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Synthesis, characterization, swelling and drug release behavior of semi-interpenetrating network hydrogels of sodium alginate and polyacrylamide

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ABSTRACT

Several semi interpenetrating network (SIPN) type hydrogels were synthesized by *in-situ* free radical crosslink copolymerization of acrylamide and crosslinker *N,N′*-methylene bisacrylamide (MBA) in aqueous solution of sodium alginate (SA).These SIPN hydrogels were characterized by FTIR, NMR SEM, DTA–TGA, XRD, PZC and also by swelling characteristics and network parameters. Adsorption (loading) and release of acetaminophen drug were studied with these hydrogels. Solution pH, crosslinker concentration and monomer to SA weight ratio of the hydrogels were found to have a strong effect on adsorption and in vitro release profile of the drug from the gel matrix.

1. Introduction

Semi interpenetrating network (SIPN) hydrogel consists of two polymers where one polymer is crosslinked in intimate presence of the other. In SIPN one linear polymer penetrates into network of another crosslinked polymer without any chemical bond formation between these two polymers (Sperling, 1981). Synthesis of SIPN is an effective way of making 'alloy' of multi functional crosslinked polymers which show much better properties than its constituent polymers (Myung et al., 2008). In recent years SIPN type hydrogels have been widely used for several applications including adsorption of metal ions (Horia et al., 2008), dyes (Mandal & Ray, 2013), artificial implants, dialysis membrane, controlled drug release system (Kulkarni, Sreedhar, Mutalik, Setty, & Sa, 2010; Matricardi, Meo, Coviello, Hennink, & Alhaique, 2013), etc.

In controlled drug release system a drug is delivered to the target site in a manner that maximizes its efficacy, minimizes the potential negative effects associated with overdosages, and/or extends the release time in which sufficient dosages are delivered. Thus, the overall objectives in the study of such techniques have been the development of a drug-loaded formulation that delivers the active ingredient at a rate matching the demand rate of the human system to which it is applied. Hydrogels made from non toxic biocompatible and biodegradable natural polymers based on polysaccharides are extensively used for controlled drug release (Lorenzo, Fernandez, Puga, & Concheiro, 2013).

Polysaccharides are easily available in nature and several functional hydrogels may be obtained by physical and chemical modification of polysaccharides. Alginic acid is a natural polysaccharide obtained from brown algae of sea weeds. This non toxic natural polymer contains random or alternating unit of 1,4-linked-β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues arranged in the polymer chains in blocks (Peppas, Hilt, Ali, & Robert, 2006). The sodium salt of alginic acid i.e. sodium alginate is a water soluble polymer which can be easily crosslinked with other multivalent cations such as calcium or organic crosslinker like glutaraldehyde (Raghavendra, Rashmi, Mohan, Mutalik, & Kalyane, 2012). Aliginate in gel, bead, film or pellet form is widely used for bioencapsulation of drug, proteins, cells and also as scaffolds for cartilage, bone and soft tissue regeneration (Tønnesen & Karlsen, 2002; Matricardi et al., 2013). However, like most of the biopolymer based hydrogels, sodium alginate based hydrogels are also of poor mechanical strength (Jeon, Lei, & Kim, 2008).

Properties of sodium alginate based hydrogel may be improved by physical or chemical modification. Hua et al. prepared hydrogel by freeze thawing polyvinyl alcohol and sodium alginate blend. This hydrogel was investigated for controlled release of diclofenac sodium (Hua, Ma, Li, Yang, & Wang, 2010). In another study polyacrylamide was grafted to PVA by UV radiation and blend of this graft polymer with sodium alginate was crosslinked with

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glutaraldehyde. From this hydrogel release of diclofenac sodium was observed to decrease with increase in amount of PVA in the blend (Sanlı, Aya, & Isıklan, 2007). Melt extruded fiber of blend of sodium alginate and starch was studied for controlled release of salicylic acid. Release rate of the drug salicylic acid decreased with increase in amount of starch in the blend (Wang, Hu, Du, & Kennedy, 2010a). IPN type hydrogel of sodium alginate and carrageenan grafted acrylamide was reported for release of ketoprofen. Release of this drug was found to increase from 10% in acid medium to 90% in alkaline medium (Raghavendra et al., 2012). Kulkarni et al. (2010) synthesized IPN of polyvinyl alcohol and sodium alginate and used it for controlled release of prazosin hydrochloride from skin. IPN type hydrogels were also prepared by crosslink copolymerization of MBA and isopropyl acrylamide in presence of sodium alginate. The thermo, pH responsive (Dumitriu, Mitchell, & Vasile, 2011) and rheological properties (Dumitriu, Mitchell, & Vasile, 2011a) of these mixed interpenetrating type hydrogels were reported.

It transpires from the above discussion that IPN type hydrogels of polysaccharides such as sodium alginate have been widely used for controlled drug release. In fact, IPNs of polysaccharides have an ability to deliver drugs at a constant rate for prolonged period in the body (Liu, Jiao, Wang, Zhou, & Zhang, 2008). Thus, in the present work semi-IPN (SIPN) type hydrogels were prepared from sodium alginate and polyacrylamide. Polyacrylamide was chosen as the second polymer of the SIPN since network gel structure of this polymer may be easily synthesized by free radical crosslink copolymerization with a bi-functional comonomer such as MBA. Further, it is biocompatible and because of its open porous structure the loaded drug may be easily transported through its network (Risbud & Bhonde, 2000). SIPN hydrogels of sodium alginate and polyacrylamide was studied for release of a water soluble drug acetaminophen from water.

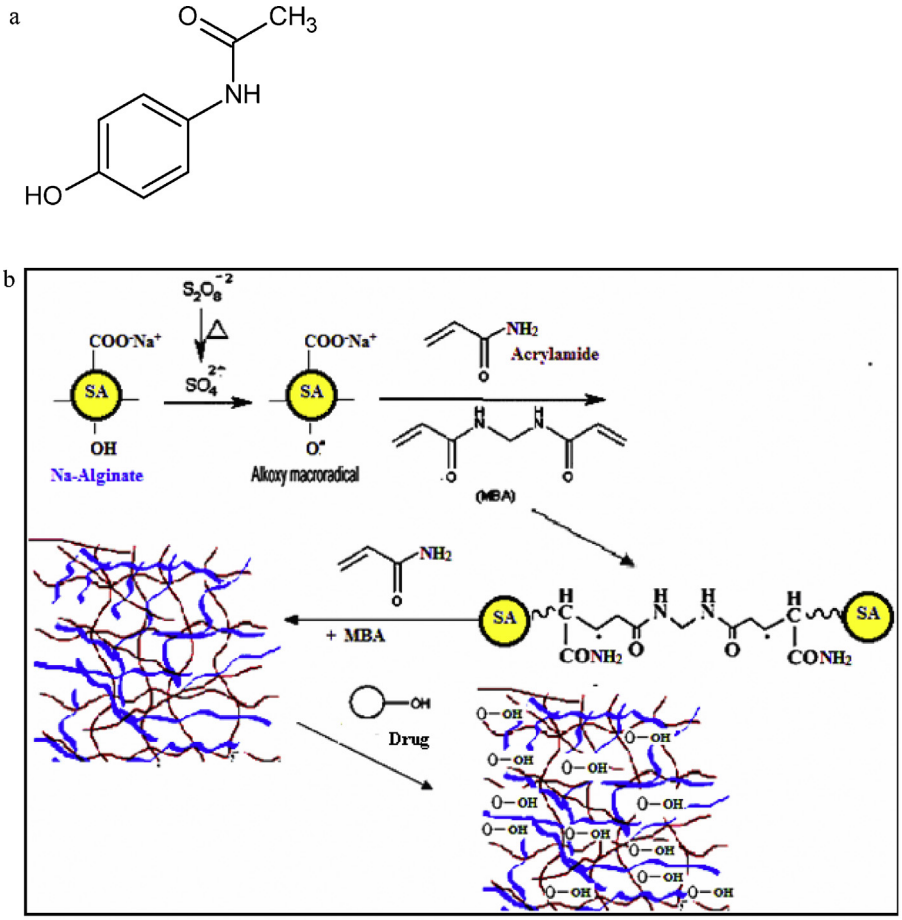
2. Materials and methods

2.1. Materials

Monomers i.e. acrylamide and *N*,*N*′-methylenebisacrylamide (MBA), redox initiator pair i.e. ammonium persulfate and sodium metabisulfite, were obtained from Merck. These chemicals were of analytical grade and used without further purification. Acetaminophen (structure shown in Scheme 1a) was obtained from Cipla, Mumbai, India. Natural polymer sodium alginate (average molecular weight 500,000 and degree of deacetylation 84%) was also procured from Merck and used as it is without any further purification. For all experiments double distilled water was used.

2.2. Preparation of hydrogel

SIPN hydrogels were prepared by free radical cross-link copolymerization of acrylamide and crosslinker comonomer MBA in aqueous solution of sodium alginate. The polymerization reaction was carried out in a three necked glass reactor equipped with a mechanical stirrer, reflux condenser and thermometer. Sodium alginate was first dissolved in water followed by addition of monomers to this viscous solution and stirring for around half an hour. The dissolved oxygen of the reaction mixtures was removed by purging nitrogen gas in the reaction mixtures before addition of acrylamide and MBA. The temperature of the reaction mixtures was raised to 40 °C with addition of required amounts of redox pair of



Scheme 1. (a) Structure of acetaminophen drug, (b) formation of SIPN and its probable interaction with drug.

initiator i.e. ammonium persulfate and sodium metabisulfite. The reaction was then continued at this temperature till the reaction mixtures gelled. The gel obtained was disintegrated in a blender, washed with water and then isopropyl alcohol, followed by filtration and finally dried to constant weight at 30 °C in a vacuum oven.

2.2.1. Yield and gel content of the hydrogel

The synthesized hydrogels were first dried to a constant weight (W_i).at 30 °C in a vacuum oven and then it was taken in water and kept for a week with occasional shaking to remove the water soluble part from the hydrogel. The water insoluble gel sample was further dried in vacuum oven to a constant weight (W_d). Yield (%) and gel (%) was obtained as

$$\text{Gel\%} = \frac{W_d}{W_i} \times 100 \quad (1)$$

$$\text{Yield\%} = \frac{W_d}{W_a} \times 100 \quad (2)$$

where W_a is total weight of monomers (acrylamide and MBA) and sodium alginate taken for synthesis of hydrogels.

2.3. Characterization of the hydrogels

The synthesized hydrogels were characterized by the following methods

2.3.1. Point zero charge (PZC) analysis

PZC of the hydrogel samples were measured by a method reported elsewhere (Mall, Srivastava, Kumar, & Mishra, 2006). For this 45 mL of 0.1 N KNO_3 solutions was taken in a 100 mL conical flask. The pH of the solution (pH_i) was adjusted from 2 to 12 by adding 0.1 N HNO_3 or NaOH solution. Around 0.1 g hydrogel sample was then added and the flask was securely capped. The gel loaded solution was then kept for 48 h to reach equilibrium with occasional shaking. The pH of the supernatant liquid was measured (pH_f). The difference between this initial and final pH ($\Delta pH = pH_i - pH_f$) was plotted against pH_i and the point of intersection of the curve at $\Delta pH = 0$ gives the value of PZC for the hydrogel.

2.3.2. FTIR spectroscopy

Fourier transform infrared (FTIR) spectra of the unfilled (drug free) and drug incorporated hydrogels were recorded on a FTIR spectrometer (Perkin Elmer, model-Spectrum-2, Singapore) using KBr pellet made by mixing KBr with fine powder of the drug free and drug loaded polymer gel samples. (10:1 mass ratio of KBr to polymer).

2.3.3. ^{13}CNMR spectra

^{13}C NMR spectra of the hydrogel samples were taken on NMR Bruker MSL 500 MHz spectrometer. The spectra of the hydrogels were obtained after seasoning and milling to particle sizes ranging from 300 to 425 mm. All measurements were done at room temperature.

2.3.4. Scanning electron microscopy (SEM)

The morphology of the gold coated SIPN gels were observed by using SEM (Scanning electron Microscope, model no. S3400N, VP SEM, Type-II, made by Hitachi, Japan) with the accelerating voltage set to 15 kV.

2.3.5. Thermal analysis

Differential thermal analysis (DTA) and thermogravimetric analysis (TGA) of the hydrogel samples were carried out in a Mettler instrument in nitrogen atmosphere at the scanning rate of 10 °C/min in the temperature range of 25 to 600 °C.

2.3.6. X-ray diffraction (XRD)

Wide angle x-ray diffraction profile of gel samples were studied at room temperature with a diffractometer (model: X′Pert PRO, made by PANalytical B.V., The Netherlands) using Ni-filtered Cu K_α radiation ($\lambda = 1.5418$ Å) and a scanning rate of 0.005° (2θ)/s). The angle of diffraction was varied from 2° to 72°.

2.4. Study of equilibrium swelling

Swelling characteristics of the hydrogels were studied in simulated gastric fluid (SGF, pH 1.5) and simulated intestine fluid (SIF, pH 7.5) at 37 °C. Accurately weighed amounts of hydrogel (~50 mg) were immersed in 50 mL media solution. The swollen hydrogels were withdrawn from the solution at different time intervals (t) and weighed (W_t) after removing excess surface water with filter paper. Each sample was weighed three times to minimize error and the average values of these three measurements were taken. Swelling experiments were continued till the hydrogels reach its equilibrium swelling value (W_e). The swelling ratio (SR) was determined by using the following Eq. (3)

$$\text{SR(g/g)} = \frac{W_t - W_d}{W_d} \quad (3)$$

At swelling equilibrium $W_t = W_e$. Thus, Equilibrium swelling ratio (ESR) was obtained from Eq. (3) by substituting W_t with W_e. The buffer solutions of varied pH was prepared by dissolving phosphoric acid, potassium phosphate (KH_2PO_4), potassium hydrogen phosphate (K_2HPO_4) and sodium hydroxide in distilled water. Ionic strengths of the buffer solutions were adjusted to 0.1 molar with sodium chloride solution. The pH values were determined by a pH meter. Swelling of the hydrogel samples were also carried out at different ionic strengths in presence of NaCl, $CaCl_2$ and $AlCl_3$.

2.4.1. Swelling kinetics

Swelling kinetics of the hydrogels were obtained by direct nonlinear fitting of swelling data (S_t) of the hydrogels at different time intervals to the following second order rate Eq. (4) (Mall et al., 2006).

$$S_t = \frac{W_e^2 k_{S2} t}{1 + k_{S2} W_e t} = \frac{r_0 t}{1 + k_{S2} W_e t} \quad (4)$$

where, k_{s2} is rate constant and r_0 is initial rate of swelling.

2.5. Diffusion kinetics through the hydrogels

For understanding the nature of diffusion of water through hydrogels, diffusion constant (k_D) and diffusional exponent (n) was obtained from fractional water uptake (F) using the following Eq. (5) (Ritger & Peppas, 1987).

$$F = \frac{W_t}{W_e} = k_D t^n \quad (5)$$

Diffusion coefficient (D) of water through cylindrical hydrogels of radius r was obtained from k and n using the following Eq. (6) (Ritger & Peppas, 1987).

$$D = \pi r^2 \left(\frac{k_D}{4}\right)^{\frac{1}{n}} \quad (6)$$

2.6. Study of water retention

The hydrogel sample was first immersed in water till it reaches its equilibrium weight (W_e). The equilibrated hydrogel samples was then quickly taken out and weighed at different time intervals (W_t)

till constant weight at a temperature of 25 °C and relative humidity of 85. Before each weight the wet gel sample was blotted with tissue paper to remove excess water. Water retention % (WR) of the gel sample was obtained as

$$\mathrm{WR}\% = \frac{W_t}{W_e} \times 100 \tag{7}$$

2.7. Network parameter of the hydrogels

The average molecular weight between crosslinks ($\bar{M}$) of the hydrogel was obtained from swelling data using the following Flory and Rehner Eq. (8) (Paul & John, 1943)

$$\bar{M} = -\frac{V_s \rho_p \left(\phi_p^{\frac{1}{3}} - \frac{\phi_p}{2}\right)}{\ln(1-\phi_p)+\phi_p+\chi\phi_p^2} \tag{8}$$

The molar volume of water, V_s at experimental temperature (25 °C) was calculated (18.18 cm^3/mole) from its density (0.99 g/cm^3) and molecular weight (18 g/mole), the density of hydrogel sample, ρ_p was calculated from its mass and volume. The volume of the polymer sample was measured by the method reported elsewhere (Chen, Park, & Park, 1999). For equilibrium swelling of m_w g water/g dry hydrogel sample, polymer volume fraction in swollen gel under equilibrium, ϕ_p will be

$$\phi_p = \left(1 + \frac{\rho_p}{\rho_i} m_w\right)^{-1} \tag{9}$$

where, ρ_p and ρ_i are density of polymer and solvent (water), respectively.

The polymer–solvent interaction parameter, χ between water and polymer hydrogel is obtained using the following Eq. (10) (Xue, Champ, & Huglin, 2001).

$$\chi = \frac{V_p}{3} + 0.5 \tag{10}$$

Crosslink density (ρ_c) of a hydrogel is obtained as (Sunil & Surinderpal, 2006)

$$\rho_c = \frac{\rho_p N_A}{\bar{M}} \tag{11}$$

N_A is Avagadro's number (6.023×10^{23}/mol). The mesh size (ς in A°) of the swollen polymeric network is calculated from the following Eq. (12) (Canal & Peppas, 1989)

$$\varsigma = \left[C_n \left(\frac{2\bar{M}}{M_r}\right)\right]^{1/2} l\phi_p^{1/3} \tag{12}$$

The Flory's characteristic ratio, C_n was taken from literature as 2 (Morris, Cutler, Ross-Murphy, Rees, & Price, 1981) and C–C bond length; 'l' was assumed as 1.54 Å (Mandal, Ray, & Bhattacharyya, 2012). M_r, the molecular weight of repeat unit was calculated as the weight average of the repeat unit of sodium alginate (M_r = 198) and polyacrylamide (M_r = 72).

2.8. Study of drug loading and entrapment efficiency of the hydrogel

Drug loading and entrapment efficiency of the hydrogel samples were carried out by similar experiments as reported elsewhere (Hua et al., 2010). For drug loading the hydrogel samples of specified weight (W_i) were first swollen in 100 mL water–ethanol mixture (2% ethanol (v/v) of constant pH and ionic strength (pH 1.5 and 7.5 and ionic strength 0.1 mol/L) and containing specified amount (W_o) of acetaminophen drug. After 24 h of swelling, the drug loaded wet hydrogel samples were carefully taken out from the aqueous buffer solution and washed with the same solution to remove free drug from the sample. Drug loading (DL) and entrapment efficiency of the hydrogel sample was determined as

$$\mathrm{DL(mg/g\ hydrogel\ sample)} = \frac{W_d - W_i}{W_i} \tag{13}$$

$$\mathrm{Entrapment\ efficiency}(\%) = \frac{W_d - W_i}{W_o} \times 100 \tag{14}$$

where W_d is weight of the drug loaded dry hydrogel sample.

2.9. In vitro drug release studies

In vitro drug release of amioacetaphen from the hydrogel samples was carried out at 35 ± 0.5 °C using Indian Pharmacopoeia (IP) Dissolution Test Apparatus Type 2 (paddle method) at a rotation speed of 50 rpm in 100 mL of buffer (pH 1.5 & 7.5) for 7–9 h. The drug loaded wet samples obtained from drug loading test were first dried overnight at ambient condition followed by drying in a vacuum oven at 50 °C for another three days. The drug loaded dry samples were then immersed in buffer solution of same composition. At several time intervals 5 mL of the solution containing released drug was withdrawn and at the same time 5 mL fresh solution was added to keep the solution volume constant. The concentration of drug in the withdrawn solution was analyzed by UV–Vis spectrophotometer at 228 nm using a calibration curve constructed from a series of acetaminophen solutions of known concentrations. All release experiments were carried out in triplicates and the average values were considered. The drug release % was obtained as

$$\mathrm{Drug\ release}\% = \frac{W_d - W_r}{W_r} \times 100 \tag{15}$$

where W_r is amount of drug released in the solution

3. Results and discussion

3.1. Synthesis of IPN hydrogels

Semi IPN hydrogels are synthesized by crosslink copolymerization of acrylamide and MBA in presence of sodium alginate by free radical polymerization. These hydrogels are semi interpenetrating since acrylamide is only crosslinked by MBA in presence of sodium alginate. In this free radical polymerization the bifunctional monomer MBA undergoes copolymerization with mono functional acrylamide and thus chemical bond (crosslink) is formed between two acrylamide moieties through MBA to form the crosslink copolymer hydrogel (Scheme 1b). During the polymerization reaction in aqueous medium, acrylamide and MBA monomer generates free radicals by reaction with redox initiator. Radicals are also generated on sodium alginate and it also takes part in propagation reactions of the polymerization (Wang & Wang, 2010). Thus, semi-interpenetrating network (SIPN) type polymer hydrogel is formed from growing radicals of monomers and sodium alginate macroradicals as shown in Scheme 1b.

3.1.1. Effect of reaction variables on gel content and gel time

Effect of wt% of sodium alginate, crosslinker (MBA), total monomer and initiator concentration in water on gel content (%), yield (%) and gel time are shown in Fig. 1a–d respectively. For studying effect of one parameter, other parameters were kept constant. From Fig. 1a it is observed that gel time, yield% and gel% increases with increase in wt% of alginate in the hydrogel. As the amount of alginate increases it becomes increasingly difficult for the same amount of crosslinker (MBA) to crosslink acrylamide in the semi-IPN. Thus, gel time increases. Further, sodium alginate takes part in the polymerization reaction as macromolecule radicals (Wang & Wang, 2010) and thus yield or gel% is observed to increase with

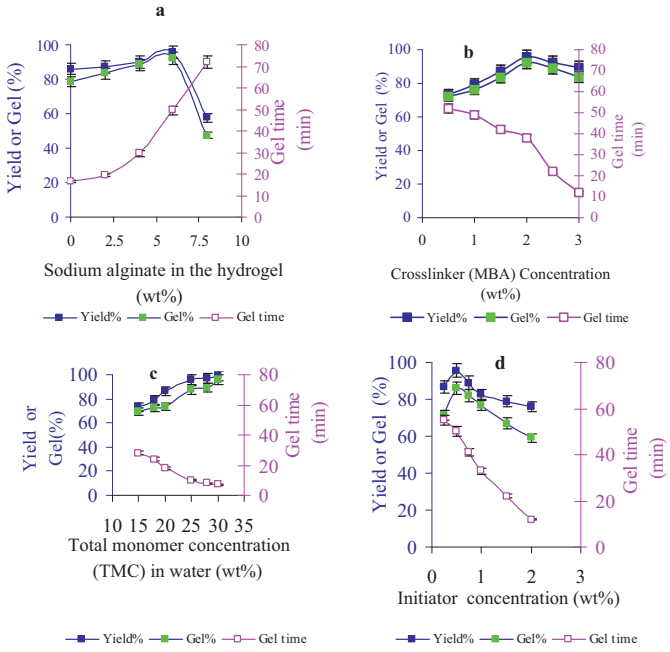


Fig. 1. Effect of (a) sodium alginate, (b) total monomer concentration, (c) crosslinker concentration and (d) initiator concentration on yield%, gel% and gel time.

increase in amount of sodium alginate in the hydrogel. However, sodium alginate is a high molecular weight polymer. Above 6 wt% alginate solution viscosity increases significantly and hence extent of polymerization reaction deceases with decrease in yield or gel% as observed in Fig. 1a. From Fig. 1b it is observed that with increase in crosslinker concentration gel time decreases while yield or gel% increases. With increase in crosslinker gel% time decreases since network (gel) in the polymer is formed at a much faster rate in presence of increased amount of MBA crosslinker. Similarly, yield or gel% increases due to increase in rate of polymerization in presence of increased amount of reactant (crosslinker). However, above 2 wt% crosslinker, yield or gel% decreases because of formation of network at an early stage of polymerization (Tomar, Gupta, Singhal, & Nagpal, 2007; Bhattacharyya, Ray, & Mandal, 2013). From Fig. 1c it is observed that with increase in total monomer concentration in water (TMC) yield or gel% increases. Increase in gel or yield % may be ascribed to availability of large number of active primary radicals at higher TMC (Odian, 1991). It is also observed from Fig. 1c that gel time decreases with TMC which may be due to increased reaction rate at higher monomer concentration in water (Bhattacharyya et al., 2013). From Fig. 1d it is observed that above 0.25 wt% initiator, yield or gel% and gel time decrease with increase in initiator concentration. Increase in initiator concentration also increases rate of polymerization and polymer of shorter chain length (lower molecular weight) is formed. Thus, gelling occurs at an early stage of polymerization resulting in shorter gel time and less gel% (Mall et al., 2006). The initiation of free radical from initiator is too low at 0.25 wt% initiator. Hence, yield or gel% increases from 0.25 to 0.5 wt% initiator in polymerization mixtures.

3.2. Characterization of the hydrogel

3.2.1. PZC analysis

Adsorption (loading) of drug on hydrogel depends on electrostatic interaction between functional groups of the drug and surface functionality of the hydrogels. However, charge characteristics of surface functionality of the hydrogels change with initial pH (pH of water without hydrogel or drug, pH_i) of water. Functional groups of the hydrogel surface deprotonates with increasing pH_i and thus pH of water changes in presence of hydrogel and drug. The difference between final pH (pH_f) and initial pH (pH_i) of the solution ($pH_f - pH_i$) is plotted against initial pH_i in Fig. 2a for SIPN hydrogel. Point of zero charge pH (pH_{PZC}) of water is obtained as pH_i for which $pH_f - pH_i$ is zero. Depending on the pH of the solution hydrogel surfaces will be positively charged for $pH_i < pH_{PZC}$, negatively charged for $pH_i > pH_{PZC}$ or neutral for $pH_i = pH_{PZC}$ (Wang et al., 2008). From Fig. 2a it is observed that pHPZC of the SIPN in water is 4.3 which is increased to 5.5 for drug loaded SIPN. In fact, the drug decreased negative charge of the hydrogel because of electrostatic interaction between NH groups of drug with COO– functional groups of hydrogels and thus pH_{PZC} shifts to a higher value for drug loaded SIPN. Adsorption of the drug will be favored at solution pH > pH_{PZC} (Mall et al., 2006).

3.2.2. FTIR Spectroscopy

FTIR spectra of sodium alginate, polyacrylamide, drug loaded SIPN, drug free SIPN and only drug (acetaminophen) is shown in Fig. 2b(i–v), respectively. Sodium alginate (Fig. 2b(i)) shows a broad peak at 3351 cm^{-1} for its hydrogen bonded OH group. Asymmetric and symmetric stretching of–COO group of alginate is observed at 1638 and 1408 cm^{-1}, respectively (Kulkarni et al., 2010). Sodium alginate also shows a characteristic peak at 1022 cm^{-1} corresponding to C–O stretching vibration of its polysaccharide structure. The peak at 862 cm^{-1} corresponds to vibration of its Na–O bond. The FTIR spectrum of polyacrylamide is shown in Fig. 2b(ii). The absorption bands at 3326 and 3168 cm^{-1} correspond to its N–H stretching vibration while 1610 cm^{-1} corresponds to its N–H bending (Zhou & Wu, 2011). The absorption band at 1655 and 1348 cm^{-1} are due to its carbonyl and C–N stretching, respectively (Xie et al., 2009). All of these peaks are shifted in SIPN and drug loaded SIPN indicating electrostatic interaction among functional groups of sodium alginate, polyacrylamide and drug in SIPN and drug loaded SIPN. Accordingly, the peak due to doublet N–H stretching vibration of polyacrylamide at 3326 cm^{-1} (Fig. 2b(ii)) and the peak due to OH stretching vibration of sodium alginate at 3351 cm^{-1} (Fig. 2b(i)) is overlapped at 3317 cm^{-1} in SIPN (Fig. 2b(iv)) (Mandal, Basu, & Sa, 2010). Similarly, 1656 cm^{-1} peak of SIPN is due to overlapping of COO^- of sodium alginate (1638 cm^{-1}) and primary amide C=O absorption band of polyacrylamide (1655 cm^{-1}). N–H stretching vibration of polyacrylamide at 1348 cm^{-1} (Fig. 2b(ii)) is also shifted to 1302 cm^{-1} in SIPN. The drug acetaminophen shows its characteristic –NH, –OH and C–O stretching bands at 3326, 3162 and 1655 cm^{-1}, respectively (Pachuaua & Mazumder, 2012) as observed in Fig. 2b(v). Other peaks of this drug i.e. 1564, 1259, 837 cm^{-1} correspond to its –NH in plane bending, C–O stretching and p-disubstituted aromatic ring, respectively (Pachuaua & Mazumder, 2012). The NH and OH peaks of drug is overlapped with NH and OH peaks of SIPN to 3351 and 3186 cm^{-1} in drug loaded SIPN as shown in Fig. 2b(iii). Similarly, its carbonyl peak is also overlapped with carbonyl peaks of SIPN to 1656 cm^{-1} while its absorption peaks at 1259 and 837 cm^{-1} is shifted to 1280 and 839 cm^{-1} in the drug loaded SIPN as observed in Fig. 2b(iii).

3.2.3. ^{13}C NMR spectra

^{13}C NMR spectra of polyacrylamide and SIPN hydrogel are shown in Fig. 2c(i) and (ii), respectively. In ^{13}C NMR of polyacrylamide (Fig. 2c(i)) peaks are observed at 177.56 and 39.54 ppm corresponding to carbon of its amide ($CONH_2$) and sp3 hybridized CH_2–CH_2 linkage, respectively (Dorkoosh et al., 2000). The sp2 hybridized carbon-carbon (CH_2=CH_2) peaks of acrylamide monomer at 130 and 133 ppm are absent in polyacrylamide confirming its polymerization to repeating units containing CH_2-CH_2 linkage with NMR peak at 39.54 ppm (Das,

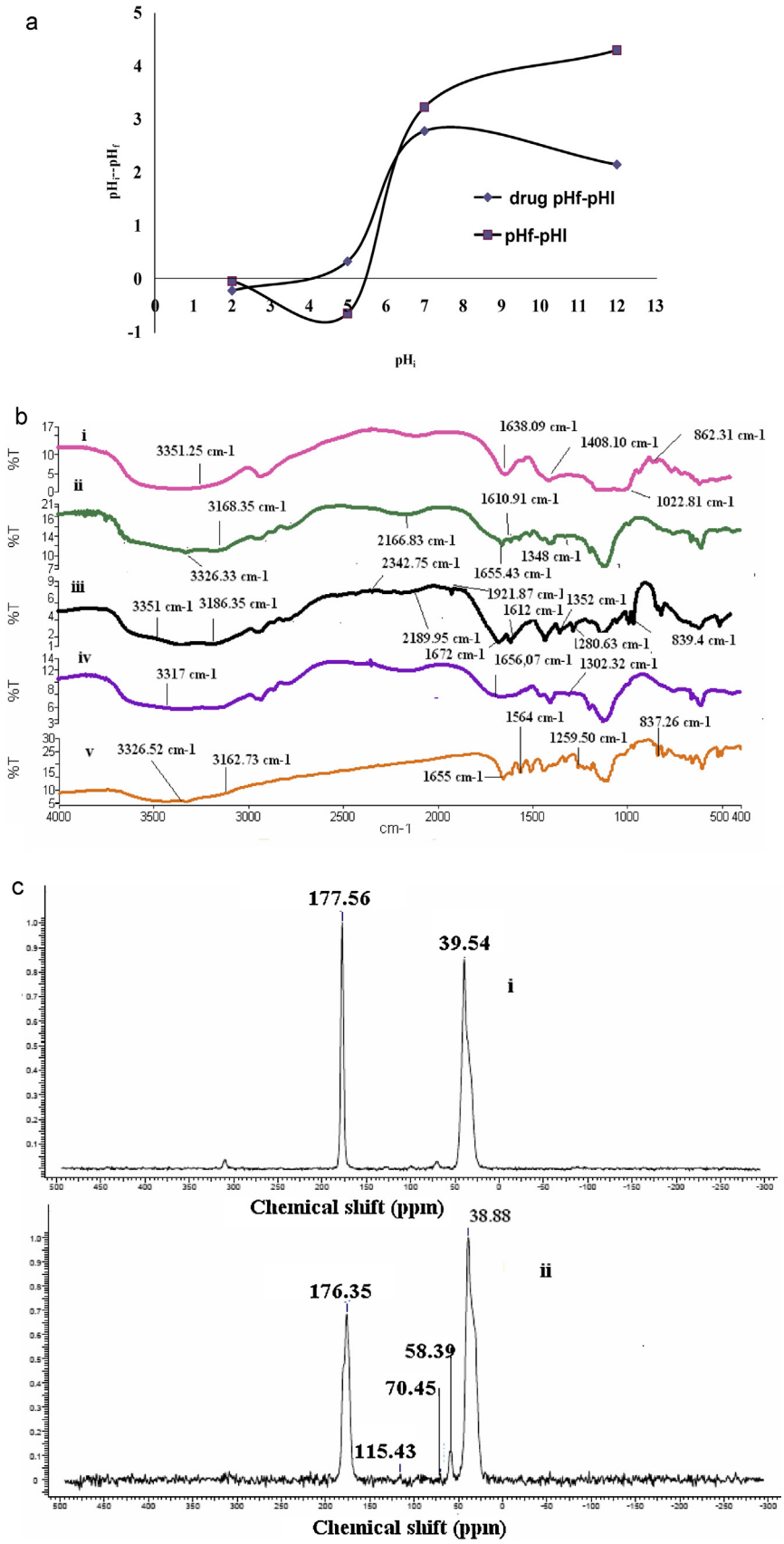


Fig. 2. (a) PZC analysis; (b) i—sodium alginate, ii—polyacrylamide, iii—drug loaded SIPN, iv—SIPN, v—acetaminophen drug; (c) NMR of i—polyacrylamide and ii—SIPN; (d) XRD of polymer and drug; (e) SEM of i—SIPN ii—drug loaded SIPN; (f) i—DTA and ii—TGA of the polymers.

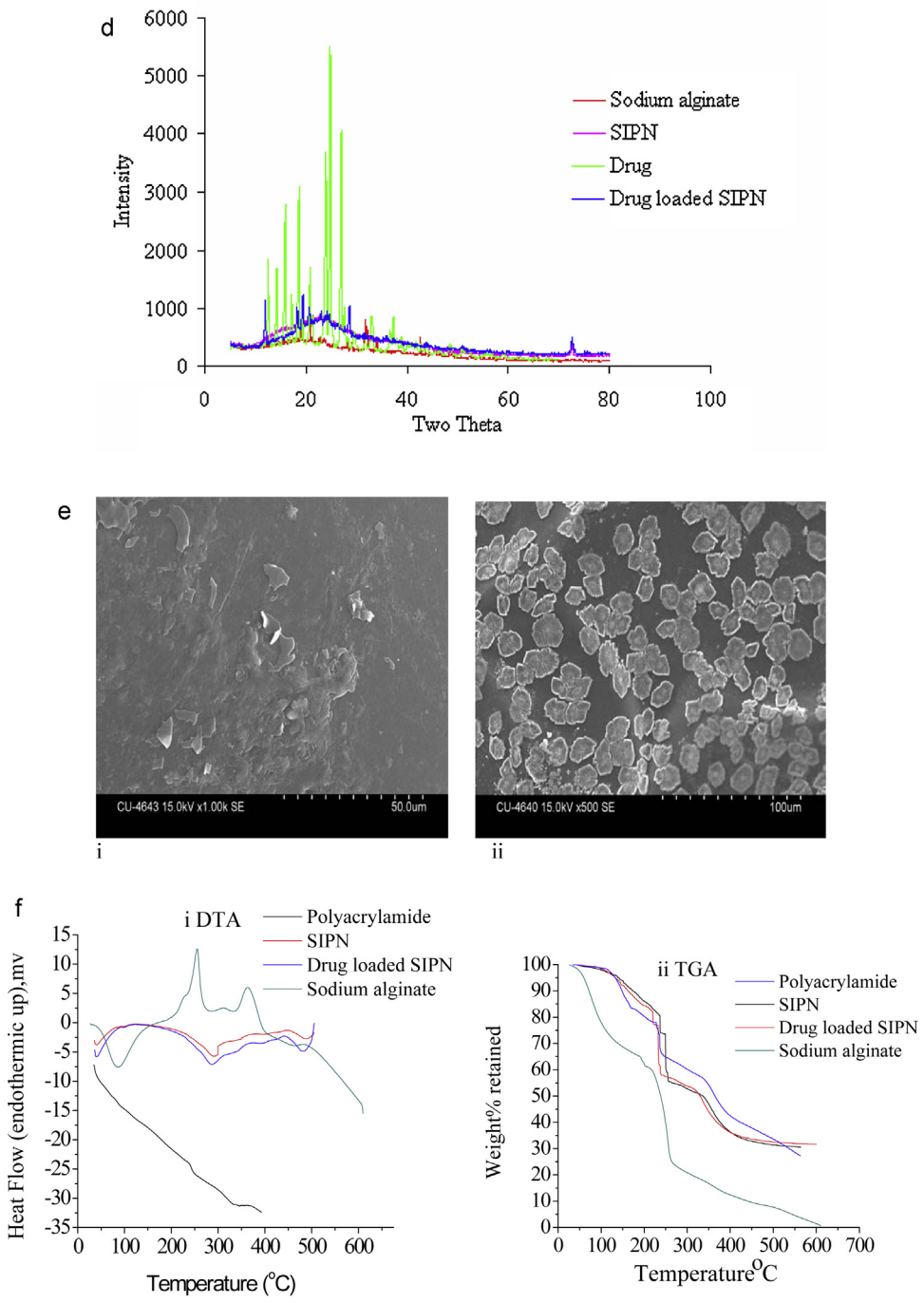


Fig. 2. (*Continued*)

Panda, & Pal, 2012). The NMR peaks of SIPN are observed at 176.35, 115.43, 70.45 and 38.88 ppm as shown in Fig. 2c(ii). The peak at 176.35 is the result of overlapping of carboxylate peak of sodium alginate at 176 (carbon 6 of both mannuronic and gluronic acid unit of alginate, M6, G6) and carbon of amide of polyacrylamide at 177.56 (Chhatbar, Meena, Prasad, & Siddhanta, 2009). The peak at 115.43 ppm was for the anomeric carbon 1 of G1 and M1 of sodium alginate (Chan, Whitney, & Ronald, 2009) while the peak at 70.45 ppm is due to carbon 3 of mannuronic acid of the ring of alginate (M3) (Chhatbar et al., 2009). SIPN also shows a peak at 38.88 ppm corresponding to CH_2–CH_2 of repeating unit of the polymer.

3.2.4. X-ray diffraction (XRD)

Synthesis of SIPN from sodium alginate and polyacrylamide results in loss of crystallinity of sodium alginate as evident from Fig. 2d. XRD of sodium alginate, SIPN, acetaminophen (drug) and SIPN hydrogel loaded with drug is shown in Fig. 2d. From Fig. 2d it is observed that sodium alginate shows several crystalline peaks at 2θ of 19.4°, 21°, 32°, 34°, 42.4°, 45.4° and 48.8° as also reported elsewhere (Chhatbar et al., 2009; Dong, Dong, Cao, Han, & Ding, 2011). The crystallinity of sodium alginate is due to hydrogen bonding among its hydroxyl groups. SIPN is formed by *in situ* polymerization of acrylamide in presence of sodium alginate and because of chemical bond formation between alginate and acrylamide, crystallinity is reduced in its SIPN (Mandal & Ray, 2013). This

reduction in crystallinity is evident in XRD of SIPN in Fig. 2d which shows only one characteristic peak at 2θ of 23.6°. It also signifies close electrostatic interaction between acrylamide unit and alginate in SIPN. From Fig. 2d it is also observed that the drug acetaminophen shows several crystalline peaks at 2θ of 12.4°, 14.2°, 15.9°, 18.5°, 20.7°, 24.7°, 26.9°, 37.2° and 33° as also reported elsewhere (Wang et al., 2011). Because of close interaction between drug and SIPN hydrogels all of these peaks are shifted in drug loaded SIPN. Accordingly, the drug loaded SIPN showed crystalline peaks at 2θ of 11.9°, 18.2°, 19.4°, 28.5°, 23°, 24°, 43.9°, and 35.8° as observed in Fig. 2d.

3.2.5. Scanning electron microscopy (SEM)

SEM of SIPN hydrogel and SIPN loaded with drug is shown in Fig. 2e(i) and (ii), respectively. The SEM of SIPN was carried out at high magnification (×1000). It is observed from SEM of SIPN (Fig. 2e(i)) that alginate and polyacrylamide shows good compatibility in SIPN. Further, introduction of alginate facilitates surface and network structure of the IPN gel (Wang & Wang, 2010) which is desirable for good absorption properties. SEM of drug filled SIPN was done at lower (×500) magnification to understand distribution of drug in SIPN. From Fig. 2e(ii) it is observed that drug molecules are uniformly distributed in the SIPN hydrogel.

3.2.6. DTA and TGA

3.2.6.1. DTA. DTA of sodium alginate, polyacrylamide, SIPN and drug loaded SIPN are shown in Fig. 2f(i). From Fig. 2f(i) it is observed that polyacrylamide shows an endothermic peak at around 100 °C indicating loss of weakly bound water molecules from the gel network and two exothermic peaks at around 241 and 370 °C corresponding to its thermal degradation as also reported elsewhere (Zhou & Wu, 2011). The endothermic peak of sodium alginate at around 86 °C due to water loss (Pongjanyakul, Priprem, & Puttipipatkhachorn, 2005) is shifted to 94 °C in SIPN as observed in Fig. 2f(i). Similarly, one exothermic peak of sodium alginate at 162 °C corresponding to its recrystallization and two exothermic peaks at 228 and 257 °C corresponding to its degradation (Pereira et al., 2013) is shifted to 298 and 332 °C, respectively in the SIPN. Drug loaded SIPN is observed to show a similar DTA profile like SIPN.

3.2.6.2. TGA. From TGA of polyacrylamide, sodium alginate, SIPN, and drug loaded SIPN (Fig. 2f(ii)) it is observed that the polymers showed several weight loss regions with onset of maximum weight loss at melting temperatures. The weight losses of the hydrogels in different temperature regions are associated with splitting of the main chain and thermal decomposition of the polymer. Accordingly, sodium alginate is observed to show three steps of degradation. About 40% of alginate degrades in the temperature range of 80–225 °C. This may be due to breaking of segments of mannuronic acid and glucuronic acid (Sand, Yadav, Mishra, & Behari, 2010). However, major degradation occurs in the second stage in the temperature range of 230–275 °C. The degradation in second and third stage (280–600 °C) accounts for braking of main polymer chains. Similarly, degradation of polyacrylamide up to around 100 °C (~1.5%) is due to loss of moisture while its main polymer chain degrade at 230–260 °C. More extensive degradation occurs in the third stage beginning at around 360 °C (Şolpan, Torun, & Guven, 2008). However, polyacrylamide is observed to show higher thermal resistance than alginate and the temperature for half life ($t_{1/2}$) of alginate and polyacrylamide are observed to be 237 and 362 °C, respectively. The SIPN shows intermediate thermal degradation profile between polyacrylamide and alginate with $t_{1/2}$ of 335 °C. Incorporation of lower melting acetaminophen drug (Chong, Yunus, Choong, Abdullah, & Spotar, 2011) reduces thermal resistance of the drug loaded SIPN and it is observed to show a lower $t_{1/2}$ (325 °C) than SIPN.

3.3. Study of swelling properties of the hydrogels

Drug release properties of hydrogels strongly depend on its swelling characteristics (Wang, Xie, Zhang, Zhang, & Wang, 2010b). The results of swelling ratios of the hydrogels synthesized with 0.25, 0.5,1 and 2 wt% initiator concentration (designated as I0.25, I0.50, I1.0 and I2.0, respectively), 1, 2 and 3 wt% MBA concentration (designated as MBA1, MBA2 and MBA3, respectively), 15, 20 and 25 wt% total monomer concentration in water (designated as TMC15, TMC20 and TMC25, respectively), 0, 2, 4, 6 and 8 wt% sodium alginate (designated as SA0, SA2, SA4, SA6 and SA8, respectively) are shown in Fig. 3a–d, respectively. All of these swelling experiments were carried out at a pH of 7.6 in water. Swelling ratios of SA6 hydrogel synthesized with optimized reaction parameters (6 wt% alginate, 2 wt% crosslinker, 1 wt% initiator at 25 wt% TMC) is also shown in Fig. 3e at pH 1.5, 5.5 and 7.6 (designated as pH 1.5, pH 5.5 and pH 7.6, respectively). From Fig. 3a it is observed that swelling ratio increases with increase in initiator concentration from 0.25 to 2 wt%. With increase in initiator concentration molecular weight of the gel decreases with more chain ends which leads to imperfection in gel network and thus increased swelling. In the present work optimum initiator concentration was found to be 1.0 wt%. Above this initiator concentration gel strength is not acceptable due to gel imperfection while below this concentration polymerization or gel time was too high. Swelling ratio of the hydrogels is also observed to increase with decrease in MBA concentration, increase in total monomer concentration (TMC) and increase in alginate concentration as observed in Fig. 3b–d respectively. This may be ascribed to lower crosslinking, increased reactivity and increased hydrophilicity, respectively of the hydrogels. From Fig. 3d it is also observed that with increase in sodium alginate wt% in the hydrogel from SA0 to SA6, swelling ratio increases. This may be attributed to increase in electrostatic repulsive force in the network because of negatively charged carboxylate functional groups (COO^-Na^+) of alginate. Thus, water absorption properties of the hydrogels improve. However, further increase of alginate (above 6 wt%, SA8) decreases swelling properties of the gels which may be due to filling up of the void spaces of the network chains by alginate (Murthy, Murali, Sreeramulu, & Mohana, 2006). From Fig. 3e it is observed that at higher pH swelling ratio increases which may be due to ionization of hydrophilic COOH groups of the hydrogels. The swelling data of the hydrogels were also found to show good non linear fitting to second order rate equation (Eq. (4)) as shown in Table 1. The calculated ESR, initial rate of swelling (r_0), rate constant (k_{s2}) and statistical parameters such as R^2, χ^2 and F of these fittings are also shown in Table 1. It is observed that regression coefficient R^2 of these fittings are close to unity (0.9513 to 0.9967) while chi square (χ^2) of these fittings are very low (0.4–0.007) and F values are very high (361–4503) which confirms close fitting of the swelling data to second order rate equation (Mandal & Ray, 2013). Further, calculated ESR of the hydrogels is also observed to be very close to its experimental ESR. The diffusion of water through the hydrogels was evaluated in terms of diffusion constant (k_D), diffusion exponent (n) and diffusion coefficient (D) of the hydrogels. These parameters were obtained by non linear fitting of swelling data to Eq. (5) and also using Eq. (6) as shown in inset of Fig. 3a–e for varied initiator concentration, MBA concentration, TMC, alginate% and pH, respectively. The experimental swelling data shows good fitting as evident from these figures. The values of k_D, n, D and the statistical parameters R^2, χ^2 and F of these fitting are shown in Table 1. The value of k_D and n signifies Case-I diffusion which may be attributed to extensive swelling of the hydrogels. Thus, relaxation of polymer

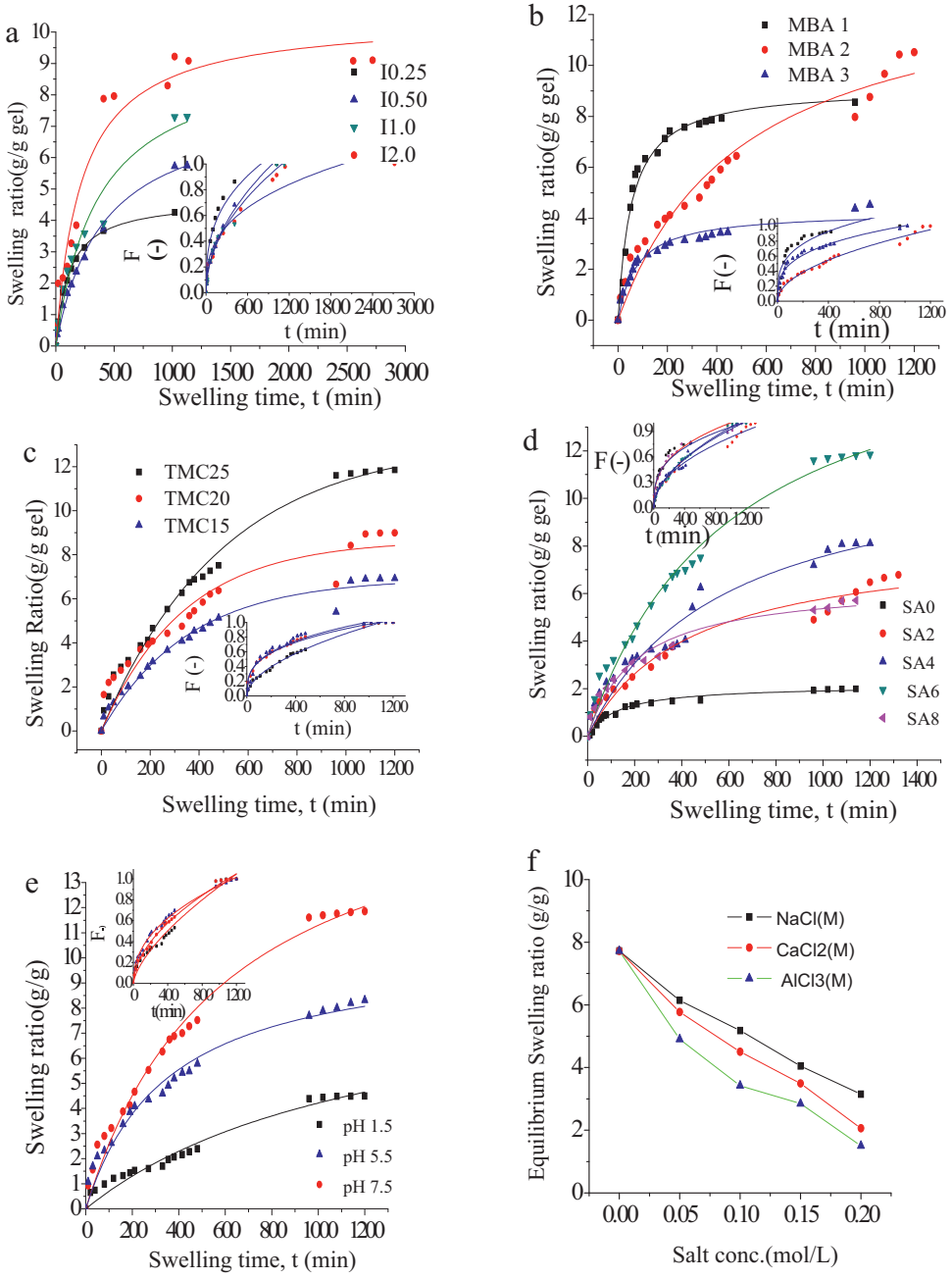


Fig. 3. Effect of (a) initiator conc., (b) crosslinker (MBA) conc., (c) total monomer conc., (d) sodium alginate (SA) and (e) solution pH, (f) salt concentration on swelling with direct fitting of swelling data to 2nd order rate equation ($S_t = W_e^2 k_2 t/(1 + k_2 W_e t)$) and to diffusion kinetics curves ($F = Kt^n$, shown in insets) in Fig. 3(a)–(e).

chain dominates diffusion of water from the network. The values of statistical parameters viz. R^2 (0.9932–0.9926), χ^2 (0.006–0.0002) and F (338–7086) for these regressions also confirm close fitting to Eq. (5).

3.3.1. Salinity and swelling

The ESR of the hydrogels decreases with increasing ionic strength of the solution in presence of salt as observed in Fig. 3f. The hydrogels of the present work containing carboxylate groups are anionic in nature and thus swelling of the hydrogel decreases by charge screening effect (Zhang, Wu, Li, & Wang, 2005) of the additional cations of the salt. Swelling of the hydrogels also decreases with increase in cationic charge in the following order trivalent $AlCl_3$ < bivalent $CaCl_2$ < monovalent NaCl as observed in the same figure. This may be ascribed to the degree of crosslinking of the hydrogels through binding of the cations with its functional COO– groups which decreases from trivalent to monovalent cation (Zhang et al., 2005).

3.3.2. Deswelling kinetics of the hydrogels

Drug release properties depend strongly on response rate of the hydrogels which may be evaluated by deswelling of the swollen hydrogels. Deswelling of the hydrogels with varied sodium alginate and crosslinker (MBA) contents were studied from its equilibrated swelled state in water at 25 °C. The results of the deswelling study are shown in Fig. 4a and b for hydrogels with varied alginate and MBA content, respectively. From Fig. 4a it is observed that deswelling time and rate depends on alginate

Table 1
Swelling diffusion and network parameters of the hydrogels.

Polymer	$k_{s2} \times 10^3/r_0 \times 10^2$	ESR_{expt}/ESR_{cal} (g/g)	$r^2/\chi^2 \times 10^2/F$	$k_D \times 10^2/n/D \times 10^{-5}$	$r^2/\chi^2 \times 10^2/F$	$\bar{M} \times 10^{-5}/\rho_c \times 10^{-18}/\varsigma$
MBA1	0.14/2.7	12.51/13.79	0.9513/40/906	3.0/0.50/10.5	0.9851/0.12/2817	15.5/0.51/1058
MBA2	0.09/3.0	11.85/11.03	0.9824/21/2504	2.1/0.52/9.45	0.9923/0.054/7086	8.45/3.24/811
MBA3	3.0/5.5	4.52/4.25	0.9587/5.7/1306	12.1/0.30/1.38	0.9711/0.16/2383	0.82/9.95/188
I0.25	4.8/4.0	4.25/4.67	0.9967/0.7/4503	7.0/0.34/2.21	0.9515/0.51/338	13.3/0.68/946
I0.50	2.2/5.0	7.79/6.74	0.9687/47/590	9.9/0.34/4.64	0.9433/0.66/448	11.3/2.31/901
I1.0	0.09/3.0	11.85/11.03	0.9825/21/2504	2.1/0.52/9.45	0.9918/0.054/7086	8.45/3.24/811
I 2.0	1.8/2.6	12.47/12.09	0.9657/22/361	3.1/0.49/13	0.9823/0.1/1115	0.84/9.67/189
SA0	7.0/1.6	1.99/3.29	0.9567/1.2/889	8.9/0.35/2.17	0.9432/0.6/609	0.02/5.51/25
SA2	3.6/1.7	6.24/7.23	0.9883/0.8/1806	2.0/0.48/5.99	0.9859/0.16/1997	2.14/4.58/338
SA4	0.28/1.9	8.11/8.24	0.9567/20/753	10.4/0.32/8.02	0.9718/0.2/1323	7.17/4.12/674
SA6	0.09/3.0	11.85/11.03	0.9824/21/2504	2.1/0.52/9.45	0.9934/0.054/7086	8.45/3.24/811
SA8	0.0007/3.1	5.71/6.48	0.9763/9.3/903	10.1/0.32/2.46	0.9854/0.165/1885	0.92/9.8/194
TMC15	0.3/2.1	8.93/6.92	0.9854/9/2139	10.6/0.32/1.4	0.9512/0.37/1445	2.17/5.2/336
TMC20	0.28/3.2	10.81/8.99	0.9289/47/676	2.2/0.54/6.6	0.9921/0.061/7086	6.47/4.1/637
TMC25	0.09/3.0	11.85/11.03	0.9823/21.7/2504	2.1/0.52/9.45	0.9926/0.054/7086	8.45/3.24/811
pH 1.5	0.08/0.1	5.59/4.49	0.9645/7.2/950	0.93/0.66/8.7	0.9843/0.2/1760	0.82/9.37/189
pH 5.5	0.27/0.2	8.31/7.56	0.9754/15.8/1784	4.3/0.44/7.58	0.9923/0.025/4844	6.47/8.1/637
pH 7.6	0.09/3.0	11.85/11.03	0.9827/21/2504	2.1/0.52/9.45	0.9915/0.054/7086	8.45/3.24/811

k_{s2} (g gel/g water. minute), r_0 (g water/g gel. minute), k_D (s^{-1}), n (−), D (cm^2/s).

content of the hydrogels. As the amount of sodium alginate increases in the hydrogel from SA0 (polyacrylamide hydrogel with 0% alginate) to SA8, deswelling rate increases up to SA6. During deswelling process a dense skin layer is formed on the surface of the hydrogels in contact with water by rapid shrinkage due to hydrophobic interaction between various hydrophobic groups on its surface (Marandi, Sharifnia, & Hosseinzadeh, 2006; Chen et al., 2010). This skin dense layer prevents water from diffusing out of the gel network. Thus, crosslinked polyacrylamide gel shows the lowest deswelling rate. The introduction of hydrophilic sodium alginate (containing hydrophilic –OH and COOH groups) inhibits the formation of skin layer and act as a water releasing channel in the IPN network structures. Thus, the IPN hydrogels show faster deswelling rate with increasing amount of alginate.

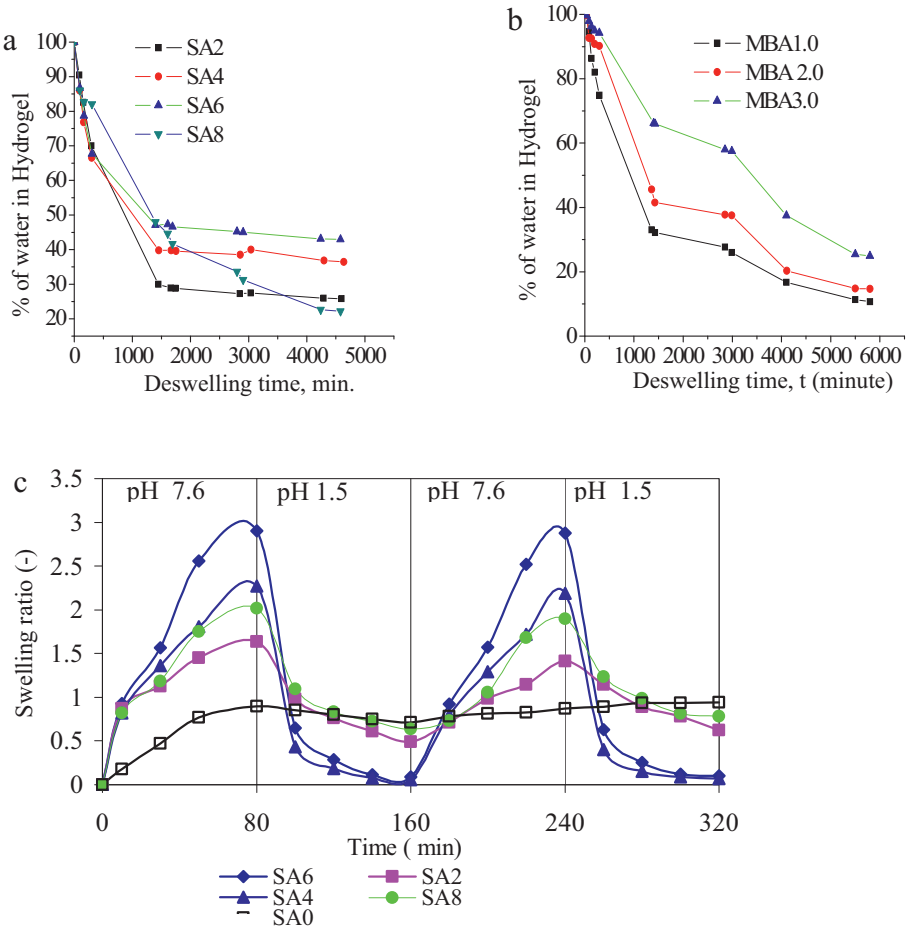


Fig. 4. Effect of (a) sodium alginate and (b) MBA on deswelling, (c) Swelling-deswelling at varied pH.

Table 2
Drug release data of the hydrogels.

Polymer	Drug loading (mg/100 mg beads)	Entrapment efficiency (%)	$K_{KP} \times 10^2/n$	$R^2/\chi^2 \times 10^3/F$
SA0	17.45	55.21	9.0/0.47	0.9865/1.0/4864
SA2	23.04	68.30	5.6/0.57	0.9856/2.0/4357
SA4	25.55	77.42	2.26/0.73	0.9990/0.08/49292
SA6	27.93	81.58	1.8/0.77	0.9983/0.14/26083
SA8	16.99	63.77	4.09/0.62	0.9942/0.48/9210
MBA1	32.69	50.75	7.0/0.48	0.9966/0.23/19592
MBA2	27.93	81.58	1.7/0.77	0.9983/0.15/26083
MBA3	24.02	72.55	1.7/0.77	0.9984/0.15/26374
pH 1.5	20.46	79.60	11/0.43	0.9560/3.9/1495
pH 7.5	27.93	81.58	1.7/0.77	0.9984/0.14/26083

However, above 6 wt% alginate, deswelling rate decreases which may be due to poorer compatibility between alginate and polyacrylamide. Thus, in the drug release study SIPN containing 6 wt% alginate (SA6) was considered. From Fig. 4b it is also observed that deswelling rate decreases with increase in % of crosslinker which may be attributed to the formation of tighter network at higher crosslinker%.

3.3.3. Oscillatory swelling-deswelling study

The result of reversible swelling-deswelling of the hydrogels under oscillatory pH of 7.5 and 1.5 is shown in Fig. 4c. It is observed that swelling-deswelling reversibility under oscillatory pH change also depends on alginate content of the hydrogels. Reversible pH response is observed to improve with increase in alginate content and the SIPN containing 6 wt% alginate showed the best pH reversibility. With increase in alginate content number of carboxylic (COOH) groups in the SIPN increases. The carboxylic groups ionize at higher pH (7.5) and thus osmotic pressure inside the gel matrix increases resulting in increased swelling of the gels. Similarly, for deswelling in acidic pH (1.5) hydrogen ions (H+) diffuses into the gel matrix and neutralizes its carboxylic groups with collapsing and deswelling of gels. Alginate also improves mechanical strength of the hydrogels as evident from pH reversibility of the IPN with 4 (SA4) and 6 wt% (SA6) alginate after many cycles of higher and lower pH. IPN with lower concentration of alginate (SA2) or polyacrylamide gel (SA0) is observed to show poor pH reversibility because of lower mechanical strength and less number of hydrophilic functional groups (Raghavendra et al., 2012).

3.4. Network parameters

Various network parameters such as average molecular weight between crosslink ($\bar{M}$), crosslink density (ρ_c) and mesh size (ς) of the hydrogels were obtained using Eq. (8)–(12) based on swelling data of these hydrogels in double distilled water at pH of 7.6. These network parameters were also obtained for SA6 hydrogel at varied pH of 1.5, 5.5 and 7.5. All of these are given in Table 1. From Table 1 it is observed that $\bar{M}$ and ς decreases while ρ_c increases with increase in crosslinker concentration from MBA1 to MBA3. This is because number of networks increases in the gel matrix with increase in crosslinker concentration. Molecular weight of the hydrogel decreases with increase in initiator concentration (Odian, 1991). Thus, both $\bar{M}$ and ς decreases while ρ_c increases from I0.25 to I2.0. $\bar{M}$ and ς of the hydrogels are also observed to increase with increase in alginate wt% from SA0 to SA6. This may be due to the formation of more branched multiple side chains in the hydrogels (Wang & Wang, 2010). However, as the alginate wt% increases further, increased viscosity of the polymerization solution decreases initiation efficiency of alginate (Wang & Wang, 2010) and thus $\bar{M}$ and ς decreases in SA8. Similarly, with increase in TMC or pH, $\bar{M}$ and ς increases while ρ_c decreases.

3.5. In vitro drug release study

Drug loading and entrapment efficiency of the hydrogels used for drug release study is shown in Table 2. It is observed that like swelling ratio drug loading or drug entrapment also increases with increase in alginate wt%, decrease in crosslinker concentration and also increase in solution pH i.e. from SGF (pH 1.5) to SIF (pH 7.5). Cumulative release profile of acetaminophen drug from the SIPN hydrogels at varied crosslinker concentration, pH and alginate wt% is shown in Fig. 5a–c, respectively. From all of these figures it is observed that the hydrogels show an initial burst release of the drug followed by a sustained rate of release. The initial burst release may be attributed to the release of drug associated with surface of the hydrogels. The concentration gradient of the drug between hydrogel surface and release medium (water) is the driving force for diffusion of drug from the gel network. Initial rapid release of drug is due to high concentration gradient of drug between these two phases (Patil, Dordick, & Rethwisch, 1996). It is also observed that drug release trend is similar to swelling characteristic of the hydrogels i.e. with decreasing crosslinking concentration or increasing alginate wt% drug release rate increases. Similarly, like swelling ratio, at higher pH release rate of drug is also faster as observed in Fig. 5c. Initially the concentration profile of drug between surface of the hydrogels and water is high which causes its rapid release. It is also observed from Fig. 5 that after around 300 min (5 h) change in release rate is marginal. This is because entrapment of the remaining drug in the gel network prevented further release at low concentration gradient (Zhang, Wu, & Chu, 2004). Similar release profiles were reported for release of model protein and drug from various IPN type hydrogels (Kulkarni et al., 2010; Matricardi et al., 2013; Raghavendra et al., 2012; Wang et al., 2010a; Patil et al., 1996). First 60% of the release data were also fitted to the following Korsmeyer–Peppas model Eq. (16) (Korsmeyer, Gurny, Doelkar, Buri, & Peppas, 1983)

$$F_D = \frac{W_{Dt}}{W_{Da}} = K_{KP} t^n \tag{16}$$

where W_{Dt} and W_{Da} are amount of drug released at time t and infinity, respectively, K_{KP} is a constant corresponding to structural and geometrical character of the dosage form and the diffusion exponent n signifies mechanism of drug release. The values of K_{KP} and n of the hydrogels used for drug release study is shown in Table 2 along with the values of statistical parameters i.e. R^2, χ^2 and F. It is observed that the values of 'n' ranges from 0.35 to 0.77 which signifies diffusion controlled drug release of the hydrogels. The values of R^2 are observed to be close to unity (0.9856 to 0.9984) while low χ^2 (0.14 to 2×10^{-3}) and high F (4357–49292) values are observed for these fittings which also confirm close fitting of the drug release profile to Korsmeyer–Peppas model by the hydrogels.

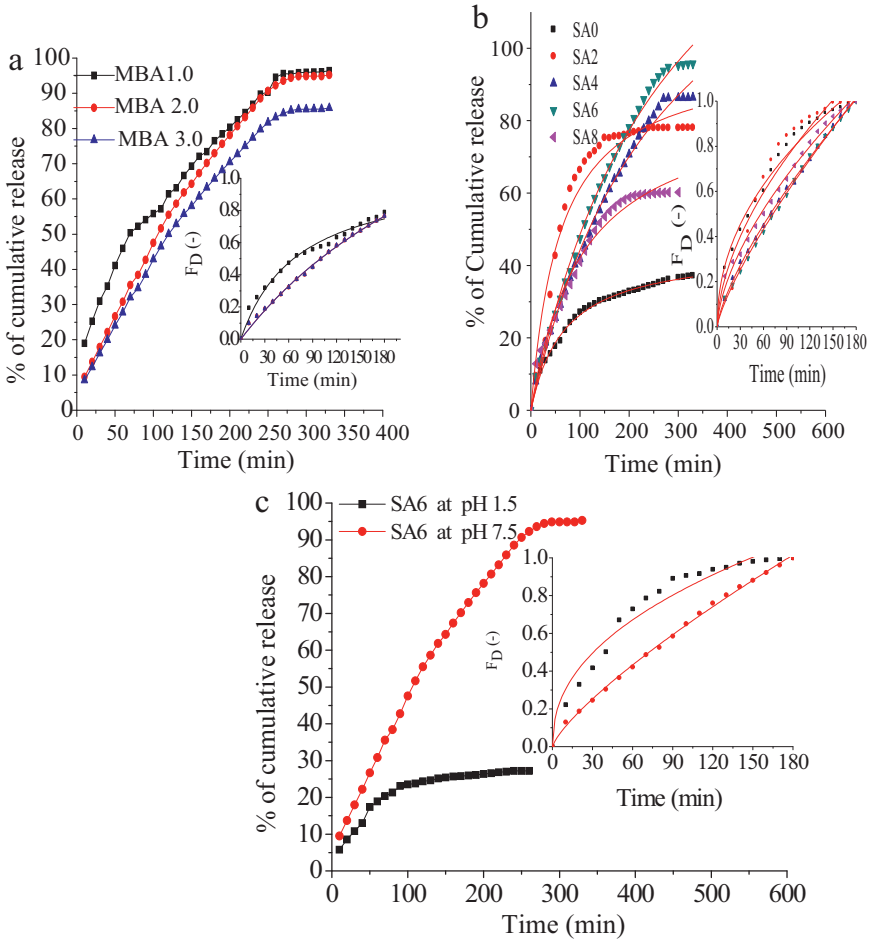


Fig. 5. Effect of (a) crosslinker (MBA) conc., (b) sodium alginate (SA) and (c) solution pH on drug release with direct fitting of release data to Korsmeyer–Peppas model Eq. $F_D = K_{KP}t^n$.

4. Conclusion

Several semi-interpenetrating network type (SIPN) hydrogels were synthesized by *in-situ* crosslink copolymerization of acrylamide and MBA in presence of sodium alginate at varied initiator, MBA, alginate wt% and total monomer concentration in water. These hydrogels were characterized by PZC, FTIR, NMR, XRD, SEM and DTA–TGA. These characterizations confirmed pH sensitivity, crosslinking and interpenetration of the SIPN hydrogels. Swelling data of the hydrogels showed close non-linear fitting to second order rate equation. Drug release data were also found to show close fitting to Korsmeyer–Peppas model. Molecular weight between two crosslink, crosslink density and mesh size of the hydrogels were also evaluated. The pH reversibility of the hydrogels increased with increase in alginate wt%. However, above 6 wt% alginate swelling and pH reversibility decreased. Hydrogels synthesized with 6 wt% sodium alginate, 1 wt% initiator, 2 wt% MBA at a TMC of 25% (termed as SA6) was observed to show optimum swelling as well as drug entrapment and drug release profile at pH of 7.5.

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