



Carbohydrate Polymers 67 (2007) 190-200

Carbohydrate Polymers

www.elsevier.com/locate/carbpol

Synthesis, characterization and swelling responses of pH sensitive psyllium and polyacrylamide based hydrogels for the use in drug delivery (I)

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Received 18 February 2006; received in revised form 5 May 2006; accepted 14 May 2006

Available online 30 June 2006

Abstract

In order to utilize the psyllium husk, a medicinally important natural polysaccharide, for developing the novel hydrogels meant for the controlled drug delivery devices, we have prepared psyllium and polyacrylamide based polymeric networks by using N,N'-methylenebis-acrylamide (N,N-MBAAm) as crosslinker. The polymeric networks thus formed were characterized with scanning electron micrography (SEM), FTIR and thermogravimetric analysis (TGA) techniques to study various structural aspects of the networks. This paper discusses the swelling responses of the polymeric networks as a function of time, temperature, pH and [NaCl]. Equilibrium swelling has been observed to be dependent on both structural aspects of the polymers and swelling environment. Percent swelling (Ps) has been observed to be decrease with increase in [NN-MBAAm] in the polymeric networks. It increases abruptly from 1437% to 4975% by changing the swelling medium from distilled water to solution of 0.5 M NaOH, which indicates the smart behavior of the network. Maximum Ps 4975 was observed at 6.4×10^{-3} mol/L of [NN-MBAAm]. These observations indicate that these hydrogels are pH sensitive and have potential for use in colon specific drug delivery.

Keywords: Drug delivery devices; Hydrogels; Psyllium; Swelling behavior

1. Introduction

Hydrogels are three-dimensional polymeric networks those swell quickly by imbibing a large amount of water or de-swell in response to changes in their external environment. The volume phase transitions as a response to different stimuli make these materials interesting objects of scientific observations and useful materials for use in advanced technologies. These changes can be induced by changing the surrounding pH, temperature, ionic strength and electro stimulus (Bajpai, Bajpai, Shukla, & Kulkarni, 2004; Chauhan, Bansal, & Mahajan, 2003; Chauhan, Kumari, & Sharma, 2003; Chauhan, Lal, & Mahajan, 2004; Elliott, Macdonald, Nie, & Bowman, 2004; Kim,

Lee, & Kim, 2004a, Kim, Lee, & Kim, 2004b; Szczubialka, Moczek, Blaszkiewicz, & Nowakowska, 2004; Xue, Champ, Huglin, & Jones, 2004a, Xue, Champ, Huglin, & Jones, 2004b). Hydrogels exhibit a thermodynamic compatibility with water, which allows them to swell in aqueous media and make them potential candidates for drug delivery devices.

Recently there is a marked thrust on research activities related to the use of natural polysaccharides for the development of the hydrogels as colon specific drug delivery devices. These include chemically or physically crosslinked polysaccharides, such as carboxymethyl cellulose (Bajpai & Mishra, 2004), starch (Bajpai & Saxena, 2004), chitin. (Mahdavinia, Pourjavadi, Hosseinzadeh, & Zohuriaan, 2004), dextran (Chiu, Hsiue, Lee, & Huang, 1999; Kim & Oh, 2005) and guar gum (Gliko-Kabir, Yagen, Penhasi, & Rubinstein, 1998; Prasad, Krishnaiah, & Satyanarayana, 1998). The rationale for the development of a polysaccharide-based

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delivery system for colon is the presence of large amount of polysaccharidases in the human colon, as the colon is inhabited by a large number and variety of bacteria, which secrete many enzymes.

Grafting and crosslinking has been general practice to improve the functional properties of polysaccharides. Graft copolymerization in the presence of crosslinker formed the three-dimensional polymeric networks, those swell quickly by imbibing a large amount of water (Mostafa & Morsy, 2004). The network formation made via the free radical polymerization mechanism was significantly influenced by the monomer concentration, pH, and ionic strength. These factors control the degree of crosslinking and primary cyclization during the network formation of multifunctional monomers (Elliott et al., 2004). The novel biopolymerbased semi interpenetrating polymer networks (IPNs) of carboxymethyl cellulose and kappa-carrageenan with crosslinked poly(acrylic acid) have been prepared and their water-sorption capacity has been evaluated as a function of chemical architecture of the IPNs, pH, and temperature of the swelling medium (Bajpai & Mishra, 2004; Pourjavadi, Harzandi, & Hosseinzadeh, 2004). The pH-reversibility and on-off switching properties of the hydrogels make them intelligent polymers and are good candidates for considering as potential carriers for bioactive agents (Bajpai et al., 2004; Mahdavinia et al., 2004). Terpolymeric devices consisting of acrylamide, methacrylamide and acrylic acid were synthesized and release of the model drug riboflavin from these devices was studied at the physiological temperature 37 °C (Bajpai & Dubey, 2004). In the present study psyllium has been modified to develop the novel drug delivery devices.

Psyllium is the common name used for several members of the plant genus *Plantago*. Its seeds are used commercially for the production of mucilage, which is obtained from the seed coat by mechanical milling/grinding of the outer layer of the seed and yield amounts to approximately 25% of the total seed yield. Mucilage is a white fibrous material that is of hydrophilic in nature and forms the clear colorless mucilaginous gel by absorbing water. Gel-forming fraction of the alkali-extractable polysaccharides is composed of arabinose, xylose and traces of other sugars (Fischer, Nanxiong, Ralph, Andersond, & Marletta, 2004). The chemical modification of mucilage of *Plantago* psyllium (Psy) is not much reported, however, some work, on the grafting of polyacrylamide and polyacrylonitrile onto psyllium has been reported for the use in flocculation studies (Agarwal, Srinivasan, & Mishra, 2002; Mishra, Srinivasan, & Dubey, 2002; Mishra, Srinivasan, & Gupta, 2003; Mishra, Srinivasan, Bajpai, & Dubey, 2004; Mishra, Yadav, Agarwal, & Rajani, 2004). Singh and coworkers have studied the metal ion sorption and swelling behavior of psyllium and acrylic acid based hydrogels (Singh, Chauhan, Bhatt, & Kumar, 2006).

Psyllium, a medicinally active natural polysaccharide, if suitably tailored to prepare the hydrogels which have potential to act as novel drug delivery devices. Therefore, the present study is an attempt, to synthesize psyllium and poly(AAm) based hydrogels by using *N*,*N*-MBAAm as crosslinker and ammonium persulfate (APS) as initiator. The polymeric networks [Psy-*cl*-poly(AAm)], thus formed, were characterized by SEM, FTIR, TGA, and swelling behavior. To observe the effect of composition of the polymeric networks and nature of swelling medium on the percent swelling, the swelling responses of the hydrogels were studied as a function of monomer concentration, crosslinker concentration, swelling time, temperature of the swelling medium, pH and salt concentration of swelling medium.

2. Experimental

2.1. Materials and method

Plantago psyllium mucilage (psy) was obtained from an Sidpur Sat Isabgol factory (Gujrat, India), Acrylamide (AAm) (Merck-Schuchardt, Germany), ammonium persulphate (APS) and N,N,-methylene bis acrylamide (NN-MBAAm) from S.D. Fine Mumbai, India, were used as received.

2.2. Synthesis of Psy-cl-poly(AAm)

The optimum reaction conditions for the modification of psyllium to hydrogels have been discussed somewhere else (Singh et al., 2006). Reaction was carried out with 1 g of psyllium husk, 1.095×10^{-2} mol/L of APS, known concentration of monomer and crosslinker in the aqueous reaction system at 65 °C temperature for 2 h. Polymers thus formed were stirred for 2 h in distilled water and for 2 h in ethanol to remove the soluble fraction and then were dried in air oven at 40 °C. Different polymeric networks [psy-cl-poly(AAm)] were synthesized by varying [AAm] (from $1.41 \times 10^{-1} \text{ mol/L}$ to $7.03 \times 10^{-1} \text{ mol/L}$) and by varying [N,N-MBAAm] (from 6.45×10^{-3} mol/L to 32.40×10^{-3} mol/L) to study the effect of monomer and crosslinker variation on the structure of three- dimensional network and thereafter on the percent swelling of these hydrogels.

2.3. Characterization

Psyllium and psy-cl-poly(AAm) polymers were characterized by scanning electron micrography (SEM), Fourier transform infrared spectroscopy (FTIR) and thermogravimetric analysis (TGA). To investigate and compare surface morphology of psyllium and psy-cl-poly(AAm), SEMs of these polymers were taken on Jeol Steroscan 150 Microscope, FTIR spectra's were recorded in KBr pellets on Perkin-Elmer to study the modified nature of psyllium and thermogravimetric analysis of psyllium and psy-cl-poly(AAm) were carried out in a Schimatdzu Simultaneous Thermal Analyzer in air at a heating rate of 20 °C/min to examine the thermal properties of the polymers.

2.4. Swelling behavior

Swelling studies of the polymeric networks were carried out in aqueous medium by gravimetric method. To attain equilibrium swelling, known weight of polymers were taken and immersed in excess of solvent for 24 h at fixed temperature, and then these polymers were taken out, wiped with tissue paper to remove excess of solvent, and weighed immediately. The equilibrium percent swelling (P_s) of the polymeric network were calculated as follows:

$$P_{\rm s} = \left(\frac{W_{\rm s} - W_{\rm d}}{W_{\rm d}}\right) \times 100$$

Where W_s and W_d are weights of swollen polymers and dried polymers.

Swelling behavior of the polymeric networks prepared with different monomer and crosslinker concentration were studied as function of time, temperature, pH and [NaCl].

3. Results and discussion

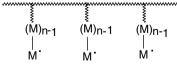
Polymeric networks were synthesized by chemically induced polymerization through free-radical mechanism. APS has generated the reactive sites, on both the psyllium and monomer, leading to the propagation of the reaction shown in Scheme 1. In the presence of crosslinker NN-MBAAm (CH₂=CHCONHCH₂ NHCOCH=CH₂), because of its poly-functionality, a new macro-radical gets formed that has four reactive sites and these sites can be linked both with the radical on the psyllium and the poly (AAm). These will result into the formation of three-dimensional networks shown in Scheme 2. In order to study the effect of crosslinker concentration on structure of three-dimensional networks and thereafter on percent swelling, polymeric networks of different [AAm] and [NN-MBAAm] were prepared and characterized.

N,N'-methylenebisacrylamide

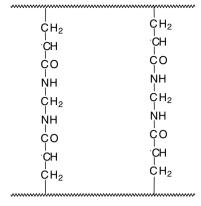
Linking sites of N, N'-methylenebisacrylamide

3.1. Characterization

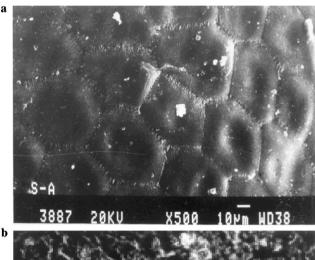
Psyllium and psy-cl-poly(AAm) were characterized by SEM, FTIR and TGA studies.



Scheme 1.



Scheme 2.



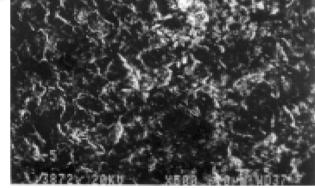


Fig. 1. (a) Scanning electron micrograph of psyllium. (b) Scanning electron micrograph of psy-cl-poly(AAm).

3.1.1. Scanning electron micrography

The morphology of psyllium and psy-cl-poly(AAm) were examined by SEM and presented in the Fig. 1a and b, respectively. It was observed that psyllium has smooth and homogeneous morphology whereas modified psyllium has structural heterogeneity. Zhang and Peppas have used scanning electron microscopy in the morphological studies of the poly(methacrylic acid)/poly(N-isopropylacrylamide) interpenetrating polymeric networks (IPN) with both conventional SEM and cryogenic SEM experiments. In order to visualize the IPN morphological behavior in its swollen

state, a new approach, cryogenic SEM, was used on the IPN samples. IPN samples were frozen in their swollen state by liquid nitrogen and investigated on a cold stage in the SEM column. The pH and temperature influence on the IPN morphology was studied. The results showed that a decrease in pH and increase in temperature resulted in a drastic decrease in the pore size of the IPNs (Zhang & Peppas, 2002).

3.1.2. Fourier transform infrared spectroscopy

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FTIR spectra of polymeric networks were recorded to study the modification of the psyllium (Fig. 2a, and b). The broad absorption bands at 3405.0 cm⁻¹ was observed due to —OH stretching which indicated association in the polymeric networks. FTIR absorption bands due to C=O stretching of amide has been prominently witnessed at 1664.5 cm⁻¹ in psy-cl-poly(AAm). 1454.3 cm⁻¹ peak due

to the NH and CN in plane bending, 897 cm⁻¹ peak due to NH and CH out of plane bending of amide and 1079.6 cm⁻¹ peak due to C—O stretching of carboxylic acid have been observed apart from usual peaks in psyllium.

3.1.3. Thermogravimetric analysis (TGA)

From the TGA of psyllium and psy-cl-poly(AAm), it was observed that the mechanism of decomposition in both the cases are different and thermograms are shown in Fig. 3a and b, respectively. The initial decomposition temperature (IDT) was observed at 245.7 °C and 164.9 °C whereas final decomposition temperature (FDT) was observed at 539.28 °C and 674.3 °C, respectively for psyllium and psy-cl-poly(AAm). It is observed that the difference in decomposition temperature (DT) for the modified psyllium is more as compared to psyllium; hence the rate of decomposition with respect to temperature was slower in

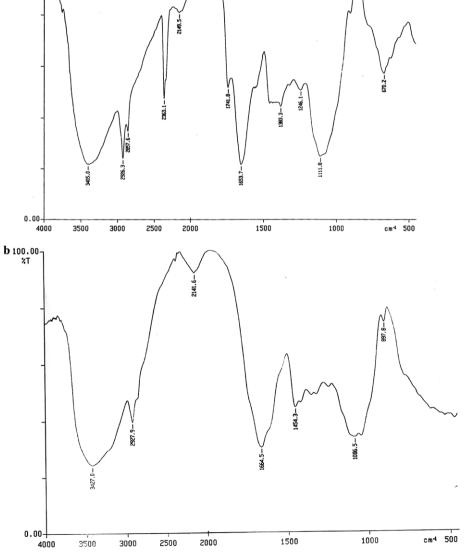


Fig. 2. (a) FTIR spectra of psyllium. (b) FTIR spectra of psyllium-cl-poly(AAm).

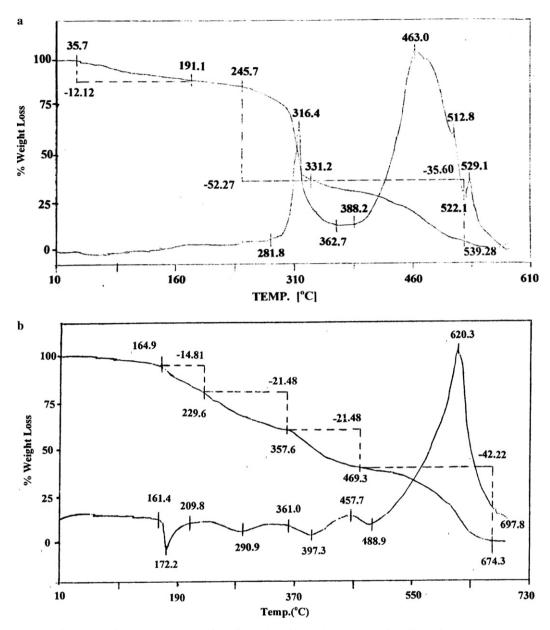


Fig. 3. (a) Primary thermogram of psyllium. (b) Primary thermogram of psyllium-cl-poly(AAm).

case of psy-cl-poly(AAm). It is thus understandable that thermal degradation for psy-cl-poly(AAm) started earlier but it becomes stable at higher temperature. Therefore, it is concluded that the modification has induced the thermal stability in the crosslinked networks. Such thermal behavior of these networks are explained by fact that —CONH₂ groups in psy-cl-poly(AAm) degrade easily by dehydration and generating more stable groups as —CN, those are

thermally very stable and can undergo cyclization reactions at higher temperature. This observation is further supported by the decomposition temperature corresponding to the 10% weight loss (Table 1). Further, from the data of different degradation stages, it is observed that maximum loss in most the polymer networks were in the second stage of decomposition where temperature range was usually corresponded to the de-polymerization process.

Table 1 Thermogravimetric analysis of psyllium and Psy-cl-poly(AAm)

Sample	IDT (°C)	FDT (°C)	DT (°C) at every 10% weight loss									
			10	20	30	40	50	60	70	80	90	100
Psyllium	245.7	539.28	155.7	284.2	305.72	310.0	316.2	320.7	410.6	464.28	494.28	539.28
Psy-cl-poly(AAm)	164.9	674.3	171.1	233.6	285.17	367.45	403.4	493.4	573.1	606.54	629.15	674.3

Differential thermal analysis (DTA) of these polymers shows that decomposition process is exothermic and fast in the psyllium whereas in case of psy-cl-poly(AAm) endothermic peak is observed at 172.2 °C temperature and sample start melting before decomposing, indicating lower glass transition temperature. Exothermic peaks were observed at 316.4 °C and 463.0 °C in case of psyllium and at 620.3 °C in crosslinked polymer. These all results indicated the change in thermal stability of the modified psyllium.

3.2. Swelling behavior of hydrogels [psy-cl-poly(AAm)]

The chemical structure of the polymer affects the swelling ratio of the hydrogels which is directly related to loading of drug to the polymers and release of drug from the polymeric matrix. The chemical structure depended upon composition of the polymeric matrix i.e. the crosslinking ratio. The higher the crosslinking ratio, the more crosslinking agent is incorporated in the hydrogels structure. Highly crosslinked hydrogels have a tighter structure, and will

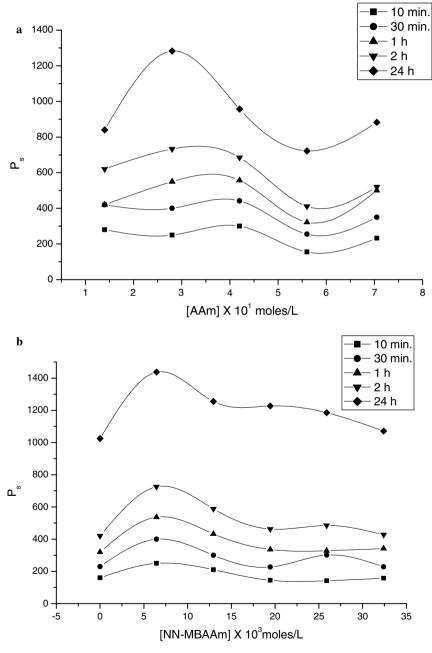


Fig. 4. (a) Effect of time on Ps of Psy-cl-poly(AAm) prepared with different [AAm]. (Swelling temp. = 40 °C, reaction time = 2 h, temperature = 65 °C, [APS] = 1.095×10^{-2} mol/L, [N,N-MBAAm] = 1.62×10^{-2} mol/L and psyllium = 1gm.) (b) Effect of time on Ps of Psy-cl-poly(AAm) prepared with different [N,N-MBAAm]. (Swelling temp. = 40 °C, reaction time = 2 h, temperature = 65 °C, [APS] = 1.095×10^{-2} mol/L, [AAm] = 7.03×10^{-1} mol/L and psyllium = 1gm.)

swell less as compared to the same hydrogels with lower crosslinking ratios. Crosslinking hinders the mobility of the polymer chain, hence lowering the swelling ratio. Swelling of environmentally-sensitive hydrogels can be affected by specific stimuli. In the hydrogels system, absorption of water from the environment changes the dimensions and physicochemical properties of the system and thus the drug release kinetics.

In the present studies swelling behavior of psy-cl-poly (AAm), prepared with different [AAm] and [NN-MBAAm] are discussed as a function of time, temperature, pH and salt concentration of the swelling medium.

3.2.1. Percent swelling as a function of time

The swelling behavior of polymeric networks was studied at different time intervals i.e. 10 min, 30 min, 1 h, 2 h, and 24 h. The effect of different [AAm] (Fig. 4a) and different [NN-MBAAm] (Fig. 4b) on the equilibrium swelling was studied at each time interval in the swelling medium at 40 °C and it was observed from the figures that Ps increases as the swelling time increases for each polymeric network till the swelling equilibrium has attained, but it decreases with increase in the [AAm] and [NN-MBAAm] in the networks. Similar observations have been reported by Singh and coworkers for the

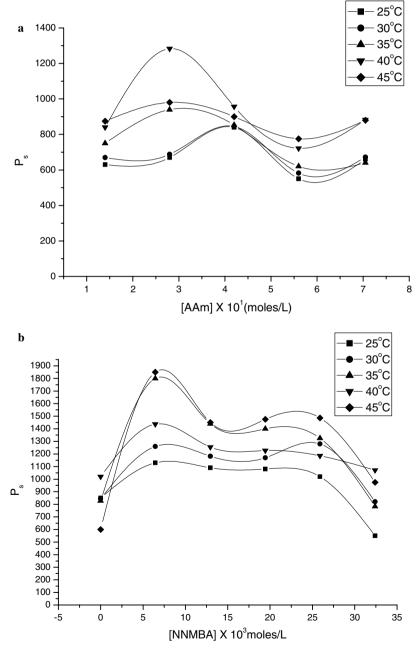


Fig. 5. (a) Effect of temperature on Ps of Psy-cl-poly(AAm) prepared with different [AAm]. (Swelling time. = 24 h, reaction time = 2 h, temperature = 65 °C, [APS] = 1.095×10^{-2} mol/L, [N,N-MBAAm] = 1.62×10^{-2} mol/L and psyllium = 1gm.) (b) Effect of temperature on Ps of Psy-cl-poly(AAm) prepared with different [N,N-MBAAm]. (Swelling time = 2 h., reaction time = 2 h, temperature = 65 °C, [APS] = 1.095×10^{-2} mol/L, [AAm] = 7.03×10^{-1} mol/L and psyllium = 1 g.)

hydrogels based on psyllium and poly(AAc) (Singh et al., 2006). Mina and coworker have described the higher swelling ratio for hydrogels prepared with lower monomer concentrations and have showed a leveling off tendency within 24 h (Mina & Alam, 2005).

3.2.2. Percent swelling as a function of temperature

To study the effect of temperature on swelling equilibrium of the polymers prepared with different monomer concentration and different crosslinker concentration, Ps was studied at different temperature (i.e. 25 °C, 30 °C, 35 °C, 40 °C and 45 °C). As the [AAm] varied from 1.41×10^{-1} mol/L to 7.03×10^{-1} mol/L, percent swelling of the psy-*cl*-poly(AAm) decreases at each fixed temperature(Fig. 5a). This observation was supported by the fact that incorporation of higher amount of monomer leads

to self-crosslinking, hence, prevents accessibility of more solvent in the matrix. But at each fixed concentration of the monomer in the polymer networks, the increase in swelling observed as the temperature rose in the swelling medium. Ps decreases with increase in [NN-MBAAm] from 6.45×10^{-3} mol/L to 32.4×10^{-3} mol/L at each temperature and maximum Ps 1850 was obtained at 6.45×10^{-3} mol/L [NN-MBAAm] at 45 °C. Only a very small concentration of cross-linker brings abrupt transition from liquid to gel state during synthesis of hydrogels. The crosslinking density increases with increase of crosslinker concentration and pore size of the crosslinked network decreases, which resulted to decrease in Ps. Percent swelling increases with increase in temperature of the swelling medium till the swelling equilibrium occur (Fig. 5b). Kim and coworkers have observed that the swelling ratio increases

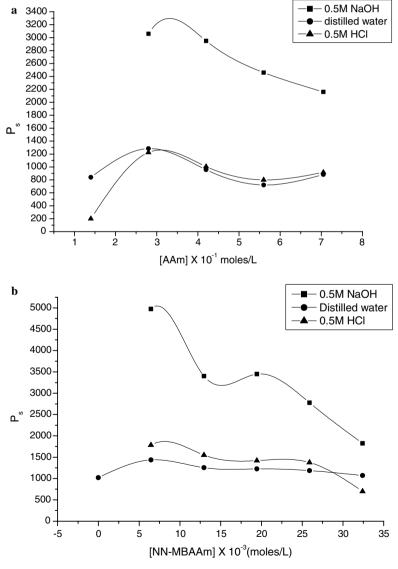


Fig. 6. (a) Effect of pH on Ps of Psy-cl-poly(AAm) prepared with different [AAm]. (Swelling time = 24 h and temp. = 40 °C, reaction time = 2 h, temperature = 65 °C, [APS] = 1.095×10^{-2} mol/L, [N,N-MBAAm] = 1.62×10^{-2} mol/L and psyllium = 1gm.) (b) Effect of pH on Ps of Psy-cl-poly(AAm) prepared with different [N,N-MBAAm]. (Swelling time = 24 h. and temp. = 40 °C, reaction time = 2 h, temperature = 65 °C, [APS] = 1.095×10^{-2} mol/L, [AAm] = 7.03×10^{-1} lmol/L and psyllium = 1 g.)

with increasing temperature in polyelectrolyte complex hydrogels, composed of various weight ratios of chitosan and hyaluronic acid (Kim et al., 2004a).

3.2.3. Percent swelling as a function of pH

It is observed that percent swelling changes smartly with change of pH of the swelling medium. It has been observed from the Fig. 6a that percent swelling of psy-cl-poly(AAm) in 0.5 M NaOH solution was more as compare to the distilled water and solution of 0.5 M HCl. At lower pH values the —CONH₂ groups do not ionizes and keep the network at its collapse state. At high pH value, it gets partially ion-

ize, and the charged —COO $^-$ groups repel each other, leading to swelling of the polymer. Further it was observed from the Fig. 6b that polymer without crosslinker dissolved in 0.5 M NaOH solution. Ps decreases with increase in [NN-MBAAm] in the polymeric networks. It was further observed that Ps changes abruptly from 1437 to 4975 by changing the swelling medium from distilled water to solution of 0.5 M NaOH, which indicates the smart behavior of the network. This observation is very important for the colon specific drug delivery devices. Maximum Ps 4975 was observed at 6.4×10^{-3} mol/L of [NN-MBAAm]. These observations indicate that these hydrogels are pH sensitive

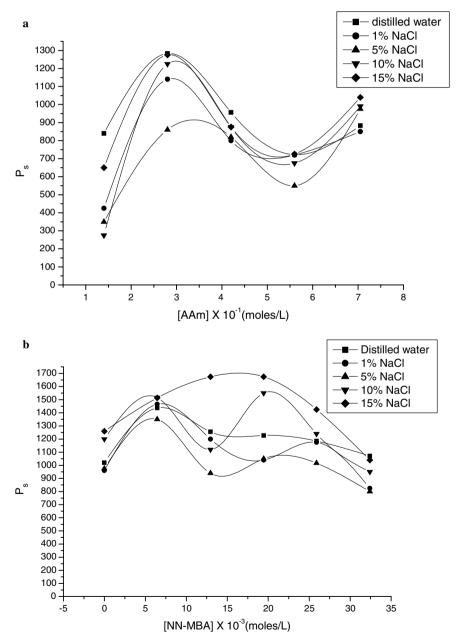


Fig. 7. (a) Effect of [NaCl] on Ps of Psy-cl-poly(AAm) prepared with different [AAm]. (Swelling time = 24 h and temp. 40 °C, reaction time = 2 h, temperature = 65 °C, [APS] = 1.095×10^{-2} mol/L, [N,N-MBAAm] = 1.62×10^{-2} mol/L and psyllium = 1 g.) (b) Effect of [NaCl] on Ps of Psy-cl-poly(AAm) prepared with different [N,N-MBAAm]. (Swelling time = 2 h and temp. = 40 °C, reaction time = 2 h, temperature = 65 °C, [APS] = 1.095×10^{-2} mol/L, [AAm] = 7.03×10^{-1} mol/L and psyllium = 1 g.)

and have potential for use in colon specific drug delivery devices. Similar observation was reported by Chauhan and coworkers during partial hydrolysis of the dextrin and poly(AAm) based hydrogels (Chauhan et al., 2004). It is also reported that the swelling of microgels, prepared with grafting of poly(AAm) onto guar gum, increases when the pH of the medium changes from acidic to alkaline because of the saponification of the —CONH₂ group to the —COOH group. (Soppimath, Kulkarni, & Aminabhavi, 2001).

3.2.4. Percent swelling as a function of [NaCl]

It is important to understand the osmotic and structural changes of hydrogels, induced by addition of salt with respect to many physical and chemical processes in biological systems. In the present study the percent swelling for the polymers, prepared with different [AAm] and different [NN-MBAAm] was studied at four different concentrations of NaCl (i.e. 1%, 5%, 10% and 15%) and results are shown in Fig. 7a and b respectively. Percent solvent uptake decreases with increase in monomer and crosslinker concentration for each brine solution and also with increase in brine concentration up to certain concentration of [NaCl] and than unexpected results were observed. Hydrogels do not swell appreciably in the presence of electrolyte salts due to ex-osmosis and even the swollen hydrogels shrink dramatically in the presence of salts. Hydrogels shriveling results from the loss of hydrophilic-hydrophobic balance of the networks in the presence of electrolyte salts. Thus, the pre-swollen gels shrink quickly and regain their original shape and weight by de-swelling when they are subjected to electrolyte salt solutions. The swelling ratios 2451 and 119 g/g of gel, have been reported in distilled water and in 0.9 % NaCl solution, respectively for the polymers prepared in an aqueous solution using acrylamide and 2-acrylamido-2-methyl-propanesulfonic acid as monomers, potassium persulfate as initiator, and NN-MBAAm as cross-linker (Liu, Xie, Zhu, & Zhang, 2004). Also the swelling ratio of the IPN hydrogels composed of poly(AAc) and poly(AN) decreased with an increasing [NaCl] in an aqueous solution (Kim et al., 2004a).

4. Conclusion

It is concluded that swelling of polymeric networks is affected by composition of the polymer i.e. synthetic conditions such as [AAm] and [NN-MBAAm] in the polymeric networks, and nature of swelling media such as pH and ionic strength of the swelling medium. Swelling of the hydrogels abruptly changes by changing the swelling media from distilled water to the solution of high pH indicating the intelligent nature of the polymers. Therefore, psyllium, when modified with acrylamide, results in the formation of the pH sensitive hydrogels and have potential to act as colon specific drug delivery devices.

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