue), and DTA (red) of this gel are given in Figure 5. All these analysis agree each other with the thermal changes occurring in the gel during three clear weight losses. The maximum decomposition temperature is roughly between 300 and 350°C. This may be due to the presence of crosslinks and possible formation of succinic anhydride units via cyclodehydration from succinic acid (MAc units in the gel) above 100°C. The glass transition temperature of PNIPAM remained same in this case also.[62]

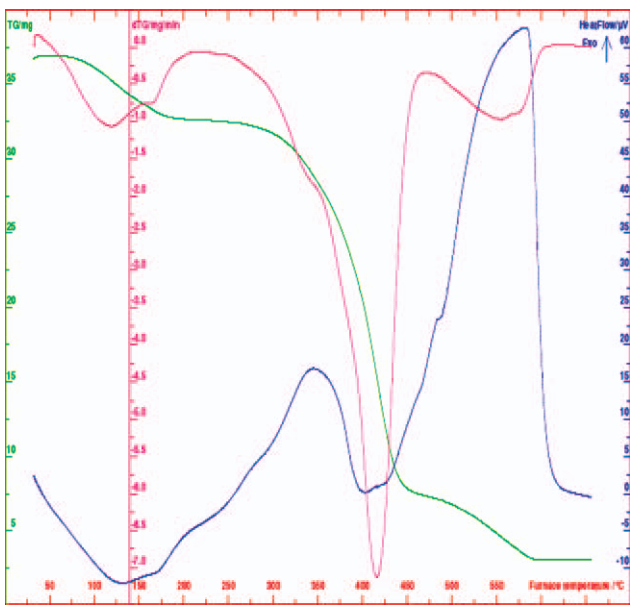


Figure 5 Thermal analysis data (Green-TGA, Blue-DSC, and Red-DTA) of NIPAM-*co*-MAc hydrogel. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Loading and release of ibuprofen

Buffer solutions of pH = 4, 7, and 9 were taken for studying loading/release of IBU. There are several reports available in the literature detailing drug release studies in acidic and basic pH conditions because of physiological relevence.[30,54–56] The solubility of IBU decreased in the order pH 9 $\geq$ 7 $\gg$ 4. This data indicated a poor solubility of IBU at pH 4 compared to almost identical value at pH 7 and 9.

TABLE III
Maximum Loading of IBU at Various pH Conditions

pH	Maximum loading (~mg/bead)
4	1.2 (pH 4)
7	2.4 (pH 7)
9	1.8 (pH 9)

The loading of the drug was carried out in pH 4 and the release was studied in pH 4, 7, and 9 at 28°C (below the LCST) and at 40°C (above the LCST). This experiment was repeated for loading in pH 7 and 9. The maximum capacity of this gel for IBU loading is presented in Table III. It can be seen that the maximum loading is at pH 7 eventhough the solubility of the drug and SR of the gel are high at pH 9. The reason could be the repulsion between charges at pH 9, since the carboxyl group in the gel as well as in IBU exists as corresponding carboxylate anion in pH 9.[30] In addition to this is the fact that IBU is a hydrophobic drug, which has less solubility in a polar environment (acidic or basic).[40] This means that at pH 4 and 9 IBU has less solubility and at pH 7 IBU has more solubility in the gel (Table III). This may be two of the reasons for comparatively low loading in pH 9 with respect to that at pH 7. Moreover, we also observed a decrease in transparency of the gel when IBU was loaded at pH 9, 7, and 4. At pH 4, the IBU loaded gel was milky white in appearance. This indicated that IBU existed as aggregate in pH 4 and to a lesser extent in pH 7 in the gel.

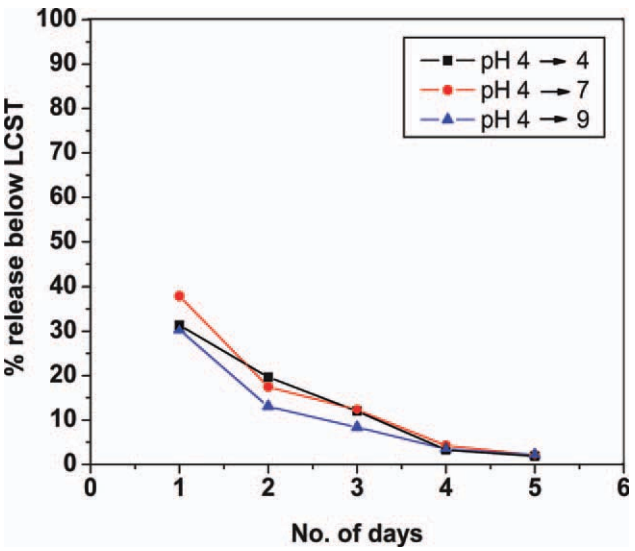


Figure 6 Release of IBU to pH 4, 7, and 9 after loading at pH 4 at room temperature. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Loading of IBU at pH 4 and release at pH 4, 7, and 9

The SR of the gel is the lowest in pH 4 and hence the chain rigidity of the hydrogel would be high at this condition.[5] This will hamper the entry of drug into the gel matrix.[4–15] Hence, there are two effects operating for the poor loading of the drug in pH 4 (Table III). They are on one hand low solubility of the hydrophobic drug in pH 4 and second the low SR of the gel during loading of the drug. This was supported by the formation of drug molecule aggregate within the gel.

Since here the amount of IBU loaded in the hydrogel was same, the release was diffusion controlled, which depended on the flexibility of crosslinked chains in the gel. The release of the drug into pH 4, 7, and 9 after loading in pH 4 (below the LCST) is presented in Figure 6. This analysis performed at room temperature gave almost similar release rate irrespective of the pH of the medium. The marginal difference in the data points for pH 4, 7, and 9 was within the experimental error. However, the slight high value of release on first day at pH 7 was due to smaller pH change (pH 4–7) compared to the change from pH 4–9.[59,60] This was supplemented by the increase in bead size at pH 9 (Table I; Fig. 2), which reduced the concentration gradient of the drug between the two phases.

The effect of temperature on release was obtained from studies at 40°C (above the LCST). The data presented in Figure 7 shows substantial increase in the first day release at pH 4, 7, and 9. Increased release of hydrophobic drug above the LCST was reported recently.[55,56] However, in our case, the variation in release at pH 4, 7, and 9 were due to other reasons

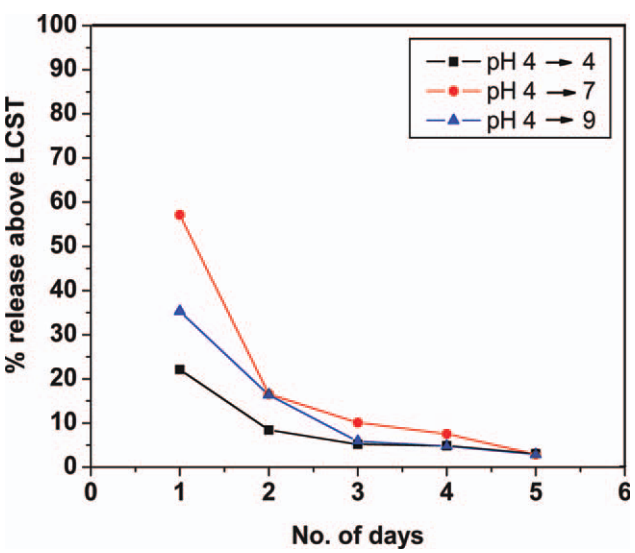


Figure 7 Release of IBU to pH 4, 7, and 9 after loading at pH 4 at 40°C. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

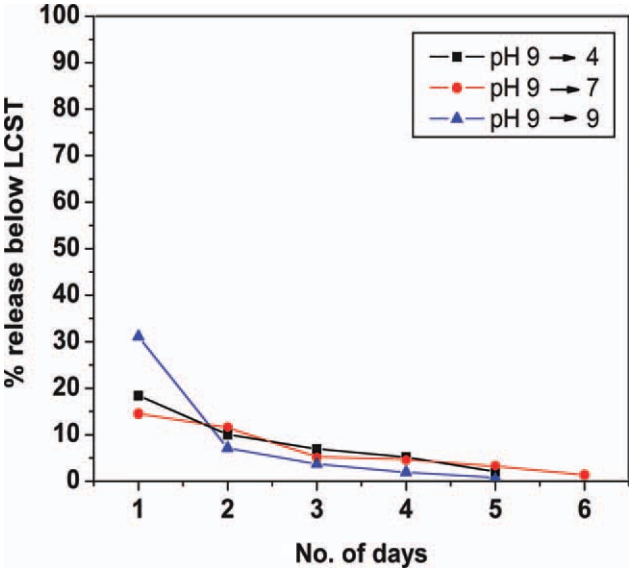


Figure 8 Release of IBU to pH 4, 7, and 9 after loading at pH 9 at room temperature. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

as well. One reason is the difference in the shrinking behavior (Table II).[26,59,60] Thus, the sudden shrinking of the gel at pH 4 resisted the flow of IBU molecules/aggregates, which resulted in the low release at pH 4. From Table II, it can be seen that the effective bead size increased in pH 9 whereas at pH 7 it remained same at this condition with reference to pH 4. Hence, an increase in volume of the gel at pH

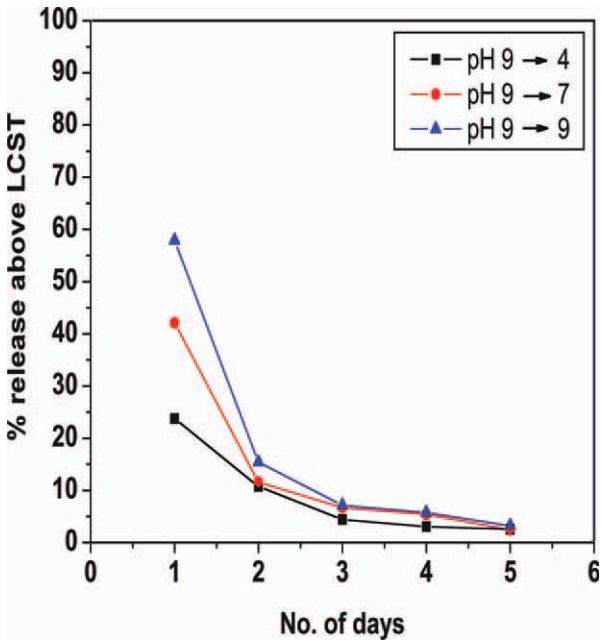


Figure 9 Release of IBU to pH 4, 7, and 9 after loading at pH 9 at 40°C. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

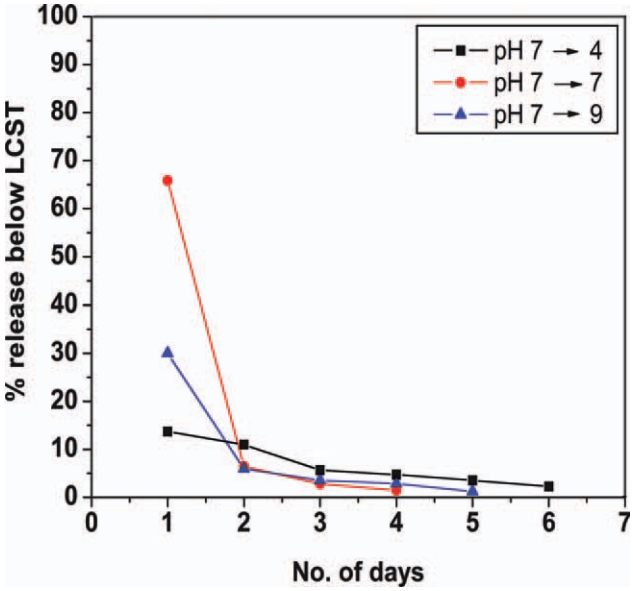


Figure 10 Release of IBU to pH 4, 7, and 9 after loading at pH 7 at room temperature. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

9 retarded the release of the drug in comparison to the release at pH 7.

In general, the high release rate at 40°C (Fig. 7) in comparison to room temperature (Fig. 6) was due to the increased acidity (polarity) of the gel.[55] This acidity increase occurred due to decrease in gel size above the LCST (Table II).

Loading of IBU at pH 9 and release at pH 4, 7, and 9

In this experiment, however, the first day release results were in favor of pH 9 both below and above the LCST (Figs. 8 and 9). The higher bead size, same pH and high solubility of IBU in pH 9 buffer medium helped to show maximum release in pH 9 on the first day. Additionally, IBU being a hydrophobic drug was released at a faster rate because of the basic (polar) nature of the gel in pH 9.[55] Afterwards, the release was identical in all cases. However, the release rate doubled at 40°C. This was similar to the result obtained at pH 4 (Figs. 6 and 7). Here also the main reason is the increase in basicity of the gel at 40°C.

Loading of IBU at pH 7 and release at pH 4, 7, and 9

Here the gel beads loaded with IBU at pH 7 was allowed to release at pH 4, 7, and 9, both below and above the LCST. The comparatively high release percentage value during the initial burst was at pH 7 as indicated in Figures 10 and 11. The same bead size and same pH are the two controlling effects for

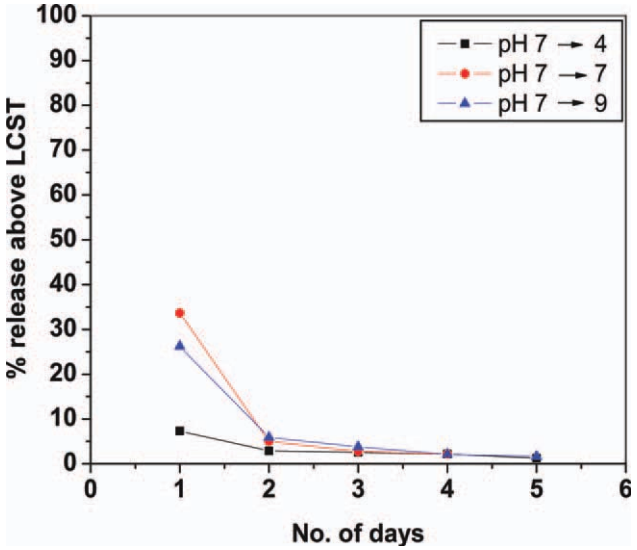


Figure 11 Release of IBU to pH 4, 7, and 9 after loading at pH 7 at 40°C. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

initial high release at pH 7. Afterwards, the data points are close to each other for all the cases.

However, at 40°C the first day release was lower than that observed at room temperature (Fig. 11). This result was different from the earlier observations at pH 4 and 9 discussed in Figures 7 and 9. It was reported that above the LCST the gel becomes hydrophobic and the hydrophobic effect is maximum at neutral condition.[40] This local environment subsequently holds the hydrophobic drug firmly within the gel at pH 7.[40,52] Where as at pH 4 and 9 the gel is acidic and basic (polar) repectively and it was reported that increase in ionic strength increases the release of a hydrophobic drug.[55] Again, the poor solubility of IBU at pH 4 is responsible for the lower release observed at pH 4.

On comparing all these combinations, it can be seen that the release percentage was comparatively high in pH 7 both below and above the LCST. This observation was different from the expected result, which was in support of pH 9 merely because of high solubility of the drug and high SR in pH 9. However, in this work, we observed that abrupt change in bead size with change in pH and "acidity or basicity" of the gel could be the main reasons for higher release in pH 7. Above the LCST, the drug release was high in the case of pH 4 and 9 loading (Figs. 7 and 9). A similar behavior was reported by other authors in the case of hydrophobic drugs at pH 4 and 9.[30] Thus, it was confirmed that the gel/water interface exhibited different properties with respect to pH and temperature of the medium.

From all the figures presenting release data, it can be concluded that controlled release of IBU from NIPAM-*co*-MAc hydrogel was in pH 4. This was clear from the slow and steady release of the drug in pH 4 over days unlike in the case of pH 7 and 9, where sudden decrease in release can be seen after 24 h. Hence, the authors anticipate that this observation in pH 4 would be advantageous for using this gel matrix for slow drug delivery applications.

Additionally, we also observed a slight decrease in swelling of the gel in the presence of IBU compared to the free condition. Future studies are directed towards, detailed microscopic investigation of the gel/water interface, cytotoxicity of the gel, use of other comonomers, etc.

CONCLUSIONS

NIPAM-*co*-MAc hydrogel for a controlled drug release was synthesized by the sedimentation polymerization. The structure of the hydrogel was analyzed using FTIR, SEM, and DSC. The morphological data from SEM revealed that the surface structure of the hydrogel was poriferous whereas the bulk a very rigid hard mass. The imbibition of the bead presented a pH dependent SR in the order pH 9 > 7 > 4. Additionally, the loading of MAc units in the polymer could be limited to 10% to get the high LCST of about 38°C. This hydrogel retained its shape and color during the period of drug delivery and degraded completely into soluble analogues after 5–10 days. The drug release from this hydrogel to different pH solutions was successfully controlled by the temperature swing between 25 and 40°C. IBU, being an acidic molecule the maximum release was expected to be high in pH 9 but the experimental result was partially in favor of pH 7. The mechanism of the drug release was discussed in relation to the diffusion rate, solubility of the drug, abrupt change in pH, and "acidity or basicity" (polarity) of the gel. Based on our studies we observed a slow and controlled release at pH 4. Since the gel is biodegradable due to ester crosslinks and MAc is a biocompatible monomer, it is a suitable candidate for retarded drug release applications.

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