J Mater Sci (2011) 46:2587–2599
DOI 10.1007/s10853-010-5111-2

Slow release of ciprofloxacin from double potential drug delivery system

Baljit Singh · Nisha Sharma · Vikrant Sharma

Received: 10 September 2010 / Accepted: 23 November 2010 / Published online: 7 December 2010

Abstract Psyllium polysaccharide is a bulk laxative and has been used for the treatment of constipation which is responsible for the diverticulitis. Ciprofloxacin is an antibiotic used for the microorganism infested in the diverticula. Hence, the functionalization of psyllium with polyvinyl alcohol (PVA) and poly(acrylamide) [poly (AAm)] will develop the drug delivery system (DDS) with potential for dual action for the treatment of diverticulitis, that is, by treating the constipation due to laxative action of psyllium and release of ciprofloxacin from DDS in controlled manner. The optimum conditions for the synthesis of hydrogels have been obtained as 42.21×10^{-2} mol/L of AAm, 3% (w/v) of PVA, 32.43×10^{-3} mol/L of *N*,*N*′-methylenebisacrylamide (NN-MBA), 17.53×10^{-3} mol/L ammonium persulfate, and 1 g of psyllium. The characterization of the hydrogels has been carried out by SEMs, EDAX, FTIR, and swelling studies. Swelling and drug release studies have also been carried out to determine the mechanism of swelling of hydrogels and drug release from the drug loaded hydrogels. The release of the drug from the hydrogels occurred through Fickian diffusion mechanism in pH 2.2 and pH 7.4 buffer.

Introduction

Stability and pH responsive behaviors of the polymers are the criterions for the design of site-specific drug delivery systems [1]. No doubt that the polysaccharides are non-toxic, safe, biocompatible, biodegradable, abundant, and colon-specific [2] but when used alone, these are not suitable materials to develop the drug delivery systems. This is due to their substantial swelling and rapid enzymatic degradation in biological fluids [3]. On the other hand, the composites of biological and synthetic polymers usefully combine the biocompatibility of the biological component with the physical and mechanical properties of the synthetic components [4]. Graft copolymerization of the polysaccharides with synthetic polymers is a powerful technique to modify the properties of polysaccharides and make them advanced materials for use in drug delivery [5, 6]. Hydrogels developed through the grafting and crosslinking remain intact in the physiological environment of the stomach and the small intestine, but are degraded by the bacterial inhabitants of the human colon, which make them potentially useful in targeted delivery systems to the colon [7, 8]. Hydrogels are three-dimensional polymeric networks that swell quickly by imbibing a large amount of water or de-swell in response to changes in their external environment, which make them useful materials for site-specific drug delivery [9, 10]. This study deals with the design of PVA, psyllium polysaccharides, and poly(acrylamide)-based hydrogels for the release of ciprofloxacin to be used for the disease associated with colon.

PVA is highly hydrophilic, non-toxic, biodegradable, and biocompatible material which has excellent film forming property [11, 12]. It adopts a globular structure in aqueous solution for being exposed to the crosslinker during the polymerization reaction [13]. PVA also provides mechanical strength, long-term thermal and pH stability to the films which enhance their suitability for biomedical applications [14]. The degree of gelation of PVA increases with increase in amount of polysaccharides in the reaction system during copolymerization [15, 16]. The relative crystallinity of PVA decreases with addition of polysaccharides due to the bulky

B. Singh (✉) · N. Sharma · V. Sharma
Department of Chemistry, Himachal Pradesh University, Shimla 171005, India
e-mail: baljitsinghhpu@yahoo.com

and rigid backbone provided by the polysaccharides [17]. Yang and coworker have reported the decrease in swelling and increase in mechanical properties of the pH responsive PVA–chitosan gels with increasing PVA and agar contents in the reaction system [18]. Further, the presence of appropriate amount of polysaccharide is necessary for gelation to provide sufficient swelling and mechanical strength to the hydrogels [19]. Poly(acrylamide) have also been reported as blood compatible hydrogels for biomedical applications [20]. PVA/poly(acrylamide-*co*-acrylamidoglycolic acid) based pH sensitive semi interpenetrating hydrogels were prepared by free radical polymerization in aqueous solution using NN-MBA as a crosslinker and were used in drug delivery applications [21].

Psyllium is gel-forming mucilage composed of a highly branched arabinoxylan units. The backbone consists of xylose units, while arabinose forms the side chains [22]. Psyllium has been reported for the treatment of constipation, diarrhea, irritable bowel syndrome, and inflammatory bowel disease-ulcerative colitis [23]. On the other hand, ciprofloxacin is a broad spectrum antibacterial agent [24] which has been reported to cure ulcerative colitis [25]. Ciprofloxacin is also used for the microorganism infested in the diverticula and acts as therapeutic agent for diverticulitis. It is effective in treating bacterial infections in diverticulitis patients with upper gastrointestinal bleeding, peritonitis, and urinary tract infections [26, 27]. Constipation is one of the reasons for the diverticulitis. Psyllium is a constipation curing agent. Hence the release of ciprofloxacin from the drug loaded polymer matrix will act with dual potential for diverticulitis. This drug delivery system will be different from the conventional drug delivery systems reported in the literature because of its dual action for the cure of diverticulitis. This system will make its reach to the site of action through GI tract. These hydrogels are made up of acrylamide which will partially hydrolyzed at higher pH and will show the pH responsive behavior and will release the drug in the colon.

In view of the pharmacological importance of gel-forming psyllium and drug delivery devices based on hydrogels, psyllium polysaccharide, if suitably tailored to prepare the hydrogels, can act as the double potential candidates to develop drug delivery systems. Therefore, in this study an attempt has been made to carry out the modification of psyllium with poly(AAm) and PVA through chemically crosslinked polymerization by using NN-MBA as crosslinker and APS as initiator. These hydrogels were characterized with scanning electron micrography (SEMs), electron dispersion X-ray analysis (EDAX), Fourier transform infrared spectroscopy (FTIR), and swelling studies. Swelling behavior of the hydrogels has been studied as a function of feed monomer, PVA, crosslinker, and initiator concentration used during the synthesis of hydrogels. Swelling was also carried out as function of temperature, pH, and [NaCl] of the swelling medium. This article discusses the swelling kinetics of the hydrogels and release dynamics of antibacterial model drug ciprofloxacin from the hydrogels to evaluate the swelling and drug release mechanism.

Experimental

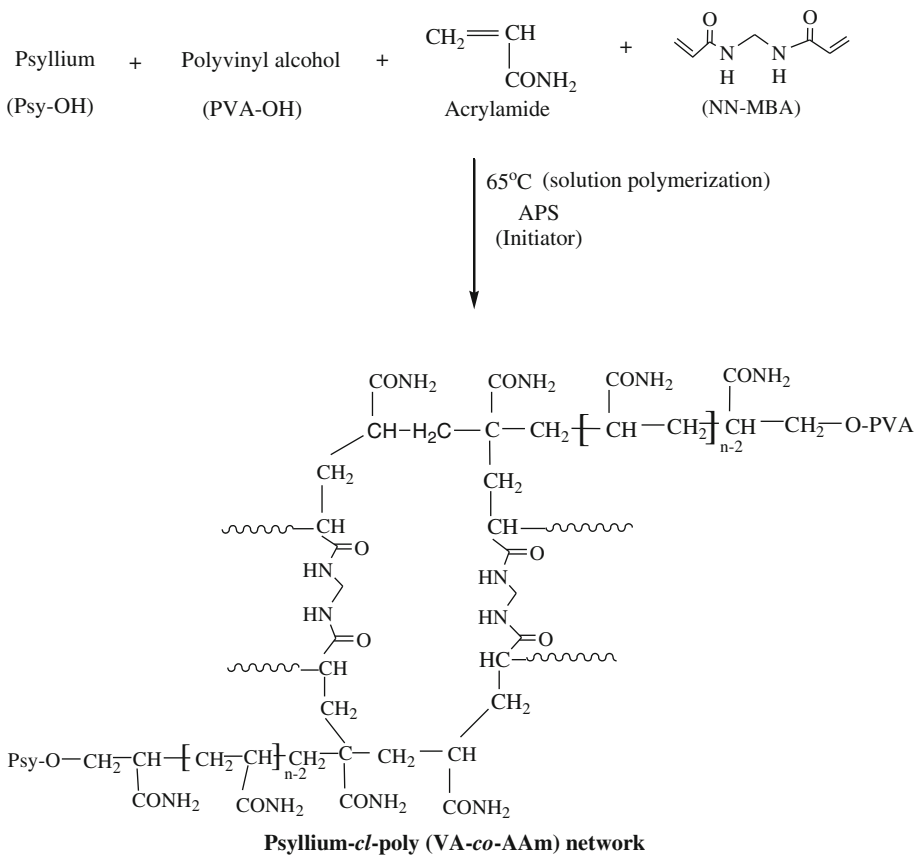
Materials and methods

Polyvinyl alcohol (PVA) (Molecular Wt. 1,25,000) was obtained from S.D. Fine Chemical Ltd., Mumbai, India, acrylamide (AAm) was obtained from Merck Specialities Private Limited, Mumbai, India, and *N*,*N*′-methylenebis-acrylamide (NN-MBA) and ammonium persulfate (APS) were obtained from Qualigens Fine Chemicals, Mumbai, India. Plantago psyllium mucilage (psy) was obtained from Sidpur Sat Isabgole factory (Gujarat, India) and the drug used, i.e., ciprofloxacin was obtained from Ranbaxy Laboratories Limited, Haridwar, India.

Preparation of psyllium-*cl*-poly(VA-*co*-AAm) hydrogels

Reaction was carried out with 1 g of psyllium husk, definite concentration of PVA, initiator, monomer and crosslinker, taken in the aqueous reaction system which was placed in water bath at 65 °C temperature for 3 h. The crosslinked hydrogel was then stirred in distilled water to remove the soluble fractions and then were dried in oven at 40 °C until the constant weight was obtained. The crosslinked polymers were named as psyllium-*cl*-poly(VA-*co*-AAm) hydrogels (Scheme 1). The optimum reaction parameters for synthesis of hydrogels were evaluated by varying the PVA from 1 to 5% (w/v), AAm from 14.07×10^{-2} to 70.34×10^{-2} mol/L, NN-MBA from 6.48×10^{-3} to 32.43×10^{-3} mol/L and APS from 4.38×10^{-3} to 21.91×10^{-3} mol/L. The optimum reaction conditions for the synthesis of hydrogels were obtained as AAm = 42.21×10^{-2} mol/L, PVA = 3% (w/v), NN-MBA = 32.43×10^{-3} mol/L, APS = 17.53×10^{-3} mol/L, and psyllium = 1 g (Table 1). These conditions were determined on the basis of swelling of the hydrogels and surface consistency maintained by hydrogels after 24 h swelling. At the optimum reaction parameters, further polymers were synthesized and were used to study the effect of pH, salt concentration and temperature of the swelling medium on hydrogel swelling. These polymer matrices were also used to study the release dynamics of the drug from the hydrogel for the evaluation of mechanism of drug release and various diffusion coefficients.

Scheme 1 Network formation of psyllium-*cl*-poly(VA-*co*-AAm) hydrogels



Psyllium-*cl*-poly (VA-*co*-AAm) network

Table 1 Reaction parameters for synthesis of psyllium-*cl*-poly(VA-*co*-AAm) hydrogels

S. No.	Psyllium (g)	[PVA]% (w/v)	[AAm] × 10^2 (mol/L)	Water (mL)	[NN-MBA] × 10^3 (mol/L)	[APS] × 10^3 (mol/L)	Weight of polymer formed (g)	Swelling per gram after 24 h (g/g of gel)
1	1.0	5	**14.07**	10	32.43	21.91	1.633	14.185 ± 0.890
2	1.0	5	**28.14**	10	32.43	21.91	1.742	8.929 ± 0.393
3	1.0	5	**42.21**	10	32.43	21.91	2.032	**7.781 ± 0.410**
4	1.0	5	**56.27**	10	32.43	21.91	2.096	7.529 ± 0.436
5	1.0	5	**70.34**	10	32.43	21.91	2.133	6.857 ± 0.285
6	1.0	**1**	42.21	10	32.43	21.91	1.460	7.767 ± 0.159
7	1.0	**2**	42.21	10	32.43	21.91	1.525	7.883 ± 0.600
8	1.0	**3**	42.21	10	32.43	21.91	1.573	**8.311 ± 0.778**
9	1.0	**4**	42.21	10	32.43	21.91	1.710	7.117 ± 0.104
10	1.0	**5**	42.21	10	32.43	21.91	2.032	7.781 ± 0.410
11	1.0	3	42.21	10	**6.48**	21.91	1.466	12.822 ± 0.217
12	1.0	3	42.21	10	**12.97**	21.91	1.506	12.211 ± 0.474
13	1.0	3	42.21	10	**19.46**	21.91	1.530	11.683 ± 0.606
14	1.0	3	42.21	10	**25.95**	21.91	1.553	9.806 ± 0.450
15	1.0	3	42.21	10	**32.43**	21.91	1.573	**8.311 ± 0.778**
16	1.0	3	42.21	10	32.43	**4.38**	1.570	15.372 ± 0.955
17	1.0	3	42.21	10	32.43	**8.76**	1.581	15.372 ± 0.955
18	1.0	3	42.21	10	32.43	**13.15**	1.555	16.356 ± 0.063
19	1.0	3	42.21	10	32.43	**17.53**	1.571	**9.839 ± 0.618**
20	1.0	3	42.21	10	32.43	**21.91**	1.573	8.311 ± 0.778

Bold values show the variation in the parameter

Characterizations

The polymers were characterized by SEMs, EDAX, FTIR, and swelling studies. SEMs and EDAX of the polymers were taken on QUANTA 200 FEG model (The Netherlands). FTIR spectra of polymers were recorded in KBr pellets on Nicolet 5700FTIR THERMO (USA). Swelling studies of the polymeric networks were carried out in different media by gravimetric method in triplicate [23].

Release dynamics of model drug from drug loaded hydrogels

The release profile of drugs from the drug loaded polymer matrix was determined in distilled water, pH 2.2 buffer, and pH 7.4 buffer. All the studies were carried out in triplicate. Preparation of buffer solution, calibration curves, drug loading, drug release, and preparation of reagents has been discussed elsewhere [23]. The calibration curves of ciprofloxacin were prepared at λ_{max} 277 nm, 277 nm, and 270 nm, respectively, in distilled water, pH 2.2 buffer, and pH 7.4 buffer solution. The loading of a drug into the hydrogels was carried out by swelling equilibrium method. The hydrogels were allowed to swell in the drug solution of known concentration (600 μg/mL) for 24 h at 37 °C and then were dried to obtain the release device. In vitro release studies of the drug were carried out by placing dried and drug loaded sample in definite volume of releasing medium for 30 min at 37 °C and then sample was transferred to the fresh releasing medium. The release of drug from the polymer samples was measured from the calibration graphs which were prepared on the UV Visible Spectrophotometer (Cary 100 Bio, Varian).

Mechanism of swelling and drug release from polymer matrix

The mechanisms of swelling and drug release have been discussed in detail in our earlier study [23]. Swelling of polymers has been classified into three types of diffusion mechanisms, on the basis of relative rate of diffusion of water into polymer matrix and rate of polymer chain relaxation. The values of diffusion exponent 'n' and diffusion coefficients have been evaluated using Eqs. 1–4 for the swelling of the polymers and for the release of the drug from the polymers [28–31].

$$\frac{M_t}{M_\infty} = kt^n \tag{1}$$

$$\frac{M_t}{M_\infty} = 4\left(\frac{D_i t}{\pi \ell^2}\right)^{0.5} \tag{2}$$

$$D_A = \frac{0.049\ell^2}{t^{1/2}} \tag{3}$$

$$\frac{M_t}{M_\infty} = 1 - \left(\frac{8}{\pi^2}\right)\exp\left[\frac{(-\pi^2 D_L t)}{\ell^2}\right] \tag{4}$$

where M_t/M_∞ is the fractional release of drug in time t, 'k' is the constant characteristic of the drug–polymer system, and 'n' is the diffusion exponent characteristic of the release mechanism. M_t and M_∞ is drug released at time 't' and at equilibrium, respectively, D_i, D_A, and D_L are the initial, average, and late diffusion coefficients, and 'l' is the thickness of the sample. $t^{1/2}$ is the time required for 50% release of drug.

Results and discussion

Characterizations

SEM and EDAX analysis

Scanning electron micrographs (SEMs) of psyllium, PVA, and psyllium-*cl*-poly(VA-*co*-AAm) hydrogels are shown in Figs. 1, 2, and 3, respectively. It is observed from the SEMs that the psyllium, PVA, and crosslinked polymer matrix have shown structural heterogeneity. The EDAX of psyllium, PVA, and psyllium-*cl*-poly(VA-*co*-AAm) hydrogels (Fig. 4a–c) was taken and quantitative elemental composition presented in the Table 2. The EDAX spectrum of psyllium and psyllium-*cl*-poly(VA-*co*-AAm) hydrogels showed the presence of carbon, oxygen, and hydrogen which are the main constituents in polysaccharides. EDAX spectrum of PVA showed highest weight percentage of carbon and lowest weight percentage of oxygen among all polymers. Presence of nitrogen in hybrid polymer has also been observed. EDAX has shown the incorporation of amide moieties in the backbone.

FTIR spectra

FTIR spectra of psyllium, PVA, and psyllium-*cl*-poly(VA-*co*-AAm) polymers are presented in Fig. 5a–c, respectively. In the case of psyllium polysaccharide the absorption bands have been observed at 3430.6, 1200–1300 cm^{-1}, respectively, due to –OH stretching and C–O–C stretching vibrations. These bands are the characteristic of the natural polysaccharide. In addition, the absorption bands in the region 930–820 and 785–730 cm^{-1} have also been observed due to vibrational modes of pyranose rings of polysaccharide. In the case of FTIR spectra of PVA, a broad band at 3430.9 cm^{-1} due to the O–H stretching vibrations, a band at 1264 cm^{-1} due to the O–H bending vibration, and

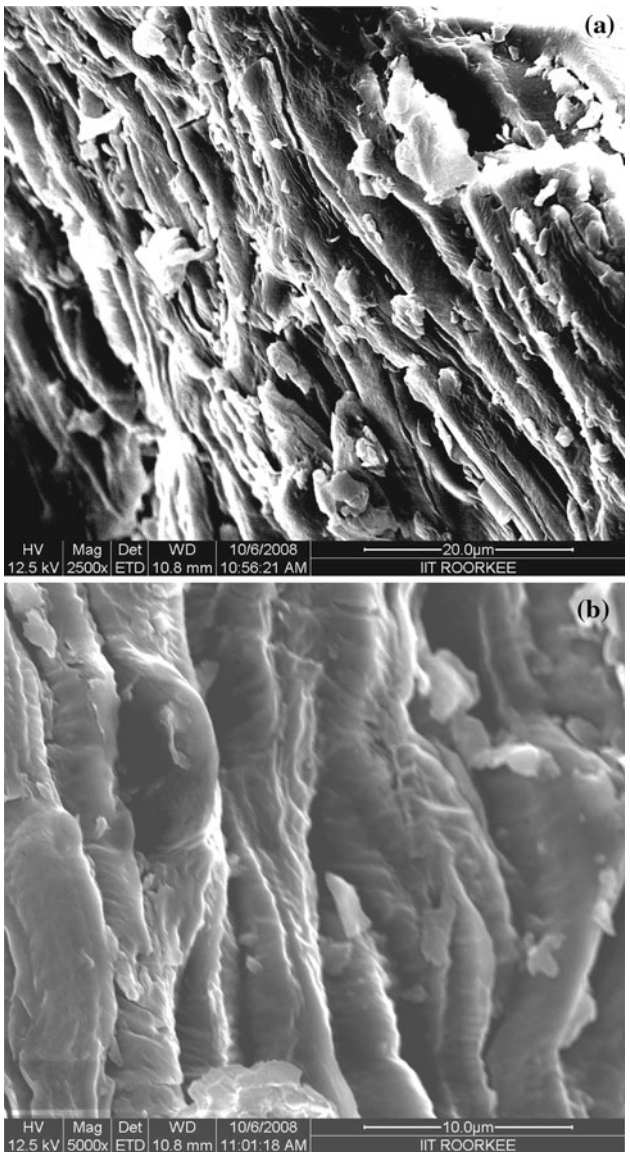


Fig. 1 Scanning electron micrograph (SEM) of psyllium at different magnification: **a** 2500× and **b** 5000×

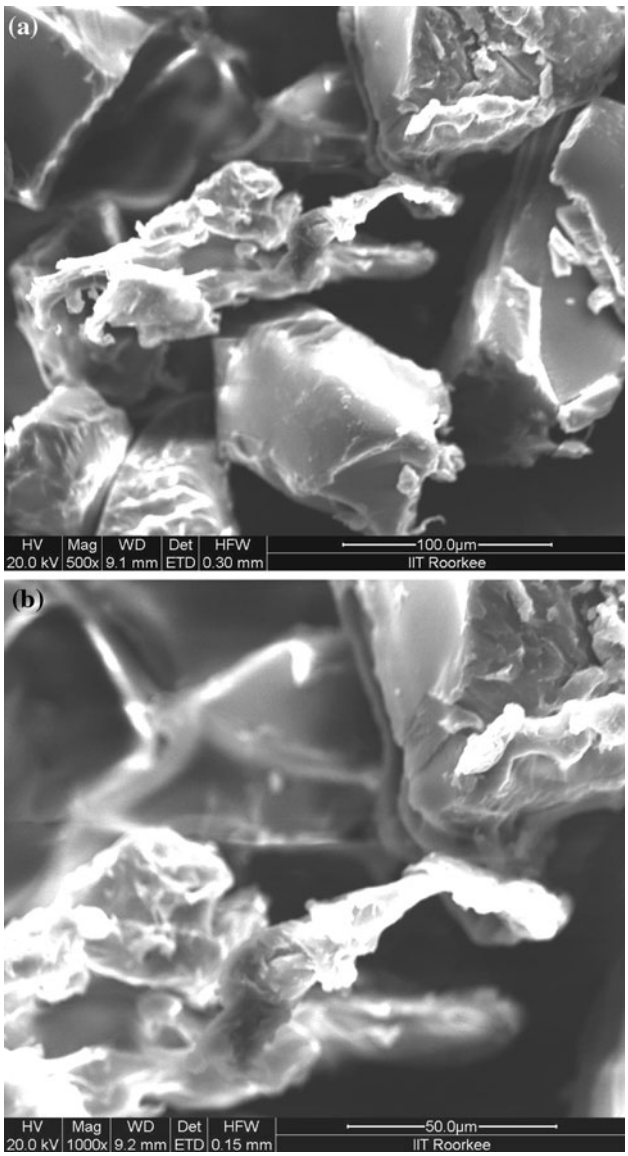


Fig. 2 Scanning electron micrograph (SEM) of PVA at different magnification: **a** 500× and **b** 1000×

bands at 2924.1 and 2854.1 cm^{-1} have been attributed to the stretching vibrations of -CH_2. The band at 1461.1 cm^{-1} due to C–H bending vibration has been observed. In the FTIR spectra of psyllium-*cl*-poly(VA-*co*-AAm) polymer, the broad band at 3376.9 cm^{-1} due to combination of –OH and N–H stretching, band at 1663.9 cm^{-1} due to C=O stretching (Amide I band), band at 1560.2 cm^{-1} due to N–H in plane bending (Amide II band), band at 1262.0 cm^{-1} due to C–N stretching (Amide III band) of the amide group present in the networks, and band at 1457.5 cm^{-1} due to -CH_2 bending vibrations have been observed apart from usual bands in psyllium and PVA.

Swelling studies

In order to study the effect of synthetic reaction parameters (i.e., concentration of AAm, PVA, NN-MBA, APS) on the structure of the polymeric networks, the swelling of the polymers was taken at 37 °C in distilled water. Effect of nature of swelling medium (pH, salt, and temperature of the swelling medium) on the swelling of the hydrogels was also studied.

Swelling as a function of feed [AAm] In order to determine the effect of feed monomer concentration on the network structure, polymers were prepared with different

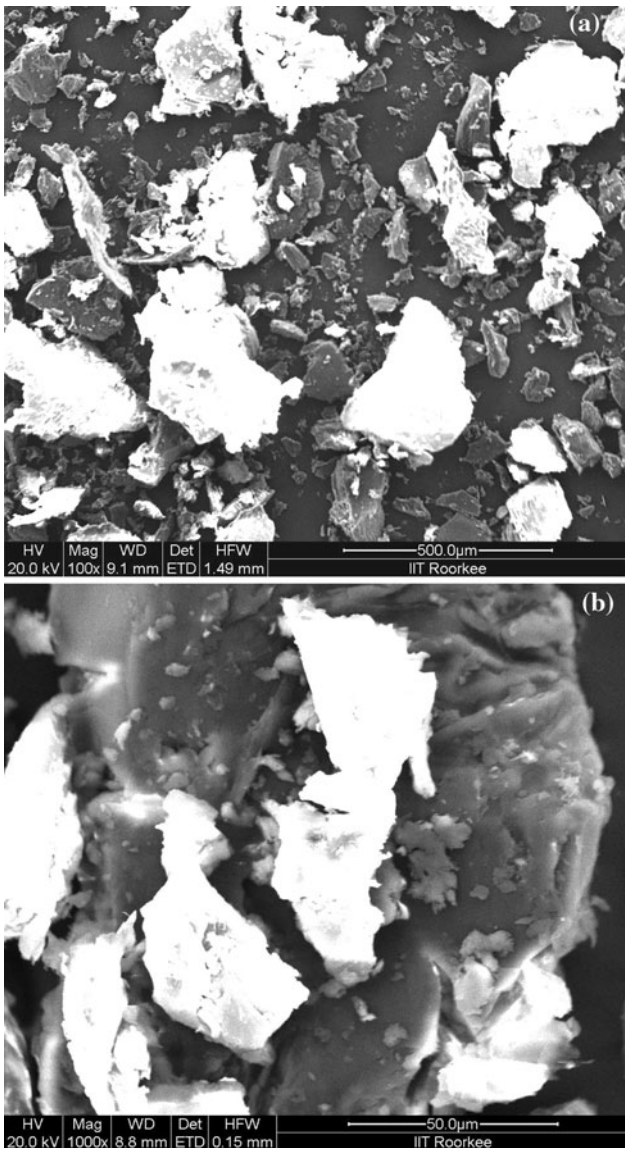


Fig. 3 Scanning electron micrograph (SEM) of psyllium-*cl*-poly(VA-*co*-AAm) at different magnification: **a** 100× and **b** 1000×

[AAm] and their swelling studies were carried out. Polymers were prepared by varying the concentration of acrylamide from 14.07×10^{-2} to 70.34×10^{-2} mol/L. The results of swelling are presented in Fig. 6. It is observed from this figure that swelling of polymers decreased, as the concentration of feed monomer increased during the synthesis of hydrogels. It means that polymers prepared with higher [AAm] have higher crosslinking density in the networks. This may be due to the increase in grafting and self-crosslinking of the poly(AAm) onto psyllium and PVA. Bajpai and Giri have also observed decrease in swelling with increase in feed concentration of the acrylamide during the synthesis of (carboxymethylcellulose-*g*-polyacrylamide) hydrogels [32]. It is worthy to mention here that when the AAm concentration was varied, all the other reaction contents were kept constant.

The values of diffusion exponent '*n*' and gel characteristics constant '*k*' have been evaluated from the slope and intercept of the plot ln (M_t/M_∞) versus ln t and results are presented in Table 3. The values of '*n*' are between 0.5 and 1 which indicate that swelling of polymers prepared with different monomer concentrations occurred through non-Fickian diffusion mechanism. In this mechanism, the rate of diffusion of water molecules into the polymer matrix and rate of polymer chains relaxation are comparable. The values of late diffusion coefficients are very less than the early stage diffusion coefficients (initial and average diffusion coefficients). In the earlier stages of swelling, the higher rate of swelling is explained on the basis of polymer chains relaxation in the hydrogels. Rate of polymer chains relaxation increases with time, which increases the rate of diffusion of water in the polymer matrix. However, in the later stages when the swelling equilibrium was about to reach, the rate of swelling decreased which is reflected in lower values of late diffusion coefficients (Table 3).

Swelling as a function of PVA contents At the optimum [AAm], the amount of feed PVA was varied from 1 to 5% (w/v) during the synthesis of hydrogels and their swelling behavior was studied (Fig. 7). It is clear from the figure that after 24 h swelling, amount of water uptake by the polymer first increased with increase in PVA contents up to 3% (w/v) then decreased with further increase in feed PVA contents during polymerization reaction. This is due to the reason that after attaining the optimum pore size at certain PVA concentration, pore size decreased with further increase in PVA content due to increase in physical and chemical crosslinking of blended hydrogels. Alupei et al. have reported decrease in swelling of xanthan and PVA-based hydrogels with increase in PVA content [13]. Maximum water uptake of (8.311 ± 0.778) g/g of gel has occurred for the polymer prepared with 3% (w/v) of PVA, and this PVA content has been taken as optimum PVA concentration for further synthesis of hydrogels. Swelling of the polymers prepared with different amount of PVA has been occurred through non-Fickian diffusion mechanism. The values of various diffusion coefficients are presented in Table 3.

Swelling as a function of crosslinker The crosslinker concentration defined the network structure of hydrogels. The role of crosslinker is to provide joints (covalent or ionic) between different polymer chains for the formation of three-dimensional networks. Crosslinks are necessary to form a hydrogel in order to prevent dissolution of the hydrophilic polymer chains in an aqueous environment. To study the effect of crosslinker on the structure of polymer networks, the swelling behavior of the hydrogels (prepared

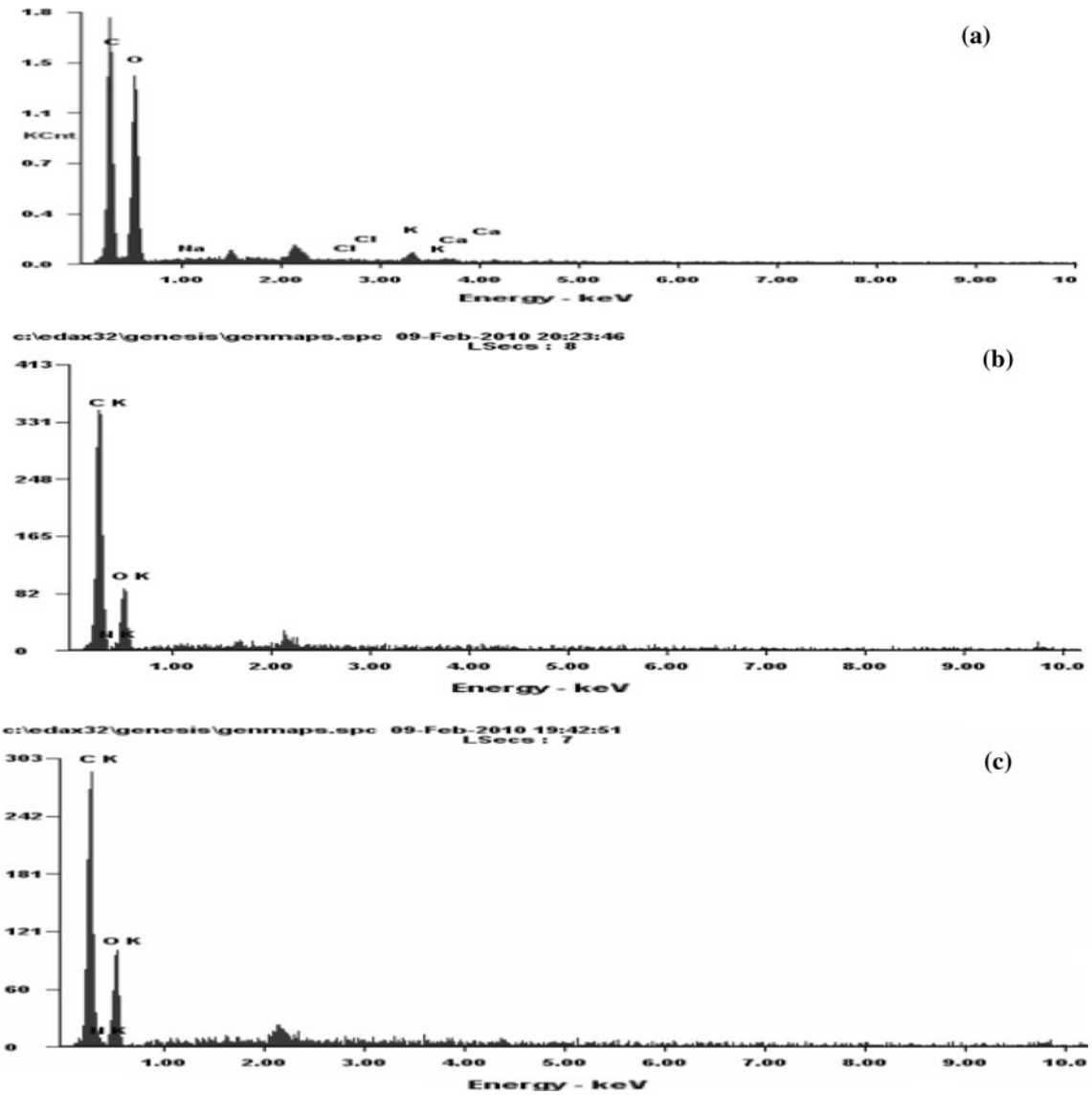


Fig. 4 EDAX of **a** psyllium, **b** PVA, and **c** psyllium-*cl*-poly(VA-*co*-AAm) hydrogel

Table 2 Energy dispersion X-ray analysis for elemental composition analysis of different polymers

Polymer	Element composition (wt%)						
	C	O	N	Na	Ca	K	Cl
Psyllium	45.66	47.79	–	0.18	1.15	2.99	0.23
PVA	65.16	30.04	4.80	–	–	–	–
Psyllium-*cl*-poly (VA-*co*-AAm)	59.48	33.88	6.64	–	–	–	–

by varying the [NN-MBA] from 6.48×10^{-3} to 32.43×10^{-3} mol/L) was studied (Fig. 8). Swelling of the hydrogels decreased with increase in crosslinker concentration due to increase in crosslinking density. Similar trends of swelling has been reported in Na–Alg/CMC hydrogel prepared with different crosslinker concentrations [33]. Maximum water uptake (12.822 ± 0.217) g/g of gel has occurred for the polymer prepared with 6.48×10^{-3} mol/L of [NN-MBA]. But for the further synthesis of hydrogels, the optimum concentration of crosslinker was taken as 32.43×10^{-3} mol/L. It is relevant to mention here that the appropriate strength of the hydrogel is required, which is used in controlled drug delivery system in the biological medium. Otherwise the immediately degradation of matrix will occur and it will release the drug immediately and will perform like conventional drug delivery system. The swelling of the hydrogels occurred through non-Fickian diffusion mechanism and results of various diffusion coefficients are reported in Table 3.

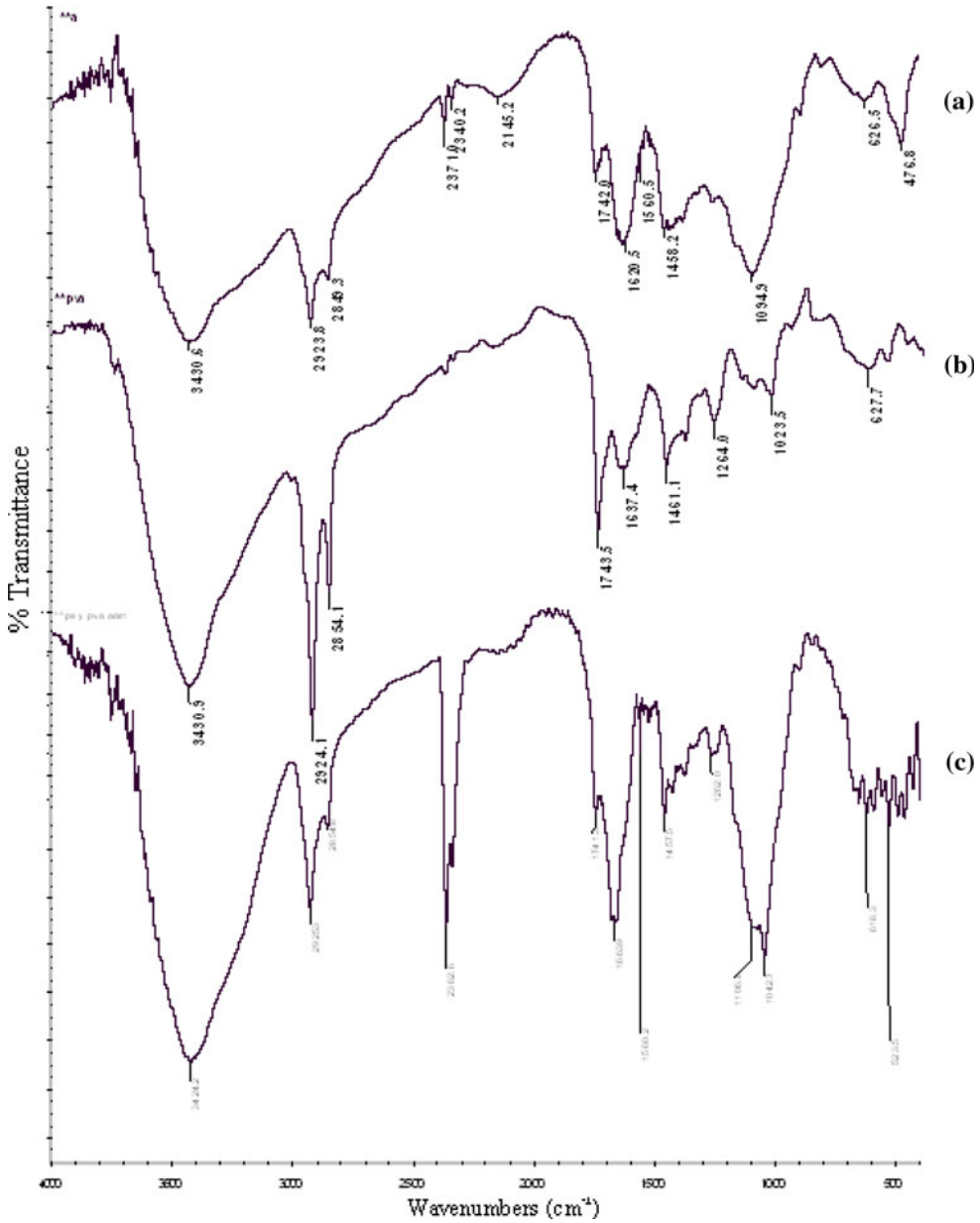


Fig. 5 FTIR spectra of **a** psyllium, **b** PVA, and **c** psyllium-*cl*-poly(VA-*co*-AAm) hydrogel

Swelling as a function of initiator To study the effect of initiator concentration on the network density the swelling of hydrogels prepared by varying the [APS] from 4.38×10^{-3} to 21.91×10^{-3} mol/L was studied (Fig. 9). From the swelling trends it has been observed that swelling first increased with increase in [APS] up to 13.15×10^{-3} mol/L then decreased with further increase in feed [APS] during the synthesis of hydrogels. This may be due to the reason that higher amount of initiator not only creates too many active centers for accelerating the rate of homo-polymerization but also increases the self-crosslinking which decreases the chain length between the two crosslinks. This will increase the crosslinking density and decrease the swelling of the polymer network [34]. Similar decrease has been observed in the swelling of (carboxymethylcellulose-*g*-polyacrylamide) hydrogels with increasing concentration of KPS [32]. The values of diffusion exponent '*n*', gel characteristics constant '*k*', and various diffusion coefficients are presented in Table 3.

Swelling as a function of pH The swelling studies of hydrogels were carried out in pH 2.2 buffer, pH 7.4 buffer, and distilled water in order to study the effect of pH of swelling medium on the swelling (Fig. 10). Swelling has been observed more in pH 7.4 buffer than in pH 2.2 buffer solutions. At lower pH values the $-CONH_2$ groups do not ionize and keep the networks at collapsed state while at high pH, it gets partially ionized and the charged COO^- groups

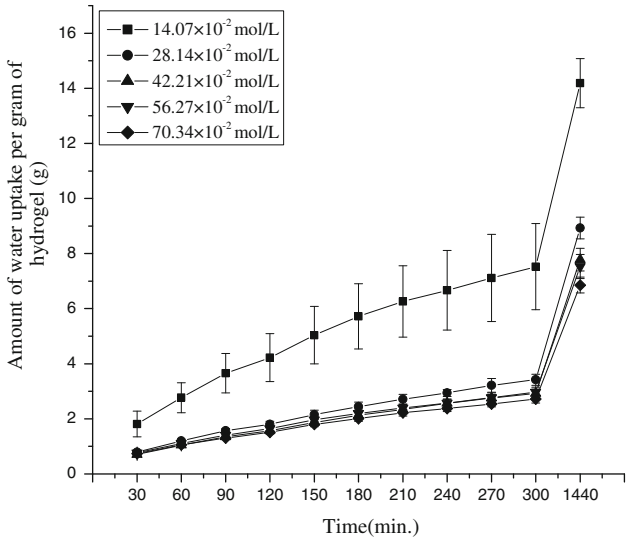


Fig. 6 Effect of [AAm] on swelling kinetics of psyllium-*cl*-poly(VA-*co*-AAm) hydrogels in distilled water at 37 °C. Reaction time = 3 h, Reaction temp. = 65 °C, Psyllium = 1 g, PVA = 5% (w/v), [APS] = 21.91 × 10^{-3} mol/L, [NN-MBA] = 32.43 × 10^{-3} mol/L, Water = 10 mL

repel each other, leading to the more swelling of polymer [32, 35]. The values of diffusion exponent '*n*' indicate that swelling is occurred through non-Fickian diffusion mechanism. The values of various diffusion coefficients show that in the earlier stages of swelling the rate of diffusion of water into hydrogel was faster than later stages (Table 4).

Swelling of polymer matrix in 0.9% NaCl solution The swelling of hydrogels in 0.9% NaCl solution has been observed less as compared to the distilled water (Fig. 11). This is due to a screening effect of the additional cations causing a non-perfect anion–anion electrostatic repulsion between $-COO^-$ ions. This will decrease the osmotic pressure (ionic pressure) difference between the hydrogel networks and the external solution [36, 37]. The swelling of hydrogels has been observed through non-Fickian diffusion mechanism (Table 4). The values of diffusion coefficients are presented in Table 4.

Swelling of hydrogels as a function of temperature Effect of temperature of the swelling medium on the swelling of

Table 3 Results of diffusion exponent '*n*', gel characteristic constant '*k*', and various diffusion coefficients for the swelling of psyllium-*cl*-poly(VA-*co*-AAm) hydrogels

S. No.	Parameter	Diffusion exponent, '*n*'	Gel characteristic constant '*k*' × 10^3	Diffusion coefficients (cm^2/min)		
				Initial $D_i \times 10^4$	Average $D_A \times 10^4$	Late time $D_L \times 10^4$
Variation of [AAm] × 10^2 (mol/L)						
1	14.07	0.627	15.195	34.24	430.25	33.51
2	28.14	0.640	9.831	45.80	823.51	53.46
3	42.21	0.629	10.366	53.53	976.91	63.74
4	56.27	0.596	13.062	46.39	841.49	55.26
5	70.34	0.576	14.696	51.01	951.68	61.33
Variation of PVA contents % (w/v)						
6	1	0.605	14.798	60.83	926.42	65.35
7	2	0.640	11.434	58.55	896.05	62.64
8	3	0.627	10.656	39.68	708.79	46.79
9	4	0.620	11.511	44.25	764.78	50.83
10	5	0.629	10.366	53.53	976.91	63.74
Variation of [NN-MBA] × 10^3 (mol/L)						
11	6.48	0.831	6.155	172.94	1233.94	135.17
12	12.97	0.792	7.936	269.45	1959.31	218.16
13	19.46	0.759	8.437	209.88	1858.57	176.48
14	25.95	0.783	8.941	375.24	2628.97	303.27
15	32.43	0.627	10.656	39.68	708.79	46.79
Variation of [APS] × 10^3 (mol/L)						
16	4.38	0.583	14.561	52.91	1001.08	63.37
17	8.76	0.638	11.847	102.05	1532.68	108.05
18	13.15	0.730	8.676	177.76	1738.16	157.67
19	17.53	0.621	14.565	63.50	860.05	64.44
20	21.91	0.627	10.656	39.68	708.79	46.79

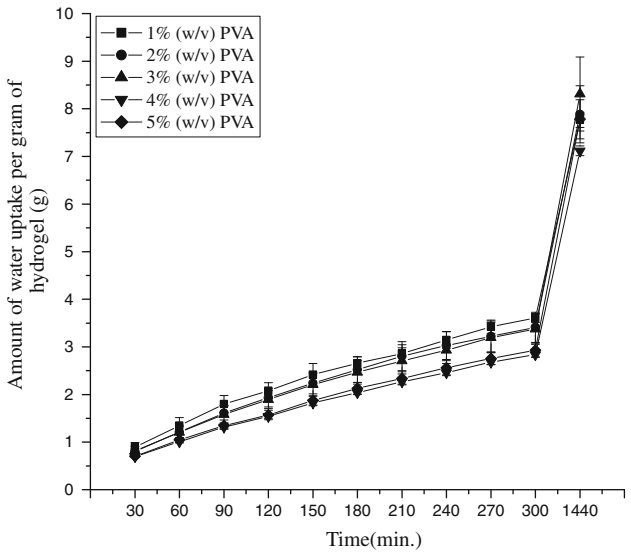


Fig. 7 Effect of PVA content on swelling of psyllium-*cl*-poly(VA-*co*-AAm) hydrogels in distilled water at 37 °C. Reaction time = 3 h, Reaction temp. = 65 °C, Psyllium = 1 g, [AAm] = 42.21×10^{-2} mol/L, [APS] = 21.91×10^{-3} mol/L, [NN-MBA] = 32.43×10^{-3} mol/L, Water = 10 mL

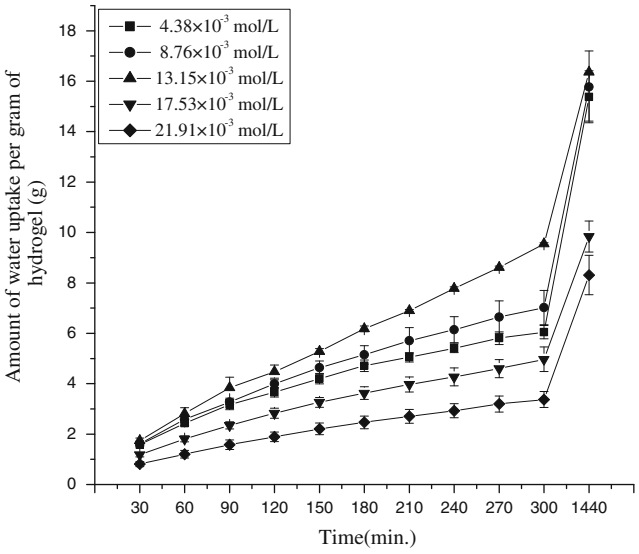


Fig. 9 Effect of [APS] on swelling kinetics of psyllium-*cl*-poly(VA-*co*-AAm) hydrogels in distilled water at 37 °C. Reaction time = 3 h, Reaction temp. = 65 °C, Psyllium = 1 g, [AAm] = 42.21×10^{-2} mol/L, PVA = 3% (w/v), [NN-MBA] = 32.43×10^{-3} mol/L, Water = 10 mL

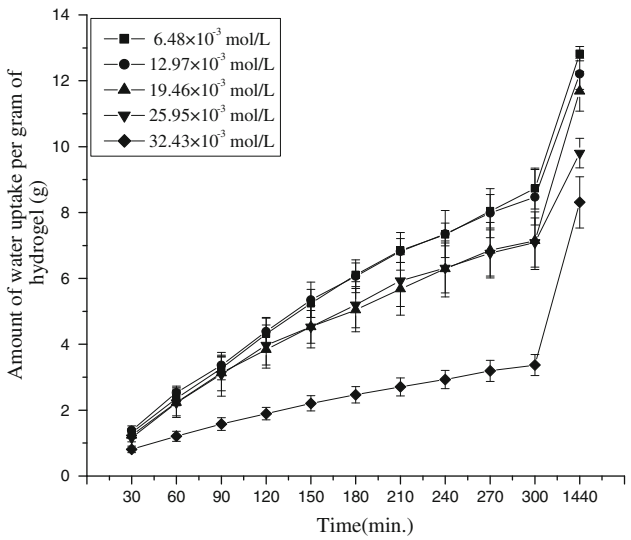


Fig. 8 Effect of [NN-MBA] on swelling kinetics of psyllium-*cl*-poly(VA-*co*-AAm) hydrogels in distilled water at 37 °C. Reaction time = 3 h, Reaction temp. = 65 °C, Psyllium = 1 g, [AAm] = 42.21×10^{-2} mol/L, PVA = 3% (w/v), [APS] = 21.91×10^{-3} mol/L, Water = 10 mL

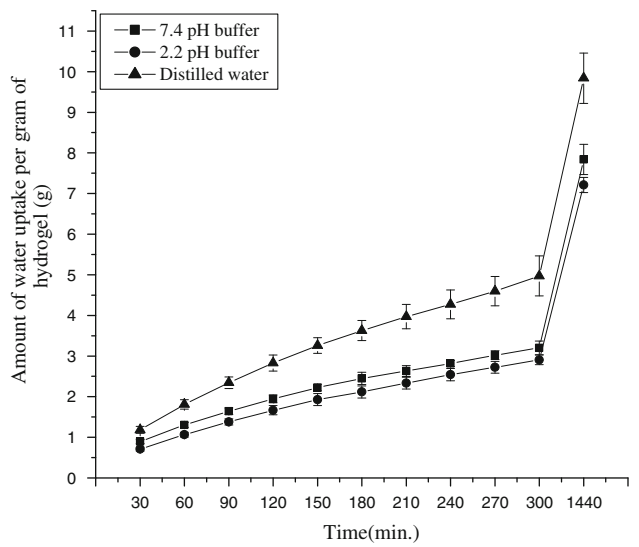


Fig. 10 Effect of pH of swelling medium on swelling kinetics of psyllium-*cl*-poly(VA-*co*-AAm) hydrogels at 37 °C. Reaction time = 3 h, Reaction temp. = 65 °C, Psyllium = 1 g, [AAm] = 42.21×10^{-2} mol/L, PVA = 3% (w/v), [NN-MBA] = 32.43×10^{-3} mol/L, [APS] = 17.53×10^{-3} mol/L, Water = 10 mL

the hydrogels is closely related to the temperature dependence of the polymer–water and polymer–polymer interactions [38] and was studied by taking the swelling at 27 and 37 °C in distilled water (Fig. 12). Swelling at 37 °C has been observed more than the swelling at 27 °C. This is due to increase in kinetic energy of solvent molecules, increase in rate of diffusion of solvent molecules and polymer chain mobility/polymer chains relaxations with increase in temperature of the swelling medium [35]. Non-Fickian type diffusion mechanism has been observed for the diffusion of water molecules in the polymer matrix. The values of diffusion coefficients in the earlier stages have been observed more as compared to later stages of the swelling (Table 4).

Table 4 Results of diffusion exponent '*n*', gel characteristic constant '*k*', and various diffusion coefficients for the swelling kinetics of psyllium-*cl*-poly(VA-*co*-AAm) hydrogels

S. No.	Parameter	Diffusion exponent '*n*'	Gel characteristic constant '*k*' × 10^3	Diffusion coefficients (cm^2/min)		
				Initial $D_i \times 10^4$	Average $D_A \times 10^4$	Late time $D_L \times 10^4$
Effect of pH						
1	7.4 pH buffer	0.555	17.302	32.32	623.76	39.27
2	2.2 pH buffer	0.615	12.078	36.23	631.11	41.61
3	Distilled water	0.621	14.565	63.50	860.05	64.44
Effect of [NaCl]						
4	0.9% NaCl	0.608	12.153	31.70	576.67	37.43
5	Distilled water	0.621	14.565	63.50	860.05	64.44
Effect of temperature						
6	27 °C	0.620	12.715	31.46	496.49	34.40
7	37 °C	0.621	14.565	63.50	860.05	64.44

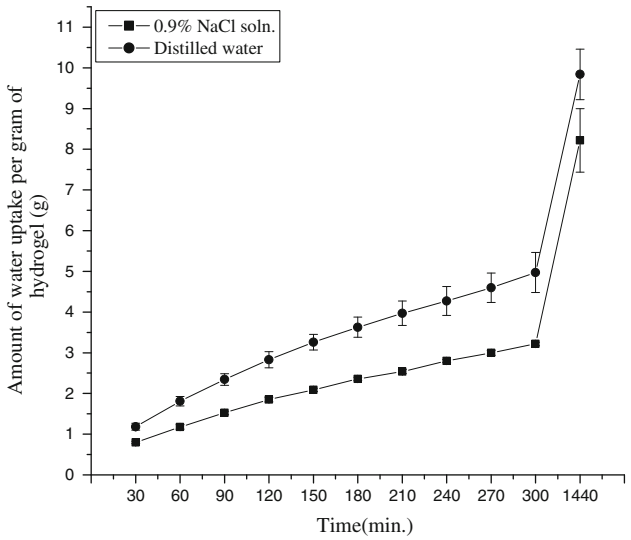


Fig. 11 Effect of 0.9% NaCl solution on swelling kinetics of psyllium-*cl*-poly(VA-*co*-AAm) hydrogels at 37 °C. Reaction time = 3 h, Reaction temp. = 65 °C, Psyllium = 1 g, [AAm] = 42.21 × 10^{-2} mol/L, PVA = 3% (w/v), [NN-MBA] = 32.43 × 10^{-3} mol/L, [APS] = 17.53 × 10^{-3} mol/L, Water = 10 mL

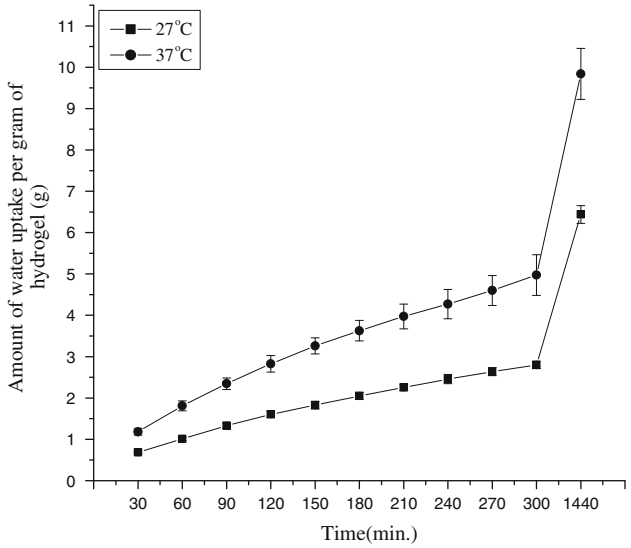


Fig. 12 Effect of temperature of swelling medium on swelling kinetics of psyllium-*cl*-poly(VA-*co*-AAm) hydrogels. Reaction time = 3 h, Reaction temp. = 65 °C, Psyllium = 1 g, [AAm] = 42.21 × 10^{-2} mol/L, PVA = 3% (w/v), [NN-MBA] = 32.43 × 10^{-3} mol/L, [APS] = 17.53 × 10^{-3} mol/L, Water = 10 mL

Release dynamics of the drug in different medium

The polymers were synthesized at the optimum conditions and were used to study the release dynamics of the model drug. The release profile of the ciprofloxacin from the drug loaded polymer matrix in different release medium at 37 °C is presented in Fig. 13. The amount of drug released in pH 7.4 buffer has been observed higher than the release in pH 2.2 buffer solution. This may be due to more swelling of hydrogel in 7.4 pH buffer solution. The percentage of the total drug release with time is shown in Fig. 14. The values of diffusion exponent '*n*' and gel characteristic constant '*k*' for the release of drug from drug loaded hydrogels in different releasing are presented in the Table 5. The release of drug in pH 7.4 ($n = 0.493$) and pH 2.2 ($n = 0.462$) buffer occurred through Fickian diffusion mechanism, while in distilled water ($n = 0.505$), the release occurred through non-Fickian diffusion mechanism. The values of various diffusion coefficients values are presented in Table 5. It has been observed from the table that in earlier stages the rate of diffusion of ciprofloxacin was higher than the later stages. This may be due to the higher concentration gradient of drug in polymer matrix and higher rate of swelling in the earlier stages. In

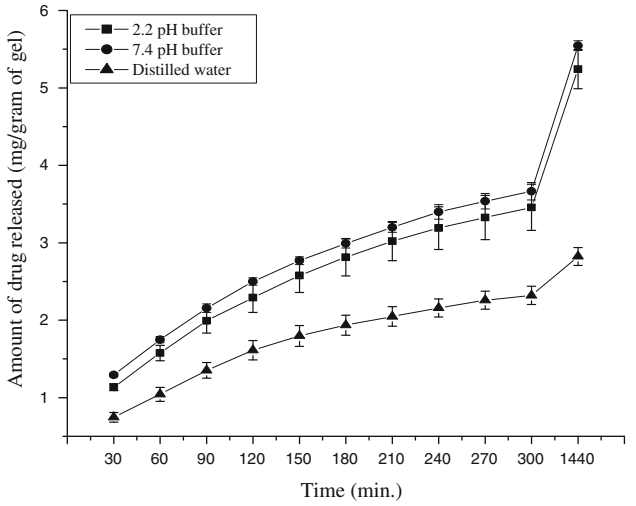


Fig. 13 Release profile of ciprofloxacin from drug loaded psyllium-*cl*-poly(VA-*co*-AAm) hydrogels in different medium at 37 °C. Reaction time = 3 h, Reaction temp. = 65 °C, Psyllium = 1 g, [AAm] = 42.21×10^{-2} mol/L, PVA = 3% (w/v), [NN-MBA] = 32.43×10^{-3} mol/L, [APS] = 17.53×10^{-3} mol/L, Water = 10 mL, drug loading = 600 μg/mL

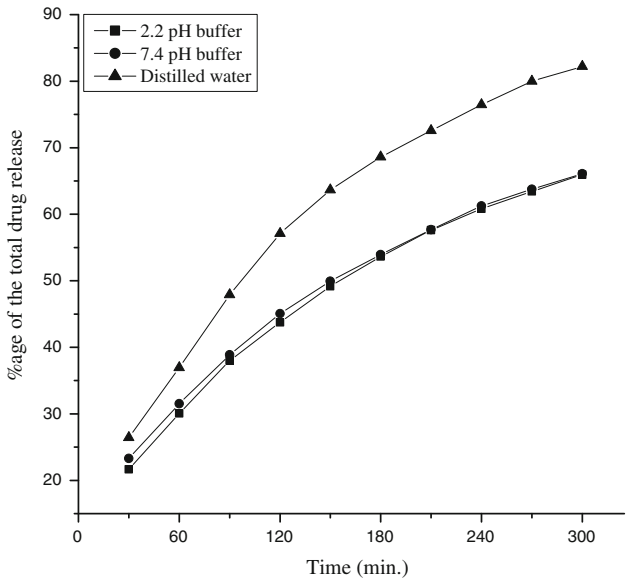


Fig. 14 Percentage of the total release of ciprofloxacin from drug loaded psyllium-*cl*-poly(VA-*co*-AAm) hydrogels in different medium at 37 °C

fact this is very good observation for the design of controlled drug delivery system, where after maintaining certain concentration, drug has to be release in control manner. Since the release is more in pH 7.4 buffer, the drug loaded hydrogels may be used as a double potential drug delivery system for the treatment of diseases associated with colon like diverticulitis. The slow release behavior of the PVA based hydrogels is further supported by the work carried out by Moretto and coworkers. These worker in one study have observed that when PVA hydrogels containing tylosin (antibiotics of veterinary interest) were administered to rats per os the drug could not be detected in the blood, but it was found in organs,: liver, kidneys, and muscles, for up to 120 h. On the other hand, when the same amount of drug was administered orally as powder, no appreciable organ accumulation was detected, while the drug was found in feces and urine. These data show that PVA hydrogels can be a suitable slow release system for tyrosine administration [39].

Conclusion

It is concluded from the foregone discussion that the composition of the composite polymer matrix and nature of the swelling medium affect the swelling of the hydrogels. In most of the cases, swelling of the hydrogels decreased with increase in feed AAm, PVA, NN-MBA, and APS concentration in the reaction system. Swelling of hydrogels and release of ciprofloxacin from the drug loaded hydrogels have been observed more in pH 7.4 buffer as compared to the pH 2.2 buffer. Hence the release of model drug ciprofloxacin from the present drug delivery system may be used as for the treatment of diseases associated with the colon. The swelling of hydrogel occurred through non-Fickian diffusion mechanism in all swelling medium conditions while the drug release from the drug loaded hydrogels has been occurred through Fickian diffusion mechanism in pH 2.2 and pH 7.4 buffer and through non-Fickian diffusion mechanism in distilled water. The values obtained for the earlier stages diffusion coefficients have been obtained higher than the later diffusion coefficients

Table 5 Results of diffusion exponent '*n*', gel characteristic constant '*k*', and various diffusion coefficients for the release of ciprofloxacin from drug loaded psyllium-*cl*-poly(VA-*co*-AAm) hydrogels

Release medium	Diffusion exponent '*n*'	Gel characteristic constant '*k*' × 10^3	Diffusion coefficients (cm^2/min)		
			Initial $D_i \times 10^4$	Average $D_A \times 10^4$	Late time $D_L \times 10^4$
pH 2.2 buffer	0.493	40.832	82.47	1116.40	90.71
pH 7.4 buffer	0.462	48.551	58.37	860.71	67.09
Distilled water	0.505	48.440	98.59	1050.09	115.45

for the release of drug from the hydrogels. The present drug delivery system may have the dual action for the treatment of diverticulitis because of laxative action of psyllium to the treatment of constipation which is responsible for the diverticulitis and slow release of ciprofloxacin for the microorganism infested in the diverticula.

Acknowledgements Authors wish to thank the University Grant Commission, New Delhi, India for providing the financial assistance for this study (UGC Sponsored Project [F. No. 33-273/2007 (SR) 28th February 2008).

References

1. Pai CM, Lee S, Park I, Seo MG, Park H (2002) Composition and pharmaceutical dosage form for colonic drug delivery using polysaccharides. US Patent 6,413,494
2. Jain A, Gupta Y, Jain SK (2007) J Pharm Pharm Sci 10:86
3. Tuovinen L, Peltonen S, Jarniven K (2003) J Control Release 91:345
4. Liu J, Lin S, Li L, Liu E (2005) Int J Pharm 298(1):117
5. Francis S, Kumar M, Varsheny L (2004) Radiat Phys chem 69:481
6. Biswal J, Kumar V, Bhardwaj YK, Goel NK, Dubey KA, Chaudhari CV, Sabharwal S (2007) Radiat Phys chem 76:1624
7. Akanksha T, Kumar SR (2009) Int J Pharm Clin Res 1(2):43
8. Sinha VR, Kumria R (2001) Int J Pharm 224:19
9. Kim SJ, Lee KJ, Kim SI (2004) J Appl Polym Sci 92(3):1473
10. Nho Y-C, Lim Y-M, Gwon H-J, Choi E-K (2009) Korean J Chem Eng 26(6):1675
11. Chiellini E, Corti A, D'Antone S, Solaro R (2003) Prog Polym Sci 28:963
12. Fundueanu G, Constantin M, Ascenzi P (2010) Acta Biomater 6:3899
13. Alupei IC, Popa M, Hamcerencu M, Abadie MJM (2002) Eur Polym J 38:2313
14. Stasko J, Kalniņs M, Dzene A, Tupureina V (2009) Proc Estonian Acad Sci 58(1):63
15. Sokker HH, Abdel Ghaffar AM, Gad YH, Aly AS (2009) Carbohydr Polym 75(2):222
16. Zhai M, Yoshii F, Kume T, Hashim K (2002) Carbohydr Polym 50(3):295
17. Cho YW, Han SS, Ko SW (2000) Polymer 41(6):2033
18. Yang X, Zhu Z, Liu Q, Chen X, Ma M (2008) Radiat Phys chem 77(8):954
19. Yang X, Liu Q, Chen X, Yu F, Zhu Z (2008) Carbohydr Polym 73(3):401
20. Peppas NA, Huang H, Torres-Lugo M, Ward JH, Zhang J (2000) Annu Rev Biomed Eng 2:9
21. Rao KSVK, Kumar ABVK, Rao KM, Subha MCS, Lee YI (2008) Polym Bull 61:81
22. Fischer HM, Nanxiong Y, Ralph RGJ, Andersond L, Marletta JA (2004) Carbohydr Res 339:2009
23. Singh B (2007) Int J Pharm 334:1
24. Chouhan R, Bajpai AK (2010) Nanomedicine 6:453
25. Turunen UM, Farkkila MA, Hakala K, Seppala K, Sivonen A, Ogren M, Vuoristo M, Valtonen VV, Miettinen TA (1998) Gastroenterology 115(5):1072
26. Hsieh WJ, Lin HC, Hwang SJ, Hou MC, Lee FY, Chang FY, Lee SD (2005) Am J Gastroenterol 93(6):962
27. Pelaez N, Pera M, Courtier R, Sanchez J, Gil MJ, Pares D, Grandea L (2006) Cir Esp 80(6):369
28. Alfrey T, Gurnee EF, Lloyd WG (1966) J Polym Sci Part C 12:249
29. Peppas NA, Korsmeyer RW (1987) In: Peppas NA (ed) Hydrogels in medicines, pharmacy, vol III. Properties and applications. CRC Press Inc, Boca Raton, p 118
30. Ritger PL, Peppas NA (1987) J Control Release 5:23
31. Ritger PL, Peppas NA (1987) J Control Release 5:37
32. Bajpai AK, Giri A (2003) Carbohydr Polym 53:271
33. Pourjavadi A, Barzegar S, Mahdavinia GR (2006) Carbohydr Polym 66:386
34. Wang Q, Qi L (2009) Iran Polym J 18(8):663
35. Mishra A, Clark JH, Pal S (2008) Carbohydr Polym 72:608
36. Kim SJ, Shin SR, Kim NG, Kim SI (2005) J Macromol Sci A Pure Appl Chem 42:1073
37. Horkay F, Tasaki I, Basser PJ (2000) Biomacromolecules 1:84
38. Pourjavadi A, Ghasemzadeh H, Mojahedi F (2009) J Appl Polym Sci 113:3442
39. Moretto A, Tesolin L, Marsilio F, Schiavon M, Berna M, Veronese FM (2004) IL Farmaco 59(1):1