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Design of psyllium–PVA–acrylic acid based novel hydrogels for use in antibiotic drug delivery

Baljit Singh*, Vikrant Sharma

Department of Chemistry, Himachal Pradesh University, Shimla 171005, Himachal Pradesh, India

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ABSTRACT

In order to exploit the potential of gel forming medicinally important polysaccharide, we have developed psyllium based hydrogels through graft copolymerization. The optimum conditions for the synthesis of psyllium–poly(vinyl alcohol) (PVA)–poly(acrylic acid) blended hydrogels have been evaluated and their characterization has been carried out by SEMs, FTIR and swelling studies. The optimum conditions for the synthesis of hydrogels have been obtained as 1% (v/v) acrylic acid, 2% (w/v) PVA and 1 g of psyllium. The use of very small amount of these petroleum products has developed the low energy, cost effective, biodegradable and biocompatible material for potential biomedical applications. It is the novelty of the present finding. The release of model antibiotic drug tetracycline HCl from the hydrogels has been observed more in pH 2.2 buffer hence these hydrogels are suitable for peptic ulcer caused by *Helicobacter pylori*. At the same time psyllium has also been reported to cure the ulcerative colitis. Hence, the present drug delivery system will have double potential to cure ulcer. The values of the diffusion exponent for the release of drug have been obtained as (0.774, 0.576 and 0.858) and gel characteristic constant have been (8.884×10^{-3}, 24.149×10^{-3} and 3.989×10^{-3}) respectively in pH 2.2 buffer, 7.4 buffer and distilled water. The release of the drug from the hydrogels occurred through non-Fickian diffusion mechanism.

1. Introduction

Recently, the improvement in drug therapy is a consequence of not only the design of new drug molecules but also the development of suitable drug delivery systems. The conventional drug delivery systems do not provide ideal pharmacokinetic profile especially for the drugs, which display high toxicity and narrow therapeutic window. In an ideal case scenario, such a profile can be achieved by use of the polymer matrix which provides controlled delivery of drug to maintain the therapeutic level. Among different drug delivery devices, hydrogels, specially based on polysaccharides have attracted considerable attention as an excellent candidate for controlled release of therapeutic agents.

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 use in drug delivery systems (Kim et al., 2004). Poly(AAc) and PVA based hydrogels are hydrophilic and have potential to deliver the drug to the colon (Ma and Xiong, 2008; Jabbari and Nozari, 2000; Lee et al., 1999; Rosiak et al., 1983). The hydrogels of poly(AAc) have special bioadhesive property which makes them to stick the mucosal lining of small intestine which after swelling releases the loaded drug (Chen and Hoffman, 1995). These hydrogels have also been reported to have biocompatibility and antibacterial properties due to their pendant carboxylic groups (Lee et al., 1999). At the same time, PVA in the hydrogels provides the mechanical strength to the hydrogels and increases their biocompatibility (Zhai et al., 2002). The release of drug from hydrogels is dependent upon the composition of the hydrogel, the possible interactions between component polymers and nature of medium (Liu et al., 2005).

Hydrogels based on natural polymers have limited applications due to the poor mechanical strength (Tang et al., 2009). Polymer blending is a simple yet attractive method to provides combined physical and mechanical properties to the hydrogels for use in drug delivery (Liu et al., 2005). Blends of biological and synthetic polymers usefully combine the biocompatibility of the biological component with the physical and mechanical properties of the synthetic components. Blends of natural polymers with either PVA or poly(AAc) have been reported in literature and have been prepared by mixing aqueous solutions of the two polymers (Giusti et al., 1994). The modification of polysaccharides to develop the hydrogels is a powerful tool, to control the interaction of the polymer with drugs, to enhance the load capability and to tailor the release profile of the drug. Grafting and crosslinking are the common practices to modify and improve the functional properties of polysaccharides (Athawale and Rathi, 1999). The synthesis of superabsorbent hydrogels has been optimized by varying the reaction parameters

* Corresponding author. Tel.: +91 1772830944; fax: +91 1772633014.
E-mail address: baljitsinghhpu@yahoo.com (B. Singh).

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

S. No.	Psyllium (g)	PVA (%, w/v)	[AAc] × 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
1	1.0	5	14.57	10	32.43	21.91	1.619	7.608 ± 0.275
2	1.0	5	29.14	10	32.43	21.91	1.917	5.804 ± 0.290
3	1.0	5	43.71	10	32.43	21.91	1.967	6.508 ± 0.379
4	1.0	5	58.28	10	32.43	21.91	2.225	4.729 ± 0.454
5	1.0	5	72.86	10	32.43	21.91	2.417	3.942 ± 0.173
6	1.0	1	14.57	10	32.43	21.91	1.272	8.872 ± 0.977
7	1.0	2	14.57	10	32.43	21.91	1.388	11.117 ± 0.377
8	1.0	3	14.57	10	32.43	21.91	1.490	8.872 ± 0.279
9	1.0	4	14.57	10	32.43	21.91	1.653	8.578 ± 0.375
10	1.0	5	14.57	10	32.43	21.91	1.619	7.608 ± 0.275
11	1.0	2	14.57	10	19.46	21.91	1.276	7.628 ± 0.296
12	1.0	2	14.57	10	25.95	21.91	1.373	7.350 ± 0.100
13	1.0	2	14.57	10	32.43	21.91	1.388	11.117 ± 0.377
14	1.0	2	14.57	10	38.92	21.91	1.379	9.078 ± 0.164
15	1.0	2	14.57	10	45.40	21.91	1.388	8.200 ± 0.120
16	1.0	2	14.57	10	32.43	4.38	1.302	17.644 ± 1.676
17	1.0	2	14.57	10	32.43	8.76	1.360	19.411 ± 1.014
18	1.0	2	14.57	10	32.43	13.15	1.375	14.222 ± 2.662
19	1.0	2	14.57	10	32.43	17.53	1.398	11.406 ± 0.258
20	1.0	2	14.57	10	32.43	21.91	1.388	11.117 ± 0.377

affecting the ultimate swelling capacity of the final product. The time–temperature variations of the polymerization reaction in the presence and absence of air showed that the molecular oxygen had no remarkable effect on the swelling behavior of the hydrogel (Pourjavadi et al., 2004).

Psyllium is gel-forming mucilage composed of a highly branched arabinoxylan. The backbone consists of xylose units, while arabinose and xylose form the side chains (Fischer et al., 2004). Psyllium has been reported for the treatment of constipation, diarrhea, irritable bowel syndrome, inflammatory bowel disease-ulcerative colitis, colon cancer, diabetes and hypercholesterolemia (Singh, 2007).

Overall, the addition of hydrophilic functional moieties in the polysaccharides hydrogels along with the PVA can exert many beneficial effects in the hydrogels properties and can enhance their applicability. Therefore, in the present study an attempt has been made to carry out the modification of psyllium with PVA and AAc through chemically crosslinked polymerization. These hydrogels have been characterized with SEMs, FTIR and swelling studies. The swelling kinetics of the hydrogels and release dynamics of antibiotic model drug tetracycline HCl from the hydrogels have been carried out to evaluate the swelling and drug release mechanism respectively.

2. Experimental

2.1. Materials and methods

Polyvinyl alcohol (PVA) (M wt. 125,000) was obtained from S.D. Fine Chemical Ltd. Mumbai-India, acrylic acid (AAc) was obtained from Merck Specialities Private Limited Mumbai-India, N,N-methylene bisacrylamide (NN-MBA) was obtained from ACROS, New Jersey, USA. Ammonium persulphate (APS) was obtained from Qualigens Fine Chemicals Mumbai-India, *Plantago psyllium* (Psy) was obtained from Sidpur Sat Isabgole factory (Gujarat, India) and the drug used i.e. tetracycline hydrochloride was obtained from Nicholas Piramal India Limited Gujarat-India.

2.2. Preparation of psyllium-cl-poly(VA-co-AAc) hydrogels

Reaction was carried out with 1 g of psyllium husk, definite amount of PVA, initiator, monomer and crosslinker, taken in the aqueous reaction system placed in water bath at 65 °C temperature for 3 h. After that polymer was stirred in distilled water to remove the soluble fractions and then was dried in oven at 40 °C. The hybrid crosslinked polymers were named as of psy-*cl*-poly(VA-*co*-AAc) hydrogels. The optimum reaction parameters were evaluated for synthesis of hydrogels by varying the PVA from 1 to 5% (w/v), AAc from 14.57×10^{-2} to 72.86×10^{-2} mol/L, NN-MBA from 6.48×10^{-3} to 45.40×10^{-3} mol/L and APS from 4.38×10^{-3} to 21.91×10^{-3} mol/L. These conditions were determined on the basis of swelling of the hydrogels and surface consistency maintained by these hydrogels after 24 h swelling. The optimum concentration of AAc, PVA, NN-MBA and APS for the synthesis of hydrogels was found to be 14.57×10^{-2} mol/L, 2% (w/v), 32.43×10^{-3} mol/L and 21.91×10^{-3} mol/L respectively (Table 1). At the optimum reaction parameters, further polymers were synthesized and were used to study the effect of pH, salt concentration and temperature on the swelling. These composite polymer matrices were also used to study the release dynamics of the drug from the hydrogel for the evaluation of drug release mechanism and various diffusion coefficients.

2.3. Characterizations

The polymers were characterized by SEMs, FTIR and swelling studies. To investigate and compare the surface morphology of psyllium and psyllium crosslinked polymers, SEMs were taken on Jeol Steroscan 150 Microscope (Japan). FTIR spectra of polymers were recorded in KBr pellets on Nicolet 5700FTIR THERMO (USA). Swelling studies of the polymeric networks were carried out in distilled water by gravimetric method (Singh, 2007).

2.4. Release dynamics of model drugs from the 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 carried out as discussed in our earlier study (Singh, 2007). The concentration of the drug in the sample solution was read from the graph as the concentration corresponding to the absorbance of the solution. The calibration graphs for model drug tetracycline hydrochloride were prepared at λ_{max} 357 nm, 359 nm and 368 nm respectively for release in distilled

Table 2
Results of diffusion exponent '*n*', gel characteristic constant '*k*' and various diffusion coefficients for the swelling of psyllium-*cl*-poly(VA-*co*-AAc) 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 [AAc] × 10^2 (mol/L)						
1	14.57	0.648	9.627	43.14	735.97	49.47
2	29.14	0.631	10.902	45.54	785.06	52.04
3	43.71	0.595	14.138	70.29	1187.83	80.33
4	58.28	0.593	14.122	63.61	1081.88	72.82
5	72.86	0.541	19.503	58.19	1047.50	69.62
Effect of PVA contents (%, w/v)						
6	0.1	0.733	10.032	57.55	505.39	48.56
7	0.2	0.752	6.337	56.28	709.41	53.82
8	0.3	0.692	8.610	42.06	599.27	42.99
9	0.4	0.683	8.111	57.66	948.43	63.76
10	0.5	0.648	9.627	43.14	735.97	49.47
Effect of [NN-MBA] × 10^3 (mol/L)						
11	19.46	0.648	16.241	31.74	338.59	29.11
12	25.95	0.694	12.153	40.24	394.01	35.44
13	32.43	0.752	6.337	56.28	709.41	53.82
14	38.92	0.707	7.623	20.99	308.29	21.85
15	45.40	0.713	7.889	21.59	292.67	21.44
Effect of [APS] × 10^3 (mol/L)						
16	4.38	0.640	9.777	32.19	602.45	38.12
17	8.76	0.664	11.153	54.42	756.41	54.78
18	13.15	0.747	7.930	92.37	931.08	80.62
19	17.53	0.649	11.223	33.36	501.69	35.15
20	21.91	0.752	6.337	56.28	709.41	53.82

water, pH 2.2 buffer and pH 7.4 buffer solution.

2.4.1. Drug loading to the polymer matrix

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 for 24 h at 37 °C and then were dried to obtain the release device.

2.4.2. Drug release from polymer matrix

In vitro release studies of the drug were carried out by placing dried and 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 amount of drug released was measured directly spectrophotometrically.

2.5. Mechanisms of swelling and drug release

The mechanism of swelling and drug release has been discussed in detailed in our earlier study (Singh, 2007). Swelling of the polymers and the drug release profile from the polymer have 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 (Alfrey et al., 1966; Peppas and Korsmeyer, 1987; Ritger and Peppas, 1987a,b). In case of water uptake, the weight gain, M_s, is described by Eq. (1):

$$M_s = kt^n \tag{1}$$

where k and n are constants. Normal Fickian diffusion is characterized by $n = 0.5$, while Case II diffusion by $n = 1.0$. A value of n between 0.5 and 1.0 indicates a mixture of Fickian and Case II diffusion, which is usually called non-Fickian or anomalous diffusion. Ritger and Peppas have shown that the above power law expression could be used for the evaluation of drug release from swellable systems (Ritger and Peppas, 1987a,b). In this case, M_t/M_∞ replace M_s in above equation to give Eq. (2):

$$\frac{M_t}{M_\infty} = kt^n \tag{2}$$

For cylindrical shaped hydrogels, the initial diffusion coefficients (D_i), average diffusion coefficients D_A and late diffusion coefficients (D_L) have been calculated from the Eqs. (3), (4) and (5) respectively:

$$\frac{M_t}{M_\infty} = 4\left(\frac{Di\, t}{\pi \ell^2}\right)^{0.5} \tag{3}$$

$$D_A = \frac{0.049\ell^2}{t^{1/2}} \tag{4}$$

$$\frac{M_t}{M_\infty} = 1 - \left(\frac{8}{\pi^2}\right) \exp\left[\frac{(-\pi^2 DL\, t)}{\ell^2}\right] \tag{5}$$

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 is the initial diffusion coefficient and 'ℓ' is the thickness of the sample. $t^{1/2}$ is the time required for 50% release of drug. The values of diffusion coefficients have been evaluated for the swelling of the polymers and for the release of the drug from the polymer and results are presented in Tables 2–4.

3. Results and discussion

3.1. Mechanism of the chemically crosslinked polymerization

This polymerization reaction is an example of free radical initiated graft copolymerization, in which APS is used as thermal initiator. Homolytic cleavage of peroxide bond (–O–O–) in the APS provides $(SO_4)^{\bullet -}$ radical anion [step (i)], which reacts with water to form hydroxyl radical [step (ii)]. These radicals have initiated the process of polymerization by generating the free radicals on the psyllium, PVA and AAc [steps (iii), (iv) and (v)] (Lakouraj et al., 2005; Singh and Sharma, 2009). During propagation, grafting of poly(AAc) onto psyllium and PVA has occurred and has formed grafted macrobiradicals I and II [step (ix) to (xii)]. In the presence of the crosslinker NN-MBA, because of its multifunctional nature, macro radicals get formed that have four reactive sites and these sites can be linked with the radicals on the psyllium, PVA and

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

S. no.	Parameter	Diffusion exponent, '*n*'	Gel characteristic constant, '*k*' $\times 10^3$	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	0.575	31.383	72.01	671.64	73.44
2	2.2 pH buffer	0.836	7.021	155.40	917.48	122.36
3	Distilled water	0.752	6.337	56.28	709.41	53.82
Effect of [NaCl]						
4	0.9% NaCl solution	0.718	10.214	54.56	530.41	47.18
5	Distilled water	0.752	6.337	56.28	709.41	53.82
Effect of temperature						
6	27 °C	0.699	8.230	34.36	470.82	34.58
7	37 °C	0.752	6.337	56.28	709.41	53.82

poly(AAc) [steps (xiii) and (xiv)]. This will lead to the formation of three-dimensional networks which are named as psy-*cl*-poly (VA-*co*-AAc) hydrogels/polymers [step (xv)]. The plausible proposed mechanism for the synthesis of psy-*cl*-poly (VA-*co*-AAc) hydrogels is given in Scheme 1.

3.2. Characterizations

3.2.1. Scanning electron micrography (SEM)

SEMs of psyllium, PVA and psy-*cl*-poly(VA-*co*-AAc) hydrogels are shown in Fig. 1(1)–(3) respectively. It is observed from the SEMs that the psyllium has smooth and homogeneous morphology whereas modified psyllium has shown structural heterogeneity. The crosslinked networks have been observed in the SEMs of the hydrogels

3.2.2. FTIR spectra

FTIR spectra of psyllium, PVA and psy-*cl*-poly(VA-*co*-AAc) polymers are presented in Fig. 2(1)–(3) respectively. In case of psyllium polysaccharide the absorption band has been observed at 3430.6 cm^{-1} due to –OH stretching along with some complex bands in the region 1200–1300 cm^{-1} due to C–O 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 cm^{-1} and 785–730 cm^{-1} have also been observed due to vibrational modes of pyranose rings of polysaccharide. In 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 at 2854 cm^{-1} is attributed to the stretching vibration of $-CH_2$. The band at 1461.1 cm^{-1} is due to C–H bending vibration has been observed. In the FTIR spectra of psy-*cl*-poly(VA-*co*-AAc) polymer, the broad band at 3376.9 cm^{-1} due to –OH stretching, band at 1727 cm^{-1} due to C=O stretching of the carboxylic group present in the networks and band at 1252.3 cm^{-1} due to C–O stretching coupled with O–H in plane bending have been observed apart from usual bands in psyllium and PVA. In addition, the absorption bands in the region 1190–1075 cm^{-1} is due to C–O stretching of carboxylic moiety.

3.2.3. Swelling studies

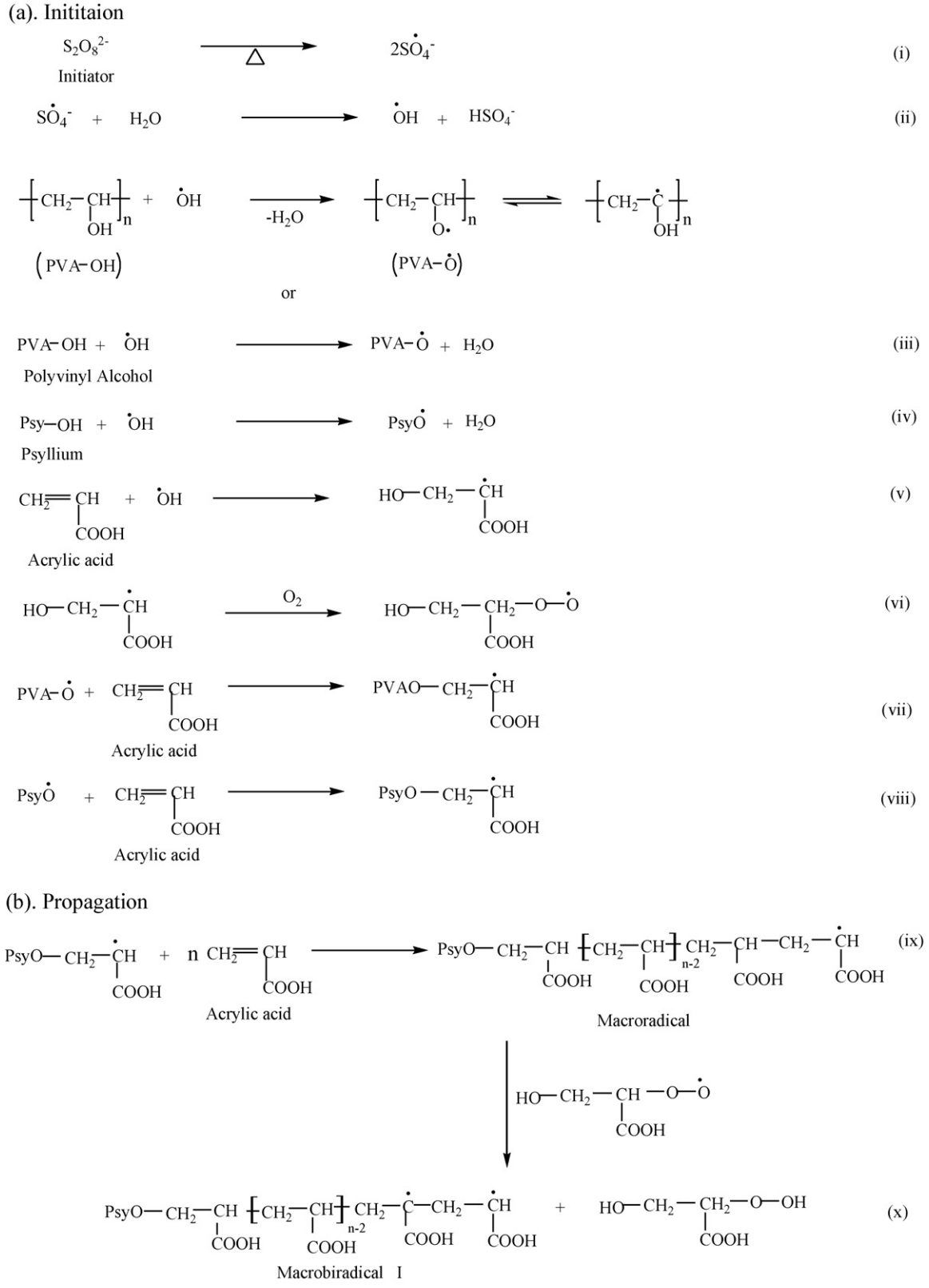
In order to study the effect of synthetic reaction parameters (i.e. concentration of AAc, PVA, NN-MBA, APS) on the structure of the polymeric networks, swelling studies of the polymers were carried out at 37 °C in distilled water. Effect of nature of swelling medium on the swelling of the hydrogels was also studied.

3.2.3.1. Swelling as a function of feed [AAc]. In order to determine the effect of feed monomer concentration on the network structure and crosslinking density, the polymers were prepared with different monomer concentration and their swelling was taken. Polymers were prepared by varying the concentration of acrylic acid from 14.57×10^{-2} to 72.86×10^{-2} mol/L. The results of swelling of the hydrogels are presented in Fig. 3(1). It is observed from the figure that swelling of the polymers decreased, as the concentration of feed monomer increased during the synthesis of hydrogels. It means that polymers prepared with higher monomer concentration have higher crosslinking density in the networks. This may be due to the increase in grafting and self crosslinking of the poly(AAc) onto psyllium and PVA. It is worthy to mention here that during the synthesis of hydrogels, when the AAc concentration was varied, the all other contents, that is, amount of PVA, psyllium, NN-MBA, APS and water were kept constant in the reaction system. After 24 h maximum (7.608 ± 0.275) g water uptake occurred in per gram of gel prepared with 14.57×10^{-2} mol/L of AAc. This concentration has been taken as the optimum for further synthesis of the polymer networks.

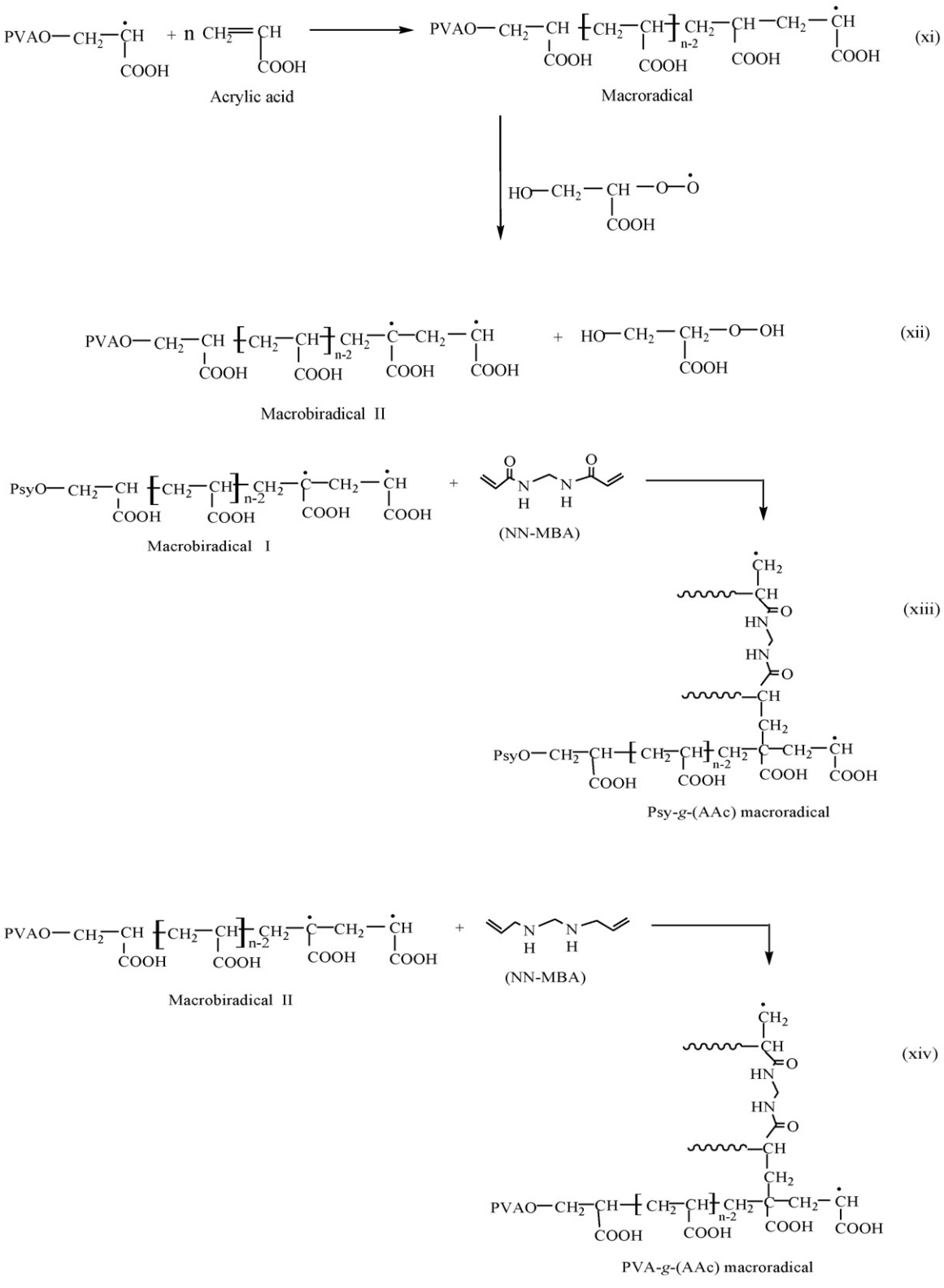
The values of diffusion exponent '*n*' and gel characteristics constant 'k' have been evaluated from the slope and intercept of the plot $\ln(M_t/M_\infty)$ versus $\ln t$ and results are presented in Table 2. The results show that the values of '*n*' are between 0.5 and 1 which indicate that swelling of the polymers prepared with different monomer concentration 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 rate of diffusion of water in the hydrogels was higher in the early stages of swelling. It is clear from table that the values of late diffusion coefficients are very much less than the early stage diffusion coefficients. In the earlier stages of swelling, the higher swelling rate may be explained on the basis of polymer chains relaxation in the hydrogels. When a glassy hydrogel is brought into contact with water, water diffuses into the hydrogel and the network expands, resulting in swelling of the hydrogel. Diffusion involves migration of water into pre-existing or dynamically formed spaces between hydrogel chains. Swelling of the hydrogel involves increase in segmental motion which ultimately increases the separation between hydrogel chains. 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 is about to reach, the rate of swelling decreases, which is reflected in their lower values of late diffusion coefficients (Table 2).

3.2.3.2. Swelling as a function of feed [PVA]. At the optimum [AAc], the amount of feed PVA was varied from 1 to 5% (w/v) during the synthesis of hydrogels and swelling was taken (Fig. 3(2)). It is clear from the figure that after 24 h, swelling of polymers first increased and then decreased with increase in feed PVA content. It means that certain minimum concentration of PVA is required to form the optimum pore size in the polymer network. At higher PVA concentration the crosslinking increased which decreases the pore size

and swelling thereafter. In literature it is reported in one study that the degree of gelation has been affected by the presence of different reacting species in the reaction system during the synthesis of hydrogels. The degree of gelation increased as chitosan, AAc and PVA content increased while the degree of gelation decreased with the increase of gelatin content (Sokker et al., 2009). Swelling of the polymers prepared with different amount of PVA has been occurred through non-Fickian diffusion mechanism (Table 2). The values of various diffusion coefficients are presented in Table 2. In this case, trends are similar as obtained in case of AAc variation.

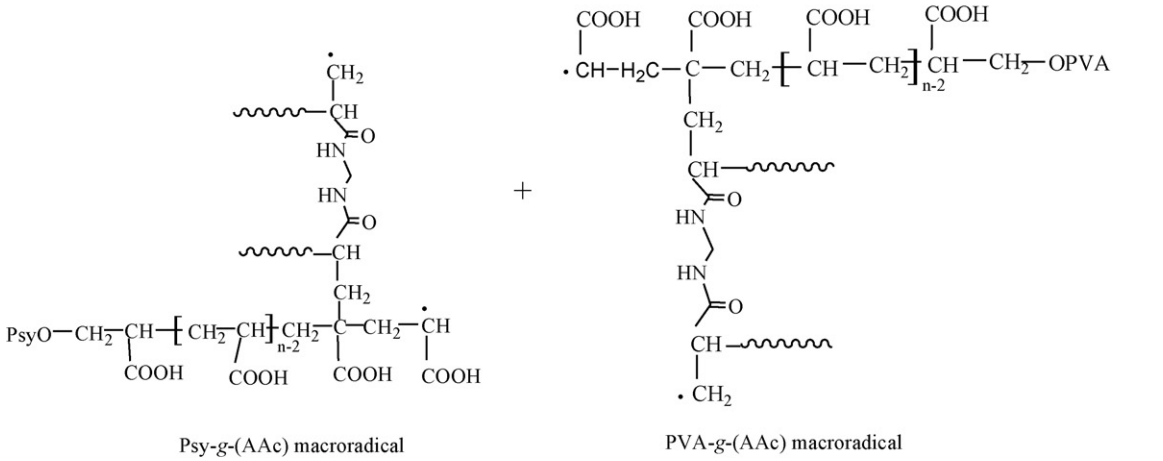


Scheme 1. Mechanism for the synthesis of psyllium-*cl*-poly(VA-*co*-AAc) hydrogels (Singh and Sharma, 2009).

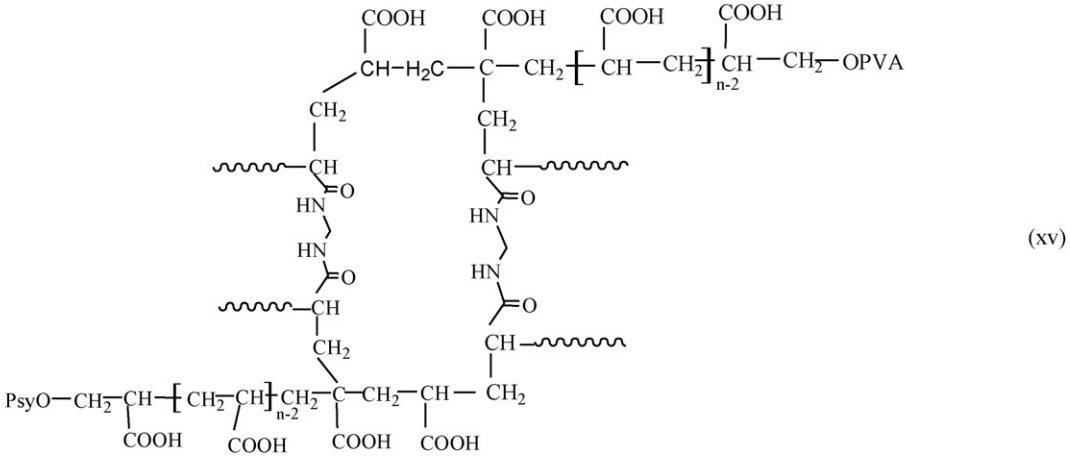


Scheme 1. (*Continued*)

(c). Termination



Psy-*g*-(AAc) macroradical + PVA-*g*-(AAc) macroradical



(xv)

Psy-*cl*-poly (VA-*co*-AAc) network

Scheme 1. (*Continued*).

3.2.3.3. Swelling as a function of feed [NN-MBA]. Effect of crosslinker concentration on the network density was studied by taking the swelling of the polymers prepared with different NN-MBA concentration. The polymers were prepared by varying the crosslinker concentration from 6.48×10^{-3} to 45.40×10^{-3} mol/L. The results of swelling are presented in Fig. 3(3). The hydrogels formed below the 25.95×10^{-3} mol/L were not stable and degradation started during the swelling. So decrease in swelling has been observed for the polymers prepared at lower crosslinker concentration and this decrease is due to the decrease in weight of polymer matrix due to matrix degradation. This polymer matrix degradation is due to poor gelation. In gels, concentration of crosslinker plays an important role in formation of the polymer networks. In dilute solution, the long chain polymer molecules are in the form of coils, each having certain mobility. As the concentration increases, the mobility of coils decreases. At a critical concentration, known as gel point, the coils no longer move as units and can no longer interchange their places. Even though all of polymerizing material still exists as monomers, dimers, trimers, and so forth, a three-dimensional network will appear. After the gel point is reached, more and more of these loose groups become attached to network. The transition from a concentrated solution to a gel corresponds to the transition of a liquid to a solid. In general, the formation of hydrogel network occurs by crosslinking in the existing polymer chain. Hence for the further synthesis of hydrogels, the optimum concentration of crosslinker has been taken as 32.43×10^{-3} mol/L. The swelling decreased with further increase in crosslinker concentration in the reaction system. This may be due to increase in crosslinking after forming the polymer matrix of optimum pore size. The values of diffusion exponent '*n*' and gel characteristic constant '*k*' have been

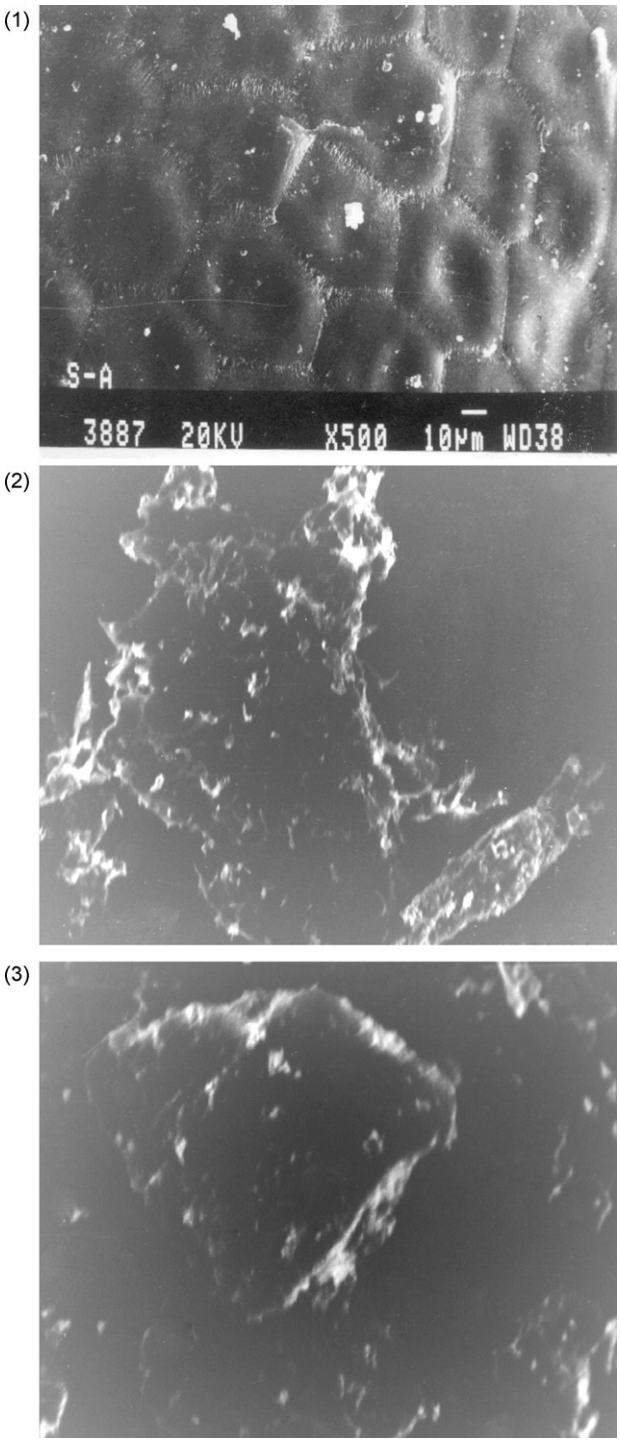


Fig. 1. (1) Scanning electron micrograph of psyllium. (2) Scanning electron micrograph of PVA [magnification = 250×]. (3) Scanning electron micrograph of psyllium-*cl*-poly(VA-*co*-AAc) [magnification = 450×].

evaluated and results are presented in Table 2. In most of the cases, when the polymers were prepared with different crosslinker concentration, the values of diffusion exponent '*n*' have been observed between 0.5 and 1, which indicate non-Fickian diffusion mechanism for the swelling. The values of diffusion coefficients are presented in Table 2.

3.2.3.4. Swelling as a function of initiator. The polymers were prepared by varying the [APS] from 4.38×10^{-3} to 21.91×10^{-3} mol/L and swelling of the polymers was taken (Fig. 3(4)). From the swelling trends it is observed that swelling first increased and then decreased with increase in feed [APS] during the synthesis of hydrogels. Initiator plays a very important role in controlling the chain length and molecular weight of the polymers which determine the network density in the hydrogels. The values of diffusion exponent '*n*' and gel characteristics constant '*k*' have been evaluated and results are presented in Table 2. The values of '*n*' have been observed between 0.5 and 1 which indicates swelling occurred through non-Fickian diffusion mechanism. The values of diffusion coefficients are presented in Table 2.

3.2.3.5. Swelling as a function of pH of swelling medium. At the optimum reaction conditions, further polymers were synthesized and were used to study the swelling kinetics in different swelling media. In the present case, the swelling of polymeric networks was taken in pH 2.2 buffer, pH 7.4 buffer and distilled water (Fig. 3(5)). Swelling has been observed more in pH 2.2 buffer (9.4 g/g of gel) than in pH 7.4 buffer (7.1 g/g of gel) solution. Normally hydrogels based on poly(AAc) show more swelling at higher pH due to ion–ion repulsion of $-COO^-$ moieties present in the hydrogels. In the present case, initially the swelling has been observed higher in pH 7.4 buffer then pH 2.2 buffer and after that swelling decreased in the pH 7.4 buffer this might be due to the presence of very less poly(AAc) contents in the polymer matrix as compared to the psyllium and also due to the hindrance provided by PVA for these types of repulsions.

This matrix has been prepared by using the 1 g of psyllium, 2% (w/v) solution of PVA and 1% (v/v) AAc. It is the novelty of the present work that very little amount of petroleum product has been used to prepare the hydrogels. This will make it cost effective, biodegradable and biocompatible. Here the 2% PVA and 1% AAc have provided the sufficient strength to the hydrogels which is required to deliver the drug to the GIT tract in controlled and sustained manner. However, the hydrogels were not formed under these optimum conditions when only AAc or PVA has been used without psyllium. In the present case the hydrogels have been prepared in the presence of PVA with psyllium:AAc ratio (1:0.1) (w:v) whereas in our earlier study the hydrogels were prepared with psyllium:AAc (1:1) (w:v) ratio without PVA and have showed more swelling and drug release in pH 7.4 buffer (Singh et al., 2008). In the present case, the PVA has provided sufficient strength to the polymer matrix for its use in drug delivery system (Pal et al., 2008). It is relevant to mention here that the appropriate strength of the hydrogel is required which are 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. In an ideal case scenario, such a profile can be achieved by use of the polymer matrix have sufficient strength to deliver the drug.

At the same time, the design of new materials based on blends of biological and synthetic polymers producing new processable polymeric materials that hopefully possess both good mechanical properties and biocompatibility. In the present case hydrogels of psyllium/AAc have been prepared in the presence of PVA. It is reported in the literature that the addition of carboxylic groups along the PVA chains had a positive effect on the miscibility degree of the synthetic component with the biological one (Cristallini et al., 2001; De Lima et al., 2009; Barbani et al., 2005). Association of poly(carboxylic acids) and non-ionic polymers in solutions via hydrogen bonding results in formation of novel polymeric materials–interpolymer complexes. These materials can potentially be used for design of hydrogels for various biomedical applications.

Swelling of hydrogels in different medium occurred through non-Fickian diffusion mechanism. The values of the diffusion coefficients have been presented in Table 3. The values of earlier stages

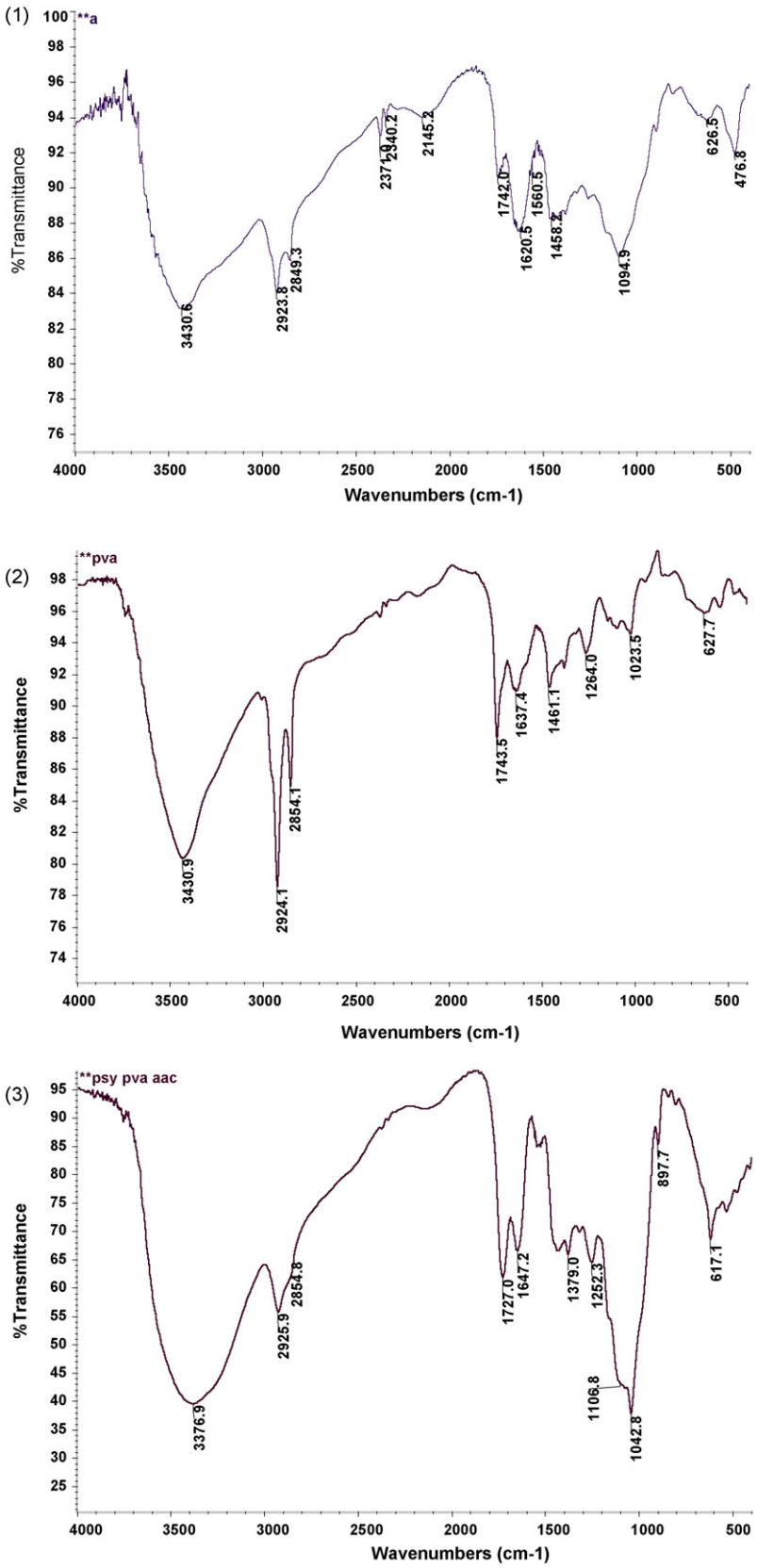


Fig. 2. (1) FTIR spectra of psyllium. (2) FTIR spectra of PVA. (3) FTIR spectra of psyllium-*cl*-poly(VA-*co*-AAc) polymer.

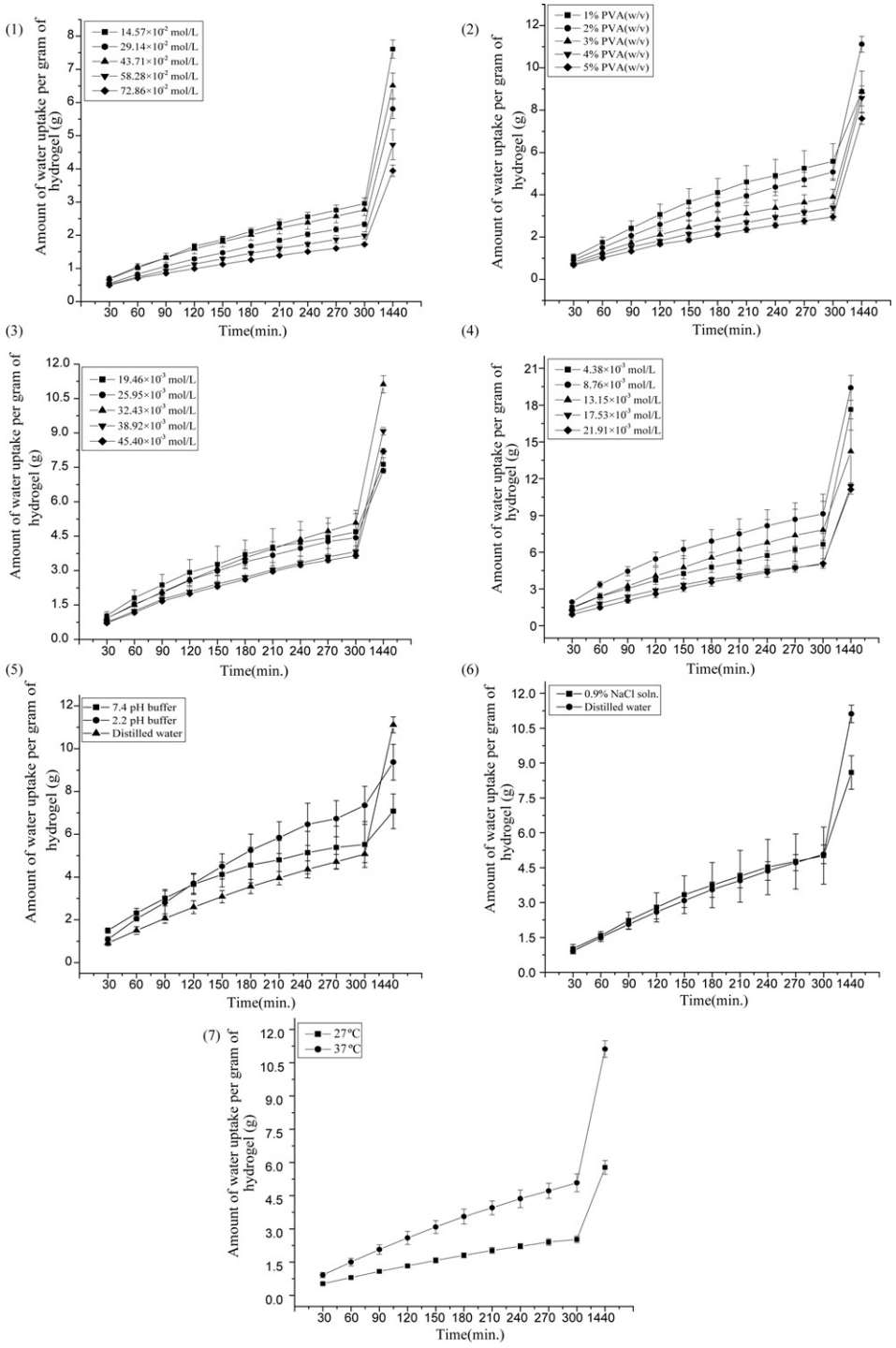


Fig. 3. (1) Effect of [AAc] on swelling kinetics of psyllium-*cl*-poly(VA-*co*-AAc) hydrogels in distilled water at 37 °C {reaction time = 3 h, reaction temp. = 65 °C, psyllium = 1 g, PVA = 5% (w/v), [APS] = 21.91 × 10^{-3} mol/L, [NN-MBA] = 32.43 × 10^{-3} mol/L, and water = 10 mL}. (2) Effect of PVA content on swelling kinetics of psyllium-*cl*-poly(VA-*co*-AAc) hydrogels in distilled water at 37 °C {reaction time = 3 h, reaction temp. = 65 °C, psyllium = 1 g, [AAc] = 14.57 × 10^{-2} mol/L, [APS] = 21.91 × 10^{-3} mol/L, [NN-MBA] = 32.43 × 10^{-3} mol/L, and water = 10 mL}. (3) Effect of [NN-MBA] on swelling kinetics of psyllium-*cl*-poly(VA-*co*-AAc) hydrogels in distilled water at 37 °C {reaction time = 3 h, reaction temp. = 65 °C, psyllium = 1 g, [AAc] = 14.57 × 10^{-2} mol/L, PVA = 2% (w/v), [APS] = 21.91 × 10^{-3} mol/L, and water = 10 mL}. (4) Effect of [APS] on swelling kinetics of psyllium-*cl*-poly(VA-*co*-AAc) hydrogels in distilled water at 37 °C {reaction time = 3 h, reaction temp. = 65 °C, psyllium = 1 g, [AAc] = 14.57 × 10^{-2} mol/L, PVA = 2% (w/v), [NN-MBA] = 32.43 × 10^{-3} mol/L, and water = 10 mL}. (5) Effect of pH of swelling medium on swelling kinetics of psyllium-*cl*-poly(VA-*co*-AAc) hydrogels at 37 °C {reaction time = 3 h, reaction temp. = 65 °C, psyllium = 1 g, [AAc]=14.57 × 10^{-2} mol/L, PVA = 2% (w/v), [NN-MBA] = 32.43 × 10^{-3} mol/L, [APS] = 21.91 × 10^{-3} mol/L, and water = 10 mL}. (6) Effect of 0.9% NaCl solution on swelling kinetics of psyllium-*cl*-poly(VA-*co*-AAc) hydrogels at 37 °C {reaction time = 3 h, reaction temp. = 65 °C, (1) psyllium = 1 g, [AAc]=14.57 × 10^{-2} mol/L, PVA = 2% (w/v), [NN-MBA] = 32.43 × 10^{-3} mol/L, [APS] = 21.91 × 10^{-3} mol/L, and water = 10 mL}. (6) Effect of 0.9% NaCl solution on swelling kinetics of psyllium-*cl*-poly(VA-*co*-AAc) hydrogels at 37 °C {reaction time = 3 h, reaction temp. = 65 °C, psyllium = 1 g, [AAc] = 14.57 × 10^{-2} mol/L, PVA = 2% (w/v), [NN-MBA] = 32.43 × 10^{-3} mol/L, [APS] = 21.91 × 10^{-3} mol/L, and water = 10 mL}. (7) Effect of temperature of swelling medium on swelling kinetics of psyllium-*cl*-poly(VA-*co*-AAc) hydrogels {reaction time = 3 h, reaction temp. = 65 °C, psyllium = 1 g, [AAc] = 14.57 × 10^{-2} mol/L, PVA = 2% (w/v), [NN-MBA] = 32.43 × 10^{-3} mol/L, [APS] = 21.91 × 10^{-3} mol/L, and water = 10 mL}.

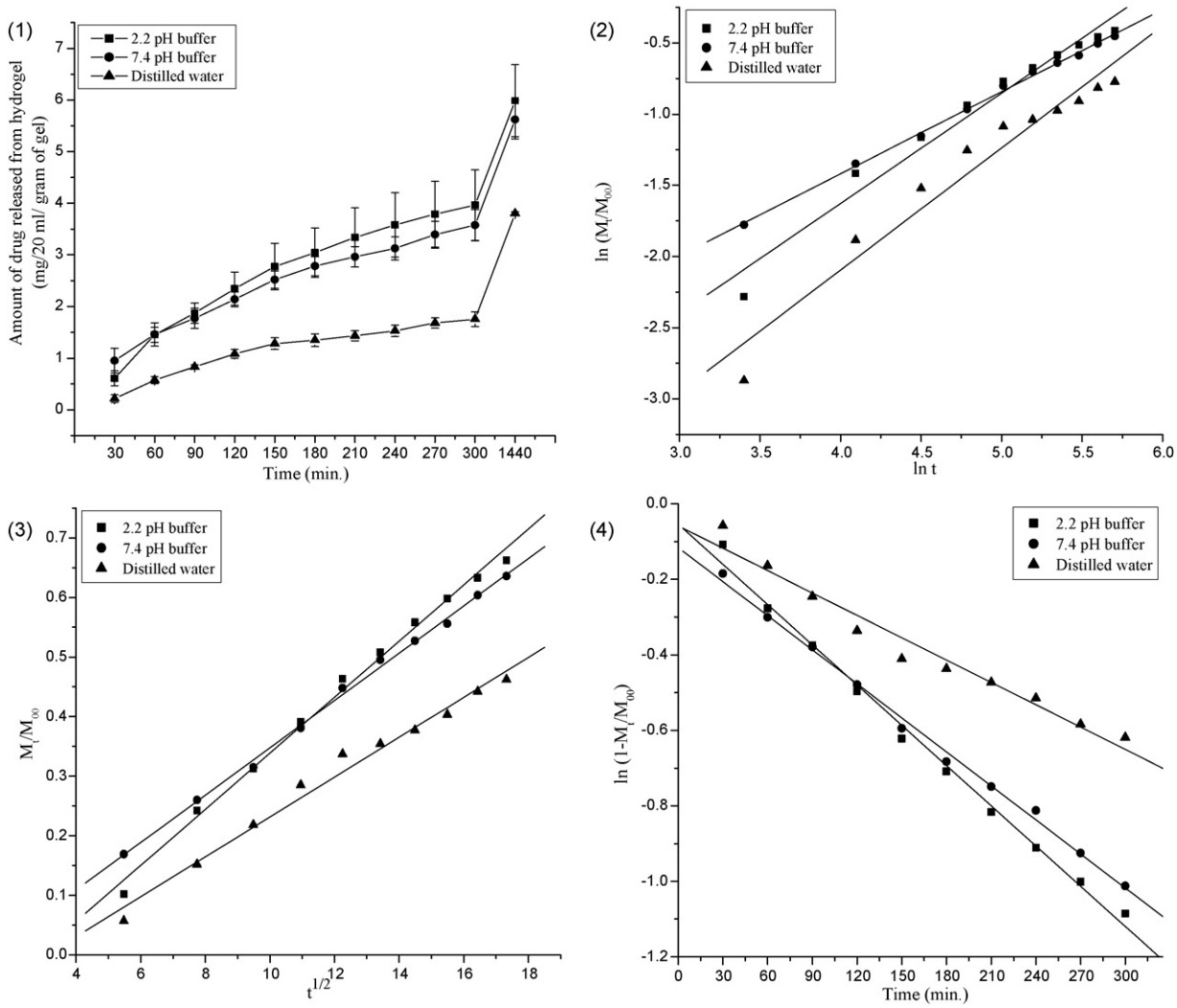


Fig. 4. (1) Release profile of tetracycline HCl from drug loaded psyllium-*cl*-poly(VA-*co*-AAc) hydrogels in different medium at 37 °C {reaction time = 3 h, reaction temp. = 65 °C, psyllium = 1 g, [AAc] = 14.57×10^{-2} mol/L, PVA = 2% (w/v), [NN-MBA] = 32.43×10^{-3} mol/L, [APS] = 21.91×10^{-3} mol/L, and water = 10 mL}. (2) Plot of $\ln(M_t/M_\infty)$ versus $\ln t$ for the evaluation of diffusion exponent '*n*' and gel characteristics constant '*k*' for the release of tetracycline HCl from drug loaded psyllium-*cl*-poly(VA-*co*-AAc) hydrogels in different medium at 37 °C. (3) Plot of M_t/M_∞ versus $t^{1/2}$ for the evaluation of initial and average diffusion coefficients (D_i and D_A) for the release of tetracycline HCl from drug loaded psyllium-*cl*-poly(VA-*co*-AAc) hydrogels in different medium at 37 °C. (4) Plot of $\ln(1 - M_t/M_\infty)$ versus time for the evaluation of late time diffusion coefficient 'D_L' for the release of tetracycline HCl from drug loaded psyllium-*cl*-poly(VA-*co*-AAc) hydrogels in different medium at 37 °C.

Table 4
Results of diffusion exponent '*n*', gel characteristic constant '*k*' and various diffusion coefficients for the release of tetracycline HCl from drug loaded psyllium-*cl*-poly(VA-*co*-AAc) hydrogels.

Drug releasing 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	0.774	8.884	70.27	589.27	58.19
pH 7.4 buffer	0.576	24.149	45.42	517.70	44.63
Distilled water	0.858	3.989	39.36	486.54	35.75

diffusion coefficients have been obtained higher than late diffusion coefficients (Table 3). It means that in the initial stages the rate of diffusion of water has been higher than the later stages.

3.2.3.6. Swelling of hydrogels in 0.9% NaCl solution. It is important to understand the osmotic and structural changes of polymeric networks, induced by addition of salt in the swelling medium with respect to many physical and chemical processes in biological system. The water uptake by the hydrogels in 0.9% NaCl solution has been less observed as compared to the distilled water (Fig. 3(6)). Maximum water uptake after 24 h has been observed (8.594 ± 0.717) and (11.117 ± 0.377) g/g of hydrogel in 0.9% NaCl solution and distilled water respectively. Hydrogels do not swell appreciably in the presence of electrolyte salt due to ex-osmosis and even the swollen hydrogels shrink dramatically in the presence of salts. The swelling of hydrogels has been occurred through non-Fickian diffusion mechanism in 0.9%

NaCl solution. The values of diffusion coefficients are presented in Table 3.

3.2.3.7. Swelling of hydrogels as a function of temperature. Effect of temperature of the swelling medium on the swelling of the hydrogels was studied by taking the swelling at 27 °C and 37 °C in distilled water. Results of swelling are presented in Fig. 3(7). 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 and increase in rate of diffusion of solvent molecules with increase in temperature of the swelling medium. The values of diffusion exponent '*n*' have been observed 0.699 and 0.752 respectively at 27 °C and 37 °C swelling. 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 3).

3.3. Release dynamics of the drug in different medium

The polymer used to study the *in vitro* release dynamics of the model drug were synthesized at the optimum reaction conditions. The release profile of the tetracycline HCl from the drug loaded polymer matrix in different release medium at 37 °C is presented in Fig. 4(1). The release of drug from the drug loaded polymer has been more observed in pH 2.2 buffer solution. This may be due to the more solubility of tetracycline HCl in pH 2.2 buffer. 50% of total release of drug in pH 2.2 buffer, pH 7.4 buffer and distilled water occurred in 180.58 min, 192.77 min and 324.72 min respectively. The values of diffusion exponent '*n*' and gel characteristic constant '*k*' for the release of drug from drug loaded hydrogels in different pH have been evaluated from the slope and intercept of the plot $\ln M_t/M_\infty$ versus $\ln t$ (Fig. 4(2)) and result are presented in Table 4. The release of drug from polymer matrix occurred through non-Fickian type of diffusion mechanism. In non-Fickian diffusion the rate of diffusion of drug from the polymer matrix is comparable to rate of polymer chain relaxation. The values of the various diffusion coefficients have been obtained from the plots given in Fig. 4(3) and (4) and values are presented in Table 4. The values obtained for the earlier stages diffusion coefficients have been obtained higher than the later diffusion coefficients. It means that in the earlier stages the rate of diffusion of tetracycline was higher than the later stages. This may be due to the concentration gradient. In fact this is very important observation for the design of controlled drug delivery system, where the after maintaining certain concentration, drug has to be release in controlled manner.

Hence, the release of antibiotic drug from this drug delivery system may be used for the antibiotic therapy of peptic ulcer developed through *Helicobacter pylori*. *H. pylori* is a Gram-negative, micro-aerophilic bacterium that can inhabit various areas of the stomach and duodenum. It causes a chronic low-level inflammation of the stomach lining and is strongly linked to the development of duodenal and gastric ulcers and stomach cancer. Once *H. pylori* is detected in patients with a peptic ulcer, the normal procedure is to eradicate it and allow the ulcer to heal. The standard first-line therapy is a one-week triple therapy consisting of the antibiotic clarithromycin, and a proton pump inhibitor such as omeprazole. In the present study we have taken model antibiotic drug tetracycline HCl. It is reported in literature tetracycline continues to be an effective and inexpensive component of *H. pylori* eradication regimens (Al-Qurashi et al., 2001).

4. 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 AAc, PVA, NN-MBA and APS concentration in the reaction system. Swelling of hydrogels and release of tetracycline HCl from the drug loaded hydrogels have been observed more in pH 2.2 buffer as compared to the pH 7.4 buffer. Hence, the release of model antibiotic drug tetracycline HCl from the present drug delivery system may be used for the antibiotic therapy of peptic ulcer developed through *H. pylori*. The swelling and release of drug occurred through non-Fickian diffusion mechanism. The values obtained for the earlier stages diffusion coefficients have been obtained higher than the later diffusion coefficients for the release of drug from the hydrogels.

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