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Evaluation of pH-Sensitivity and Drug Release Characteristics of (Polyacrylamide-*Grafted*-Xanthan)–Carboxymethyl Cellulose-Based pH-Sensitive Interpenetrating Network Hydrogel Beads

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Novel pH-sensitive interpenetrating network hydrogel beads of polyacrylamide-*grafted*-xanthan (PAAm-*g*-XG) and sodium carboxymethyl cellulose (NaCMC) loaded with ketoprofen were prepared and evaluated for pH sensitivity and drug release characteristics. The pH-sensitive PAAm-*g*-XG copolymer was synthesized by free radical polymerization under the nitrogen atmosphere followed by alkaline hydrolysis. The grafting and alkaline hydrolysis reactions were confirmed by Fourier transform infrared spectroscopy. Differential scanning calorimetry and X-ray diffraction studies were carried out to know the crystalline nature of encapsulated drug. Scanning electron microscopic study revealed that the interpenetrating polymer network (IPN) beads possess porous matrix structure in alkaline pH whereas nonporous matrix structure was observed in acidic pH. The swelling of the beads and drug release was significantly increased when pH of the medium was changed from acidic to alkaline. The results of pulsatile swelling study indicated that the IPN beads changed their swelling behavior when pH of the external medium was altered. As pH of the medium was changed from 1.2 to 7.4, a considerable increase in swelling was observed for all the beads. However, swelling process was slower than the deswelling. At higher pH values, the carboxyl functional groups of hydrogels undergo ionization and the osmotic pressure inside the beads increases resulting in higher swelling. Drug release followed case II transport mechanism in acidic medium whereas anomalous/non-Fickian transport mechanism was observed in alkaline medium.

Keywords interpenetrating polymer network; graft copolymer; pH-sensitive hydrogel; drug release; beads

INTRODUCTION

The stimulus-sensitive drug delivery systems can be prepared using hydrogel, a cross-linked three-dimensional polymer network. Stimuli-responsive hydrogels can show dramatic changes in their swelling behavior, network structure, permeability, or mechanical strength in response to different stimuli such as temperature, pH, mechanical pressure, light, and electric current (Kulkarni & Sa, 2007). Such hydrogels have attracted a considerable attention as intelligent materials finding applications in biochemical, drug delivery, and biomedical and sensing fields (Dincer, Tuncel, & Piskin, 2002; Hoffman et al., 2000; Jeong & Gutowaka, 2002; Kulkarni & Sa, 2008a). The drug delivery systems designed using stimuli-responsive hydrogels can release the required quantity of loaded drugs at a right time and right place in the body in response to the stimulus. The pH-dependent swelling or shrinking of the hydrogels is driven by the ionization of carboxyl functional groups of polymer. The –COOH functional groups will undergo ionization at higher pH values, but they will be protonated at lower pH. Upon ionization, the counterion concentration inside the network increases, and an osmotic pressure difference exists between the internal and external solutions of the hydrogel. The increased osmotic pressure will be balanced by the swelling of the hydrogel (Drummond, Klier, Almeda, & Peppas, 1989). The pH-sensitive hydrogels can be weakly acidic (anionic) or weakly basic (cationic) depending on the nature of the ionizable moieties on their polymer backbones.

In recent years, use of polysaccharides to prepare multiunit controlled release dosage forms has attracted the attention of researchers (Davis & Huglin, 1990; Desai & Hubbel, 1992; Khare & Peppas, 1993). The naturally available polysaccharides are often preferred to synthetic materials due to their nontoxic, low cost, free availability, and biodegradability. However, the natural polysaccharides exhibit some limitations, such as uncontrolled rate of hydration, microbial contamination, and drop in viscosity on storage. These limitations can be reduced following modification by cross-linking, blending, etc. Many attempts have been made to conquer such limitations by

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the modification of polysaccharides. Among these, development of interpenetrating polymer network (IPN) structures has attracted the attention (Burugapalli, Bhatia, Koul, & Choudhary, 2001; Changez, Koul, Burugapalli, & Dinda, 2004). IPN is a combination of two polymers in network form, at least one of which is synthesized and/or cross-linked in the immediate presence of the other (Hsieh, Hsieh, Simon, & Tiu, 1999; Kosmala, Henthorn, & Peppas, 2000). IPNs prepared using natural polymers are capable of delivering drugs at constant rate over an extended period of time (Kulkarni & Sa, 2008b). Homopolymers alone cannot meet such divergent demand in terms of both properties and performance. Therefore formation of IPN appears to be a better approach (Changez, Burugapalli, Koul, & Chowdary, 2003).

Xanthan gum (XG) is a high-molecular-weight anionic extracellular polysaccharide that is produced by gram-negative bacterium *Xanthamonas campestris*. It has been widely used in cosmetics, food industry, and drug delivery (Talukdar, Michoel, Rombaut, & Kinget, 1996; Talukdar & Plaizier-Vercammen, 1993). A recent report indicated that if XG is derivatized to sodium carboxymethyl xanthan, it could be used to formulate microparticles through interaction with aluminum ions (Maiti, Ray, Mandal, Sarkar, & Sa, 2007). Polyacrylamide (PAAm) is a widely used polymer that possesses soft tissue biocompatibility and an open porous structure that allows the transport of incorporated molecules. It swells in water and retains a significant fraction of water within its structure. These desirable features make PAAm a suitable carrier for drug delivery applications (Risbud & Bhonde, 2000). The sodium carboxymethyl cellulose (NaCMC) has been used as a matrix material to sustain the release of drugs using ionotropic gelation method by various researchers (Hosny & Al-Helw, 1998; Hosny, Al-Helw, & Al-Dardiri, 1997). Recently, semi-IPN microspheres of NaCMC–gelatin have been developed for the controlled release of ketorolac tromethamine using emulsion cross-linking method (Rokhade et al., 2006). However, there is no report in the literature on pH-sensitive IPNs of polyacrylamide-*grafted*-xanthan (PAAm-*g*-XG) and NaCMC for the drug delivery application. The development of IPN of hydrolyzed PAAm-*g*-XG and NaCMC is beneficial because, it contains two cross-linked polymers in a network form to give a three-dimensional pH-sensitive network structure, which produces more free volume for the easy entrapment of drugs and improves mechanical strength.

The objective of this study was to develop novel pH-sensitive IPN beads using PAAm-*g*-XG and NaCMC for controlled release of ketoprofen. The PAAm-*g*-XG copolymer was synthesized by free radical polymerization under the nitrogen atmosphere followed by alkaline hydrolysis to obtain pH-sensitive copolymer. During alkaline hydrolysis, $–CONH_2$ groups of PAAm present on the backbone of XG are converted to –COOH groups resulting in pH-sensitive copolymer. As the beads carry –COOH functional groups, they remain unionized at gastric pH leading to negligible swelling and drug release, but they undergo ionization at higher pH leading to maximum swelling and drug release in the intestine. This could reduce the severity of gastric irritation, ulceration, and perforations associated with ketoprofen.

MATERIALS AND METHODS

Materials

Ketoprofen and XG were obtained as gift samples from Rhone-Poulenc, (Mumbai, India) and Himalaya Drug Co. (Bangalore, India). Carboxymethyl cellulose sodium salt, high-viscosity grade (500–800 cPs), acrylamide (AAm), ammonium peroxodisulfate (APS), aluminum chloride hexahydrate, sodium hydroxide, concentrated HCl, and methanol were purchased from S.D. fine Chemicals (Mumbai, India). Double distilled water was used throughout the study. All other chemicals were used as received.

Synthesis of PAAm-*g*-XG Copolymer

The PAAm-*g*-XG copolymer was synthesized by free radical polymerization following the method reported earlier (Pourjavadi, Sadeghi, & Hosseinzadeh, 2004). Two grams of XG was dissolved in 100 mL double distilled water in a three-necked round-bottom flask and allowed to hydrate for 4 h with continuous purging of slow stream of nitrogen gas. The flask was heated at 80°C; 0.12 mol of acrylamide and 0.002 mol of APS were added to XG solution. Polymerization was carried out for 60 min with continuous purging of nitrogen gas. After 60 min, the resulting copolymer was allowed to cool at ambient temperature and the product was poured into excess methanol and kept for 24 h to dewater. The copolymer was then filtered, washed repeatedly with methanol, dried at 50°C overnight, and finally kept in a desiccator. Mass of the graft copolymer was taken and the percent grafting efficiency was calculated using the following relation (Eromosele, Eromosele, & Zanna, 2002):

$$\% \text{ grafting efficiency} = \frac{W_1 - W_0}{W_2} \times 100,$$

where W_0, W_1, and W_2 are the weights of XG, graft copolymer, and AAm, respectively.

Alkaline Hydrolysis of PAAm-*g*-XG Copolymer

Two grams of PAAm-*g*-XG copolymer was dissolved in 100 mL of 0.9M NaOH solution and stirred at 75°C for 60 min in a thermostatic water bath. At the end of reaction time, the solution was cooled and poured in excess methanol. The hydrolyzed copolymer was separated by filtration and washed repeatedly with methanol and dried overnight at 50°C.

Fourier Transform Infrared Spectroscopy

Fourier transform infrared spectroscopy (FTIR) spectra of XG, PAAm-*g*-XG, and hydrolyzed PAAm-*g*-XG were recorded using FTIR spectrophotometer (Model Magna 550, Nicolet, WI, USA). The samples were crushed with potassium bromide to make pellets under hydraulic pressure of 600 kg and scanned between 450 and 4,000 cm^{-1}.

Preparation of IPN Beads

An accurately weighed quantity of ketoprofen was dispersed in an aqueous solution of hydrolyzed PAAm-*g*-XG and NaCMC (total polymer concentration 3%, wt/vol) and mixed homogeneously using a magnetic stirrer. A volume of 20 mL of the dispersion was dropped slowly into an aqueous solution of $AlCl_3$ using 25-mL hypodermic syringe through a needle (number 23) under constant stirring. After incubating for additional 15 min in $AlCl_3$ solution, the beads were removed and washed with distilled water repeatedly to make free from unreacted ions. The beads were dried at room temperature for 24 h and then at 40°C for 10 h. The formulation details are given in Table 1 and schematic representation of the IPN matrix is given in Figure 1.

Scanning Electron Microscopic Studies

The IPN beads were mounted onto stubs using double-sided adhesive tape and sputter coated with platinum using a sputter coater (S 150, Edward, UK). The coated beads were observed under scanning electron microscopy (SEM) (JSM-6360, JEOL, Kyoto, Japan) at the required magnification at room temperature. The acceleration voltage used was 10 kV with the secondary electron image as a detector.

Measurement of Bead Size

The bead size was measured using a digimatic micrometer (MDC-25S, Mitutoyo, Tokyo, Japan) having an accuracy of 0.001 mm. The average diameter of the 100 particles per batch was calculated.

TABLE 1
Composition of IPN Beads

Formulation Codes	PAAm-*g*-XG (%, wt/vol)	NaCMC (%, wt/vol)	Drug[a]	$AlCl_3$ (%, wt/vol)
XIB1	1.5	1.5	20	5
XIB2	1.5	1.5	20	10
XIB3	1.5	1.5	20	15
XIB4	1.5	1.5	40	15
XIB5	2.0	1.0	20	5
XIB6	2.0	1.0	20	10
XIB7	2.0	1.0	20	15
XIB8	2.0	1.0	40	15

[a]Dry polymer (%, wt/wt).

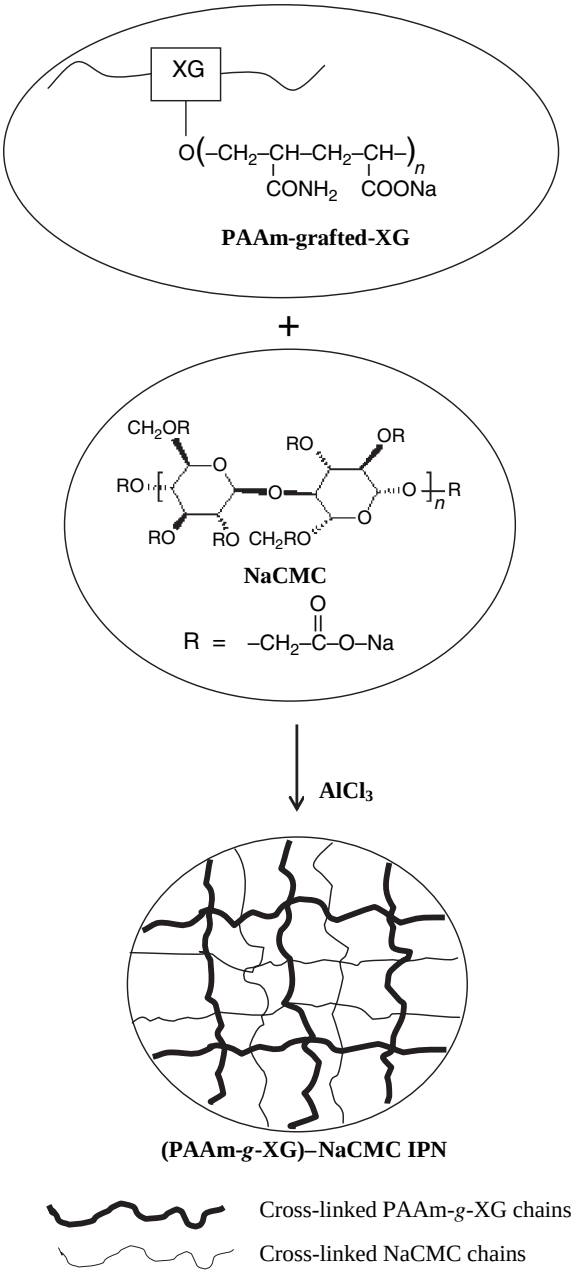

FIGURE 1. Schematic representation of the IPN matrix.

Estimation of Drug Entrapment Efficiency

Known amounts of IPN beads were incubated in 100 mL USP phosphate buffer of pH 7.4 for complete swelling at 37°C. Then the beads were crushed in a glass mortar with pestle, the solution was then heated gently for 3 h to extract the drug completely and centrifuged to remove the polymeric debris. The clear supernatant solution was analyzed for the drug content

using UV–visible spectrophotometer (Model Pharmaspec UV-1700, Shimadzu, Kyoto, Japan) at 260 nm. The drug entrapment efficiency (DEE) was calculated using the following equation:

$$\text{Drug entrapment efficiency} = \frac{\text{Experimental drug content}}{\text{Theoretical drug content}} \times 100.$$

Differential Scanning Calorimetric Analysis

The differential scanning calorimetric (DSC) analysis was performed on the ketoprofen, drug-free IPN beads, and drug-loaded IPN beads. The samples were heated from 0 to 300°C at a heating rate of 10°C/min under argon atmosphere using a microcalorimeter (DuPont-9900, DuPont, GA, USA).

X-Ray Diffraction Studies

The X-ray diffraction (XRD) study was performed on the ketoprofen and drug-loaded IPN beads to know the crystallinity of the entrapped drug. The spectra were recorded using a Philips, PW-171, X-ray diffractometer with Cu–NF filtered Cu Kα radiation. Quartz was used as an internal standard for calibration. The powder X-ray diffractometer was attached to a digital graphical assembly and computer with Cu–NF 25 kV/20 mA tube as a Cu Kα radiation source in the 2θ range 0–50°.

Pulsatile Swelling Studies

The pulsatile swelling of the IPN beads was studied in 25 mL solutions of pH 1.2 and pH 7.4 at 37°C by mass measurement. An arbitrary sequence of step changes was used to analyze the mass response. The pH of the surrounding medium was changed alternatively. At different time intervals, beads were separated from the buffer medium using stainless-steel grid; excess surface liquid was removed by blotting with soft tissue paper and the beads were weighed using electronic microbalance (Model BL-220H, Shimadzu, Kyoto, Japan). The mass % uptake, Q, was calculated from the following relationship:

$$Q = \frac{W_2 - W_1}{W_1} \times 100,$$

where W_1 is mass of the dry beads and W_2 is the mass of swollen beads.

In Vitro Drug Release

In vitro drug release study was carried out in triplicate using a dissolution tester (TDT-06P (USP), Electrolab, Mumbai, India). The dissolution rates were measured at 37.0 ± 0.5°C and 50 rpm speed. Drug release from the beads was studied in 900 mL acidic medium (pH 1.2) and alkaline medium (pH 7.4 phosphate buffer). At predetermined time intervals, 5 mL aliquots were withdrawn and replaced with the same volume of fresh solution. The samples were passed through a 0.45-μm membrane filter and the amount of drug released was analyzed using UV–visible spectrophotometer at 260 nm following suitable dilutions.

RESULTS AND DISCUSSION

The grafting of AAm on the backbone of XG was carried out by free radical polymerization using APS as reaction initiator under nitrogen atmosphere. The reaction temperature was maintained at 80°C; at this temperature the APS undergoes decomposition to produce sulfate anion free radical, which abstracts the hydrogen from hydroxyl groups of XG to form alkoxy radical on the substrate. Then the resulting macroradical initiate the graft copolymerization of AAm onto the backbone of XG. The grafting efficiency was found to be 86.16%.

FTIR Characterization of Graft Copolymer

Figure 2 shows the FTIR spectra of pure XG, PAAm-*g*-XG, and hydrolyzed PAAm-*g*-XG. The pure XG showed a peak at 3,411 cm^{-1} due to the presence hydrogen bonded OH groups. Two other peaks at 1,613 and 1,405 cm^{-1} are due to COO^- groups. In the spectrum of PAAm-*g*-XG, apart from these peaks, additional peaks were observed at 3,399, 3,195, 1,662, 1,450 and 1,100 cm^{-1}. The peaks at 3,399 and 3,195 cm^{-1} are assigned to the overlap of N–H stretching band of amide group and O–H stretching band of hydroxyl groups of XG. The peaks at 1,662 and 1,450 cm^{-1} are because of the primary amide group on the backbone of XG. The peak at 1,100 cm^{-1} is due to

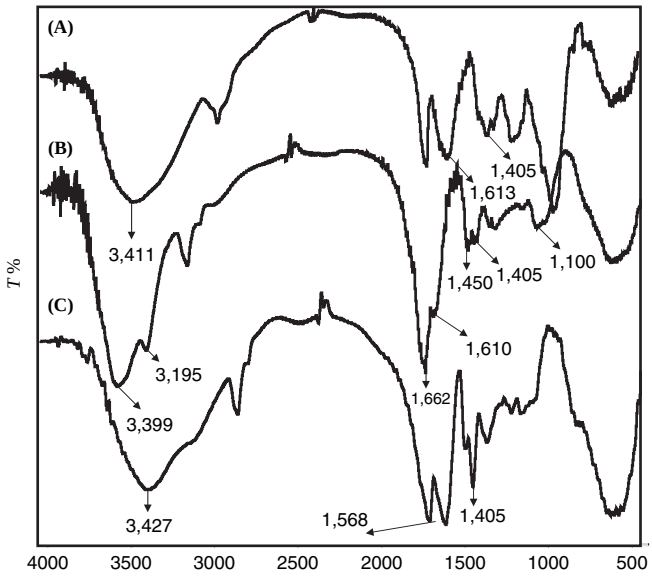

FIGURE 2. FTIR spectra of XG (A), PAAm-*g*-XG (B), and hydrolyzed PAAm-*g*-XG (C).

the ether linkage formed by the reaction between OH groups of XG and acrylamide. This is supportive evidence for grafting. In case of hydrolyzed PAAm-*g*-XG, the sharp peaks appearing at 3,399 and 3,195 cm^{-1} were absent, indicating the absence of N–H band. The peaks at 1,568 and 1,405 cm^{-1} are due to COO^- groups. This confirms the hydrolysis reaction. Similar observations were reported earlier (Adhikary & Singh, 2004; Mundaragi, Patil, Agnihotri, & Aminabhavi, 2007).

Formation of IPN Beads and Drug Entrapment Efficiency

During the preparation of beads, as soon as the (PAAm-*g*-XG)–NaCMC solution was brought in contact with Al^{3+} cations ($AlCl_3$ solution), there will be a formation of ionic cross-linking between two polymer chains. The exchange of Na^+ from the polymer occurs with Al^{3+} ions. These Al^{3+} are ionically substituted at the carboxylate site and a second strand of NaCMC or PAAm-*g*-XG can also be connected with Al^{3+} forming a link in which the cations are attached to two or three NaCMC or PAAm-*g*-XG strands together to form spherical IPNs. The prepared IPN beads were spherical in shape having surface foldings as evidenced by SEM (Figure 3) and they fell in the size range of 910–1,208 μm (Table 2). As the concentration of $AlCl_3$ was increased, smaller beads were produced (1,081, 944, and 910 μm for 5, 10, and 15 wt/vol of $AlCl_3$, respectively).This suggests that during cross-linking, the hydrogel might have undergone rapid shrinking leading to the formation of smaller and rigid IPN matrix at higher cross-link densities. Similar result has been reported earlier at higher cross-link densities in the case of poly(vinyl alcohol) hydrogels (Korsmeyer & Peppas, 1981). On the contrary, as the amount of ketoprofen increases, the bead size increases because ketoprofen might have occupied the interstitial spaces between polymer segments (910 and 923 μm for 20 and 40% drug loadings, respectively). Also by increasing the ratio of graft copolymer in the beads, an increase in size of the beads was observed, which could be attributed to the formation of bigger droplets due to increase in the viscosity of the solution with increasing concentration of graft copolymer during extruding through a needle. This is in agreement with the previously published results (Agnihotri & Aminabhavi, 2006).

The DEE of the beads was found to be in the range of 81.8–92.9%. Table 2 shows that DEE of the beads prepared with lower concentration of $AlCl_3$ was lowest as compared with those prepared with higher concentration of $AlCl_3$. At lower concentration of $AlCl_3$, the IPN matrix might be loose and have larger pores due to insufficient cross-linking, which results in higher leakage of drug into the counterion medium from IPN matrix during the preparation of beads, which may lead to lower DEE. Whereas, at higher concentration of $AlCl_3$, the IPN matrix is rigid and leakage of drug from polymer matrix is low resulting in high DEE. Similar observation was also reported by other authors (Bhopatkar, Anal, & Stevens, 2005).

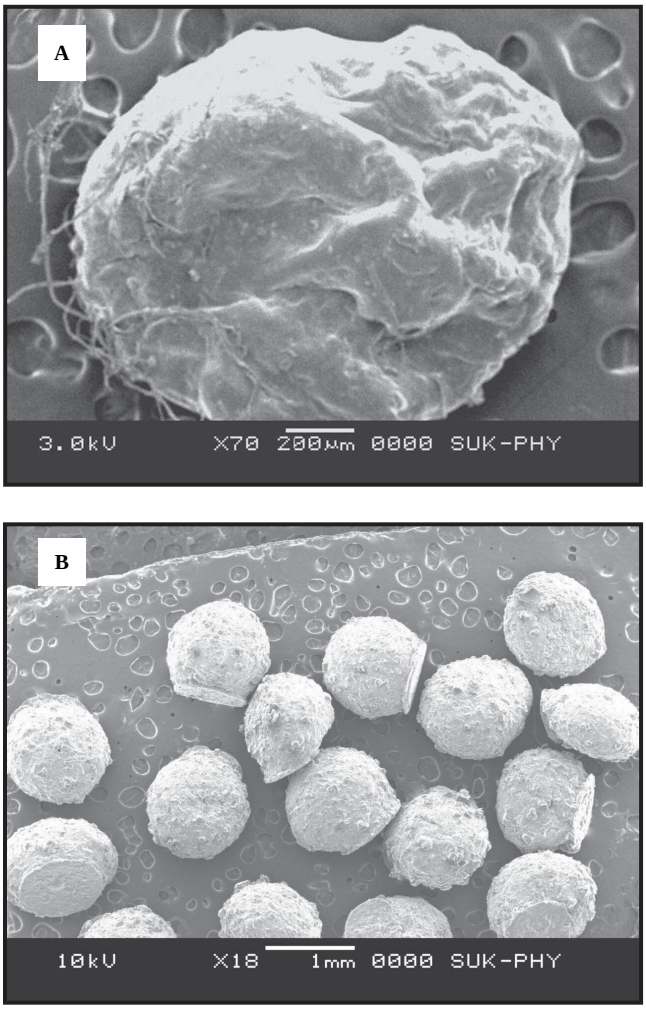

FIGURE 3. SEM photographs of the single IPN bead (A) and group of beads (B).

Differential Scanning Calorimetric Analysis

The DSC thermograms for ketoprofen (A), drug-free IPN beads (B), and drug-loaded IPN beads (C) are presented in Figure 4. The drug-free beads have shown a sharp endothermic peak at 182°C, whereas the drug-loaded beads showed an endothermic peak at 123°C. This decrease in melting temperature may be due to the formation of loose polymer matrix as a result of creation of extra free space after drug loading. The pure ketoprofen has shown a sharp endothermic peak at 96°C due to melting of the drug, but this peak has not appeared in the drug-loaded beads. This indicates that the drug was uniformly dispersed in an amorphous state in the IPN matrix.

X-Ray Diffraction Studies

The XRD studies are useful to investigate the crystallinity of the drugs after entrapment into the dosage forms. The X-ray diffractograms of ketoprofen and drug-loaded IPN beads are

TABLE 2
Mean Bead Size, Drug Entrapment Efficiency (DEE), Diffusion Coefficients (D), and Release Parameter (n) of the IPN Beads in Different pH Solutions

Beads	Mean Size (μm) ± *SD*	DEE (%)	D (cm^2/s)		n		r^a	
			pH 1.2	pH 7.4	pH 1.2	pH 7.4	pH 1.2	pH 7.4
XIB1	1081 ± 55.68	81.8	8.11×10^{-7}	5.28×10^{-6}	0.82	0.60	0.98	0.97
XIB2	944 ± 54.22	87.2	3.81×10^{-7}	2.95×10^{-6}	0.84	0.64	0.99	0.98
XIB3	910 ± 36.52	91.1	2.02×10^{-7}	2.33×10^{-6}	0.90	0.73	0.98	0.99
XIB4	923 ± 40.46	91.9	2.08×10^{-7}	2.39×10^{-6}	0.90	0.72	0.98	0.99
XIB5	1,208 ± 58.44	82.9	1.86×10^{-6}	7.83×10^{-6}	0.73	0.62	0.97	0.96
XIB6	1,048 ± 70.39	88.3	9.08×10^{-7}	4.82×10^{-6}	0.89	0.69	0.99	0.97
XIB7	948 ± 55.05	92.0	6.16×10^{-7}	2.96×10^{-6}	1.05	0.70	0.99	0.99
XIB8	959 ± 29.33	92.9	6.45×10^{-7}	3.26×10^{-6}	1.05	0.73	0.99	0.99

[a]Correlation coefficient.

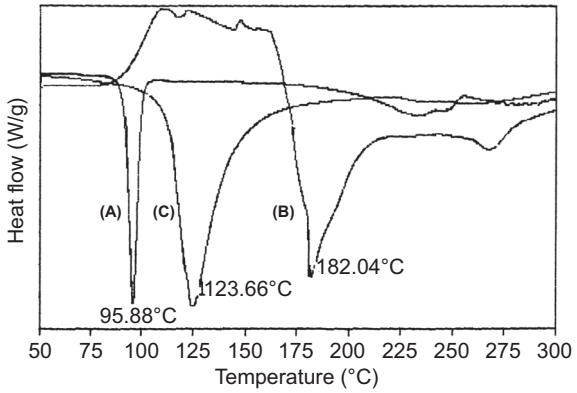

FIGURE 4. DSC thermograms of ketoprofen (A), drug-free IPN bead (B), and drug-loaded IPN bead (C).

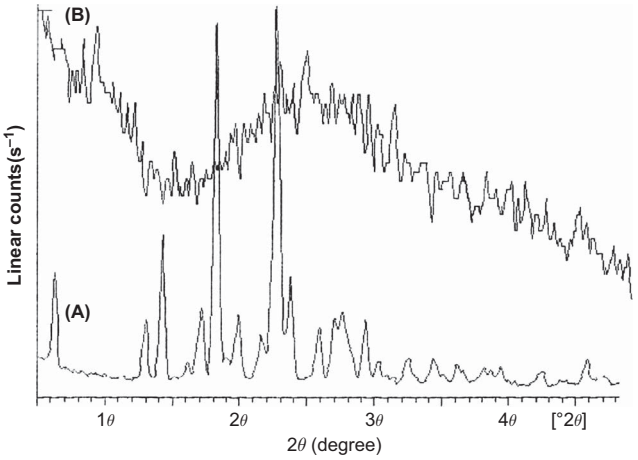

FIGURE 5. X-ray diffractograms of ketoprofen (A) and drug-loaded IPN bead (B).

presented in Figure 5. Ketoprofen has shown characteristic intense peaks between the 2θ of 6° and 29° due to its crystalline nature. Whereas in the case of drug-loaded IPN beads, no intense peaks were observed between the 2θ of 6° and 29°. This indicates the amorphous dispersion of the drug after entrapment into IPN matrix.

Pulsatile Swelling Studies

The results of swelling studies indicated that the beads changed their swelling behavior when pH of the external medium was altered. As pH of the medium was changed from 1.2 to 7.4, a considerable increase in swelling was observed for all the beads. At higher pH values, the carboxyl functional groups of hydrogel can undergo ionization and the osmotic pressure inside the beads increases resulting in higher swelling (Soppimath, Kulkarni, & Aminabhavi, 2001). However, the swelling depends upon the extent of cross-linking and ratio of graft copolymer in the beads. It was observed that swelling of the beads increased with an increasing amount of graft copolymer in the beads, which may be accounted for the larger beads produced at higher concentration of graft copolymer that absorbs more amount of water. This is in agreement with the previous results (Kulkarni & Sa, 2008b). Whereas, swelling decreased with an increasing amount of $AlCl_3$, due to the formation of more rigid hydrogel network. At lower cross-link density, the hydrogel network is loose with a greater hydrodynamic free volume and can absorb more of the solvent resulting in higher swelling. This is in agreement with the previously published results (Kulkarni & Sa, 2008c; Soppimath et al., 2001).

It is evident from the pulsatile swelling study that swelling process is slower than the deswelling as shown in Figure 6. During the deswelling process, H^+ ions diffuse into the beads and neutralize the negatively charged polycarboxylate groups. A neutral layer of the polymer that deswelled is formed around the inner part of the polymer, which was still ionized and swollen. While diffusing into the network, H^+ can be rapidly captured

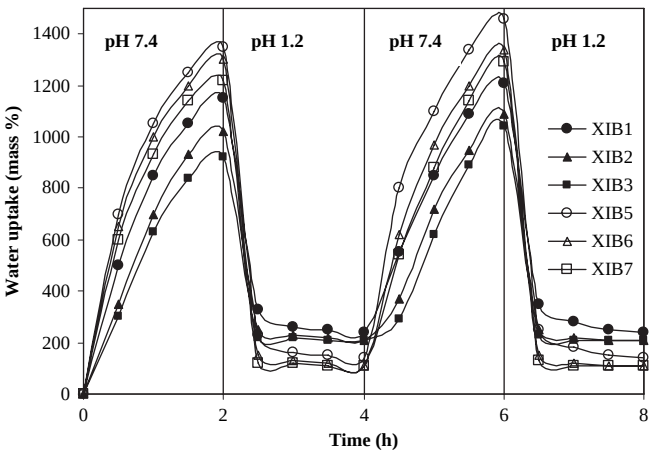

FIGURE 6. Pulsatile swelling behavior of the IPN beads. The pH was varied between 1.2 and 7.4.

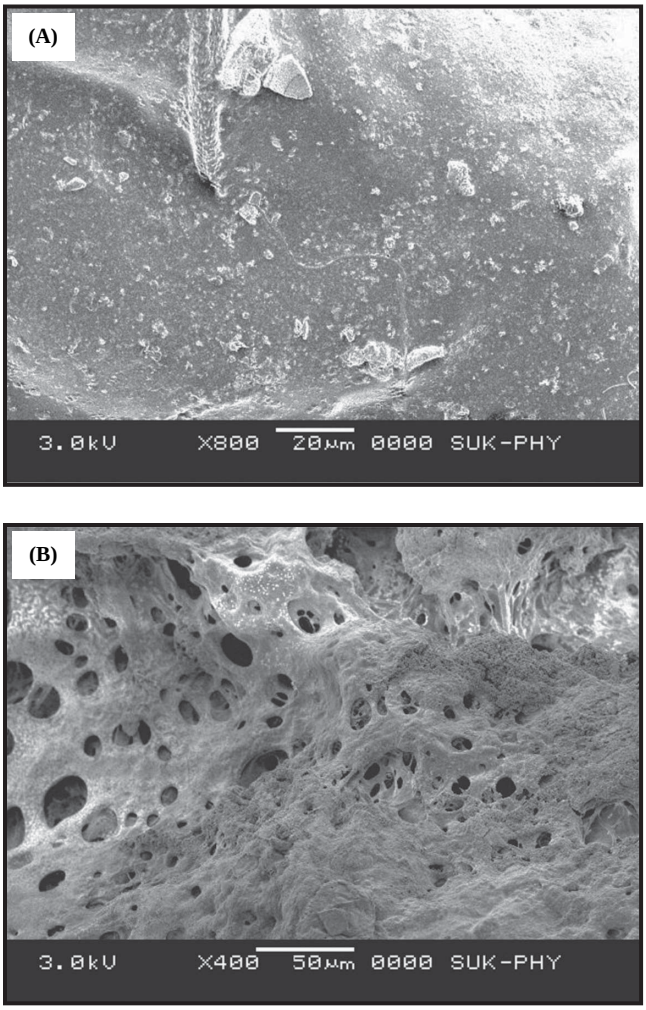

FIGURE 7. The surface morphology of IPN beads incubated in pH 1.2 solution (A) and pH 7.4 buffer solution (B) as studied by SEM.

by the $RCOO^-$ groups. A moving front separating the nonionic shell from an ionized core will develop. Because the shell was nonionic, H^+ can rapidly diffuse into the shell while Na^+ diffuses out. On the contrary, during the swelling process, hydrogel matrix was initially in its nonionic (–RCOOH) form, and was then converted to ionized state on changing the pH to 7.4 and soon the ionized shell was formed around the nonionized core (Jianqi, Zhang, Zhong, & Gu, 2002).

The pH-dependent swelling behavior was confirmed by examining the surface morphology of beads exposed to acidic and alkaline pH using SEM (Figure 7). In acidic media (pH 1.2), beads showed no surface pores as there was minimum swelling. This suggests why drug release is minimal in acidic pH. The surface morphology of the IPN beads exposed alkaline pH (pH 7.4) revealed highly porous matrix, compared with the surface of IPN beads incubated in pH 1.2 solution. These pores are formed due to ionization of –COOH groups of PAAm-*g*-XG copolymer and electrostatic repulsion of the ionized groups. Hence, swelling was higher in alkaline pH leading to easy liberation of the entrapped drugs through porous matrix.

In Vitro Drug Release

The drug release was studied in both simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 7.4) and the profiles are depicted in Figures 8–10. The release of drug in pH 1.2 solution was slower compared with that in pH 7.4 buffer solution. This was due to a higher swelling of IPN beads in alkaline pH condition. It was observed that release rates depend upon the amount of $AlCl_3$ used as a cross-linking agent during the preparation. Release was slower for the beads in which higher amount of $AlCl_3$ was used as compared with those beads in which lower amount of $AlCl_3$ was present (Figure 8). This could be due to the fact that at higher cross-linking, free volume of the matrix will decrease, thereby hindering the

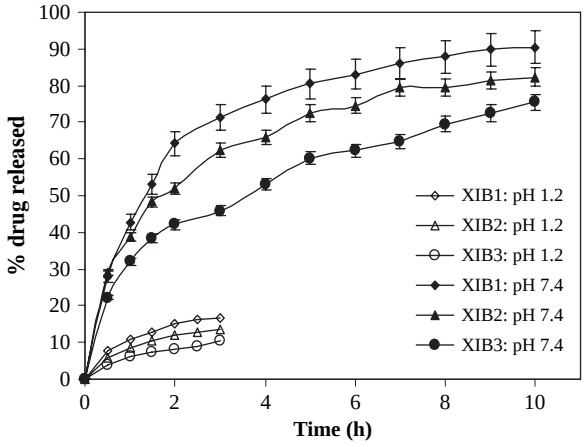

FIGURE 8. Effect of cross-link density on in vitro release of ketoprofen from pH-sensitive IPN beads in pH 1.2 and pH 7.4 buffer solutions.

transport of drug molecules through the matrix. This could also reduce the swelling as well as release rate from the matrix. Drug release was higher for the beads having higher amount of graft copolymer as compared with those having lower amount of graft copolymer (Figure 9). This may be due to higher swelling of IPN beads at higher amount of graft copolymer in the IPN beads (Kulkarni & Sa, 2008b). Figure 10 shows the effect of initial drug loading on the drug release. Keeping all the variables constant, increase in initial drug loading increased the drug release. Increase in initial drug load decreases the proportion of polymer per unit weight and this weakens the gel network structure. Moreover, higher drug loading increases the free volume within the network and creates a more tortuous path for water to penetrate through. Consequently, increase in initial drug loading increases the drug release (Agnihotri & Aminabhavi, 2006; Kulkarni & Sa, 2008a).

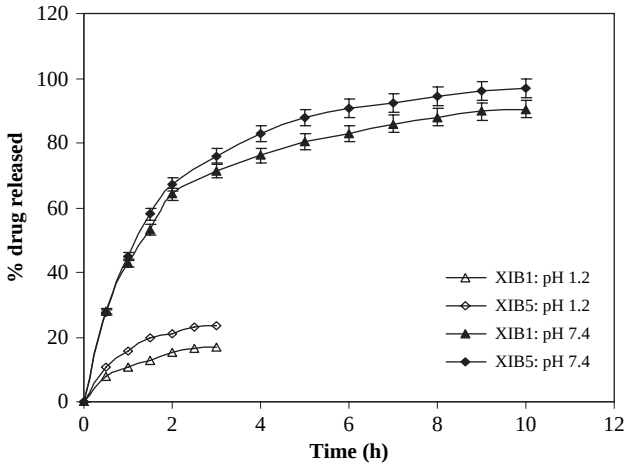

FIGURE 9. Effect of the graft copolymer concentration on in vitro release of ketoprofen from pH-sensitive IPN beads in pH 1.2 and pH 7.4 buffer solutions.

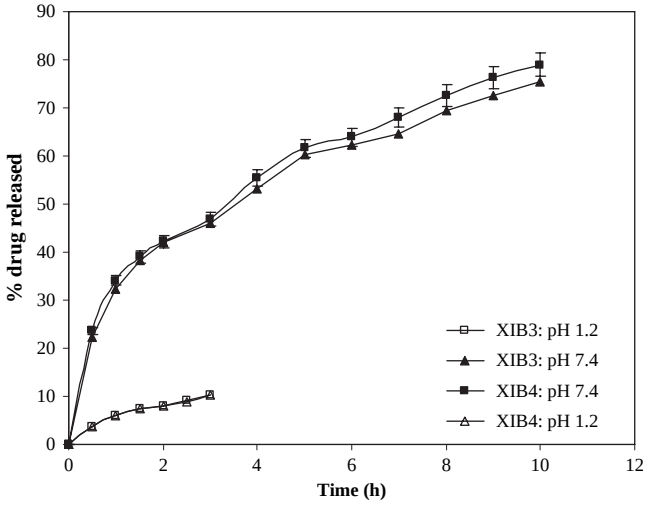

FIGURE 10. Effect of initial drug loading on in vitro release of ketoprofen from pH-sensitive IPN beads in pH 1.2 and pH 7.4 buffer solutions.

The diffusion coefficient values, D, for the transport of drug through the IPN beads were calculated using the following relation (Agnihotri & Aminabhavi, 2006):

$$D = \left(\frac{r\theta}{6M_\infty} \right)^2 \pi,$$

where θ is the slope of linear portion of the plot of $M_t/M\infty$ versus $t^{1/2}$, r is radius of the beads, and $M\infty$ is the total amount of drug loaded. The diffusion coefficients have been estimated based on the Fickian diffusion model and the D values are given in the Table 2. These values suggest that with an increase in pH of the dissolution medium from 1.2 to 7.4, an increase in diffusion coefficient of drug was observed. The extent of cross-linking showed an effect on the drug release characteristic of IPN beads (Figure 8). The values of D were decreased systematically with increasing amount of cross-linking agent. This may be attributed to the fact that with increasing amount of crosslinking agent, a stiffer IPN matrix is likely to be formed, which would prohibit the transport of drug molecules. Also, with increasing the amount of graft copolymer in the IPN beads, the D values were increased due to increased swelling of beads (Figure 9). Similar observations were reported previously (Agnihotri & Aminabhavi, 2005; Kulkarni & Sa, 2008b).

To understand the drug release mechanism from IPN beads, the release data was fitted to the following empirical equation (Ritger & Peppas, 1997):

$$\frac{M_t}{M_\infty} = Kt^n,$$

where M_t is the amount of drug released at time t, and $M\infty$ is the total amount of drug loaded, n values indicate the type of release mechanism. For spheres, values of n between 0.4 and 0.8 indicate both the diffusion controlled and swelling controlled release mechanism (anomalous transport). The values above 0.8 indicate case II transport that relates to polymer relaxation during swelling (Ritger & Peppas, 1997). The n values have been calculated and given in the Table 2 along with correlation coefficients. The values of n were in the range of 0.73–1.05 in acidic medium and 0.60–0.73 in alkaline medium. Here the n values are greater than 0.8 in pH 1.2 medium indicating that the transport mechanism follows case II. However, anomalous transport is observed in pH 7.4 buffer solution as the n values are between 0.4 and 0.8. The observed n value increases with increased cross-link density. In acidic medium, the solvent front moves slowly; the swollen hydrogel is expected to be nearly at equilibrium with the external medium, resulting in case II transport mechanism, whereas at pH 7.4, the solvent front moves faster and deviates from Fickian diffusion resulting in anomalous transport.

CONCLUSION

Novel pH-sensitive IPN beads of PAAm-*g*-XG and NaCMC were prepared by ionotropic gelation technique for the controlled release of ketoprofen. The FTIR spectra confirmed the grafting of PAAm on XG and alkaline hydrolysis of the copolymer. DSC and XRD studies confirmed the amorphous dispersion of the drug in IPN matrix. SEM study revealed that the beads showed no surface pores in acidic pH and highly porous matrix structure in alkaline pH. The swelling of the beads and drug release was significantly increased when pH of the medium was changed from acidic to alkaline. The drug release depends upon the extent of cross-linking and amount of graft copolymer used in the IPN matrix. This study demonstrates the possibility of preparing PAAm-*g*-XG–NaCMC IPN beads that may be useful as pH-sensitive controlled drug delivery systems.

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