Available online at www.sciencedirect.com
ScienceDirect
Carbohydrate Polymers 73 (2008) 446–455
Carbohydrate Polymers
www.elsevier.com/locate/carbpol

Radiation crosslinked psyllium and polyacrylic acid based hydrogels for use in colon specific drug delivery

Baljit Singh *, Nirmala Chauhan, S. Kumar

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

Received 27 October 2007; received in revised form 2 December 2007; accepted 13 December 2007
Available online 23 December 2007

Abstract

In order to utilize the psyllium husk, a medicinally important natural polysaccharide, to develop the hydrogels meant for the drug delivery, we have prepared psyllium and polyacrylic acid based polymeric networks by radiation-induced crosslinked copolymerization. Polymeric networks (hydrogels) thus formed were characterized with SEMs, FTIR and swelling studies. Swelling behavior of the hydrogels was studied as a function of monomer concentration in the hydrogels and temperature, pH and [NaCl] of the swelling medium. This paper discusses the swelling kinetics of the hydrogels and release dynamics of anticancer model drug 5-fluorouracil from the hydrogels for the evaluation of swelling and drug release mechanisms. It has been observed from the release dynamics of drug that diffusion exponent 'n' have 0.7, 0.8 and 0.7 values and gel characteristics constant 'k' have 9.13×10^{-3}, 6.22×10^{-3} and 9.01×10^{-3} values for the release of 5-fluorouracil, respectively, in distilled water, pH 2.2 buffer and pH 7.4 buffer. The values of the diffusion exponent show that the release of drug from drug-loaded hydrogels has occurred through Non-Fickian diffusion mechanism. It has also been observed from the swelling and release of drug in the different pH buffer that the polymer matrix is pH responsive and can be exploited for the delivery of anticancer drug to the colon.

Keywords: Copolymerization; Drug delivery; pH responsive hydrogels; Functionalization; Psyllium

1. Introduction

Grafting and crosslinking are common practice to improve the functional properties of polysaccharides and are carried out by chemical initiation (Mostafa & Morsy, 2004) or radiation initiation polymerization (Karadag, Saraydin, & Güven, 2001; Saraydin, Karadag, & Güven, 1997, 1995a, 1995b). In case of chemical initiated copolymerization, sometime initiator and crosslinking agent left in the polymeric networks which affect structural homogeneity, swelling behavior and mechanical properties of the hydrogels. In order to prepare the hydrogels for technological important applications the network should be free from these impurities. This can be achieved by synthesizing the polymers through irradiation-induced copolymerization (Rosiak, Burczak, Czolozynska, & Pekala, 1983). Graft copolymerization of vinyl monomers onto polysaccharides has been carried out by a simultaneous irradiation technique using gamma-rays as the initiator (Abdel-Aal, Gad, & Dessouki, 2006) and reaction has been controlled by incorporating a homopolymer-inhibiting agents (Khan, 2005). Percentage grafting increases with increase in the monomer concentration and total dose (Huang, Shen, Sheng, & Fang, 2005) and it affects the mechanical and thermal properties of the polymers. El-Hag Ali and coworkers have carried out the acrylic acid/vinyl sulfonic acid based copolymerization by using γ-radiation and have observed that the comonomer composition and irradiation dose affects the swelling property of the hydrogels (El-Hag Ali, Abd El-Rehim, Hegazy El-Sayed, & Ghobashy, 2006). The hydrogels prepared by the irradiation have been used to study the release of anticancer drug and diffusion of 5-fluorouracil (5-FU) solution from the hydrogels has been found the

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

0144-8617/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carbpol.2007.12.009

Non-Fickian type (Taşdelen, Kayaman-Apohan, Güven, & Baysal, 2005). The in vitro release dynamics of the drug from the hydrogels is not only dependent upon the extent of crosslinking, but also on the amount of drug loaded, method of drug loading and pH of the release medium (Soppimath, Kulkarni, & Aminabhavi, 2000; Soppimath & Aminabhavi, 2002).

Cancer of the colon is a major health problem which can develop with other conditions, such as ulcerative colitis, a chronic inflammation in the colon. Diets that include wheat bran in combination with psyllium is an effective means of reducing colon cancer risk in human populations addicted to high-risk western diets (Alabaster, Tang, Frost, & Shivapurkar, 1993, 1996). The presence of *n*-butyrate in the distal colon may be important in the prevention of colon cancer because the majority of tumors in both human and experimentally induced rodent cancer models occur in the distal colon (Bufill, 1990; Holt, Mokulo, Distler, Liu, & Reddy, 1996). *n*-Butyrate possesses anti-neoplastic effects in human colon carcinoma cells and it exerts a concentration-dependent slowing of the rate of cancer cell proliferation and promotes expression of differentiation markers in vitro (Kim et al., 1980; Whitehead, Young, & Bhathal, 1986), and leading to reversion of cells from a neoplastic to a nonneoplastic phenotype (Wilson, 1989). Also, fecal *n*-butyrate concentration of patients with colorectal cancer has been reported to be lower than those of healthy controls (Weaver, Krause, Miller, & Wolin, 1988). The end products of microbial carbohydrate fermentation in the large bowel include short-chain fatty acids (SCFA), among which acetate, propionate and *n*-butyrate are quantitatively most important (Cummings, 1981; Cummings, Beatty, Kingman, Bingham, & Englyst, 1996, 1987; Pouillart, 1998). Psyllium delayed the fermentation rate of high amylose cornstarch in the cecum and shifts the fermentation site of starch toward the distal colon, leading to the higher *n*-butyrate concentration in the distal colon and feces (Morita et al., 1998, Morita, Kasaoka, Hase, & Kiriyama, 1999). Beside its cancer lowering property it has been reported for the treatment of constipation, diabetes, diarrhea, inflammation bowel diseases-ulcerative colitis, obesity in children and adolescents and high cholesterol (Singh, 2007). Psyllium mucilage obtained from the seed coat by mechanical milling/grinding of the outer layer of the seeds and yield amounts to approximately 25% of the total seeds yield. Mucilage is fibrous, hydrophilic and forms the clear colorless mucilaginous gel by absorbing water. Gel-forming fraction of the alkali-extractable polysaccharides composed of arabinose, xylose and traces of other sugars (Fischer, Nanxiong, Ralph, Andersond, & Marletta, 2004).

Keeping in view, the pharmacological importance of psyllium polysaccharides and drug delivery devices based on hydrogels, psyllium, if suitably tailored to prepare the hydrogels, can act as the double potential candidates for the novel drug delivery systems. Therefore, the present study is an attempt, to synthesize psyllium and poly(-AAc) based hydrogels by using radiation-induced cross-linked polymerization and thereafter use as drug delivery devices. Polymeric networks thus formed have been characterized with SEMs, FTIR and swelling studies. Swelling behavior of the hydrogels has been studied as a function of monomer concentration in the hydrogel and temperature, pH and [NaCl] of the swelling medium. This paper discusses the swelling kinetics of the hydrogels and release dynamics of anticancer model drug 5-fluorouracil from the hydrogels for the evaluation of swelling and drug release mechanism from the polymer matrix.

2. Experimental

2.1. Materials and methods

Plantago psyllium mucilage (Psy) was obtained from Sidpur Sat Isabgol factory (Gujarat, India), acrylic acid was obtained from Merck-Schuchardt, Germany. 5-Fluorouracil was procured from Dabur India Ltd.

2.2. Synthesis of psy-cl-poly(AAc)

Reaction was carried out with 1 g psyllium husk and definite concentration of acrylic acid in a test tube. The reaction mixture was irradiated with gamma rays from ^{60}Co gamma chamber for 24 h with total dose of 58.32 kGy. Polymers thus formed were named as psy-*cl*-poly(AAc) and were stirred in distilled water and ethanol for 1 h each to remove the soluble fraction and then were dried in an oven at 40 °C. The optimum reaction parameters were evaluated for the synthesis of psy-*cl*-poly(AAc) by varying the monomer concentration from 2.91×10^{-1} to 14.55×10^{-1} mol/L on the basis of swelling and surface consistency of the polymer after 24 h in distilled water at 37 °C.

2.3. Characterization

Polymers were characterized by SEMs, FTIR spectroscopy and swelling studies. SEMs were taken on Jeol Steroscan 150 Microscope and FTIR spectra of polymers were recorded in KBr pellets on Nicolet 5700FTIR THERMO.

2.4. Swelling kinetics

Swelling kinetics of the polymeric networks was carried out in triplicate by gravimetric method. Known weight of polymers were taken and immersed in excess of water for different time intervals at 37 °C and then polymers were removed, wiped with tissue paper to remove excess of solvent, and weighed immediately. The difference in weight has given the amount of water uptake by the polymers after definite time intervals.

2.5. Release dynamics of drug from psy-cl-poly(AAc)

2.5.1. Preparation calibration curves

In this procedure, the absorbance of a number of standard solutions of the reference substance at concentrations encompassing the sample concentrations were measured on the UV Visible Spectrophotometer (Cary 100 Bio, Varian) at λ_{max} 258 nm and calibration graph was constructed. The concentration of the drug in the sample solution was read from the graph as the concentration corresponding to the absorbance of the solution. Three calibration graphs were made to determine the amount of drug release from the drug-loaded polymeric matrix in distilled water, pH 2.2 buffer and pH 7.4 buffer.

2.5.2. Drug loading to the polymer matrix

The loading of a drug onto 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 than dried to obtain the release device.

2.5.3. 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 at 37 °C temperature. The amount of 5-fluorouracil released was measured spectrophotometrically in distilled water, pH 2.2 buffer and pH 7.4 buffer after every 30 min in each case. The absorbance of the solution of 5-fluorouracil was measured at λ_{max} 258.0 nm.

2.5.4. Preparation of buffer solution

Buffer solution of pH 2.2 was prepared by taking 50 mL of 0.2 M KCl and 7.8 mL of 0.2 N HCl in volumetric flask to make volume 200 mL with distilled water. Buffer solution of pH 7.4 was prepared by taking 50 mL of 0.2 M KH_2PO_4 and 39.1 mL of 0.2 N NaOH in volumetric flask to make volume 200 mL with distilled water (Pharmacopoeia of India, 1985).

2.6. Mechanism and mathematical modeling of drug release from polymer matrix

Based on the relative rate of diffusion of water into polymer matrix and rate of polymer chain relaxation, swelling of the polymers and the drug release profiles from the swelling polymers have been classified into three types of diffusion mechanisms (Alfrey, Gurnee, & Lloyd, 1966; Peppas & Korsmeyer, 1987). These mechanisms are Case I or Simple Fickian Diffusion, Case II Diffusion and Non-Fickian or Anomalous Diffusion (Ritger & Peppas, 1987a, 1987b). In the 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 constant. 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 (Alfrey et al., 1966). Ritger and Peppas showed that the above power law expression could be used for the evaluation of drug release from swellable systems (Ritger & Peppas, 1987a, 1987b). In this case, M_t/M_∞ replace M_s in above equation to give Eq. (2). For cylindrical shaped hydrogels, the initial diffusion coefficients (D_i), average diffusion coefficient D_A and late diffusion coefficients has been calculated from the Eqs. (3)–(5), respectively (Ritger & Peppas, 1987a, 1987b).

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

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

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

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

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 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 polymer and for the release of the drug from the polymer and results are presented in Tables 1 and 2.

3. Results and discussion

A radiation technique has been used for the modification of psyllium with AAc to develop the crosslinked polymeric networks. The free radicals are generated on both psyllium and polyacrylic acid by the irradiation with gamma rays which after crosslinking have formed three dimensional crosslinked networks.

3.1. Characterization

The morphology of psyllium and psy-*cl*-poly(AAc) has been examined by SEMs which are presented in Fig. 1a and b, respectively, for psyllium, and modified psyllium. It has been observed from the SEMs that psyllium has smooth and homogeneous morphology whereas modified psyllium has structural heterogeneity. FTIR spectra of polymeric networks has been recorded to study the modification of psyllium and incorporation of poly(AAc) into the networks. The broad spectrum at 3425.5 cm^{-1} due to —OH stretching indicates association in the polymer. Absorption band due to C=O stretching of carboxylic group has been observed at 1660.3 cm^{-1}, band at 1257.9 cm^{-1} due to C—O stretching coupled with O—H

Table 1
Results of diffusion exponent '*n*', gel characteristic constant '*k*' and various diffusion coefficients for the swelling kinetics of psy-*cl*-poly(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 monomer concentration						
1	2.91×10^{-1} mol/L	0.64	12.29	7.93	12.66	1.22
2	5.82×10^{-1} mol/L	0.51	30.72	6.83	13.19	1.17
3	8.73×10^{-1} mol/L	0.55	24.01	12.12	19.77	1.97
4	11.6×10^{-1} mol/L	0.6	15.26	4.15	9.50	0.74
5	14.55×10^{-1} mol/L	0.52	24.42	8.09	17.11	1.46
Effect of temperature						
1	25 °C	0.5	23.55	3.87	10.97	0.96
2	37 °C	0.6	15.26	4.15	9.50	0.74
Effect of pH						
1	Distilled water	0.6	15.26	4.15	9.50	0.74
2	pH 2.2 buffer	0.5	24.15	4.91	11.1	0.91
3	pH 7.4 buffer	0.7	6.95	3.88	8.65	0.70
Effect of [NaCl]						
1	Distilled water	0.6	15.26	4.15	9.50	0.74
2	0.9% NaCl	0.5	23.49	4.85	11.06	0.90

Table 2
Results of diffusion exponent '*n*', gel characteristic constant '*k*' and various diffusion coefficients for the release of 5-fluorouracil from drug-loaded psy-*cl*-poly(AAc) hydrogels in different medium at 37 °C

Drug in releasing medium	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 $D_L \times 10^4$
Distilled water	0.7	9.13	6.83	10.41	2.83
pH 2.2 buffer	0.8	6.22	8.66	11.41	1.69
pH 7.4 buffer	0.7	9.01	7.24	10.72	1.46

in plane bending and peak at 1043.3 cm^{-1} due to —COC stretching has been observed apart from usual peaks in the psyllium (Fig. 2a and b).

3.2. Swelling kinetics of hydrogels

3.2.1. Swelling as a function of monomer concentration

In present studies, the effect of monomer concentration on the swelling of the psy-*cl*-poly(AAc) polymers has been determined and results are presented in Fig. 3. The monomer concentration was varied from 2.91×10^{-1} to 14.55×10^{-1} mol/L in the polymer and amount of water uptake by the polymers has been taken after fixed interval of 30 min upto 300 min (Fig. 3) and after that equilibrium swelling has been taken after 24 h. It has been observed from the Fig. 3 that amount of water uptake by per gram of gel decreases with increase in monomer concentration in the polymer composition. This observation is supported by the fact that the incorporation of higher amount of monomer into polymer has led to the self-crosslinking, which has prevented the accessibility of water in the polymer matrix. The maximum swelling (17.97 ± 0.30) g/g of the gel and the minimum swelling (9.40 ± 0.10) g/g of the gel has been observed in case of polymers prepared with 2.91×10^{-1} and 14.55×10^{-1} mol/L of [AAc], respectively. But percentage of the total swelling have shown some irregular trends and 50% of the total swelling has occurred in 322, 249, 244, 474 and 308 min, respectively, for the polymers prepared with 2.91×10^{-1}, 5.82×10^{-1}, 8.73×10^{-1}, 11.64×10^{-1}, 14.55×10^{-1} mol/L of monomer. The values of diffusion exponent '*n*' and gel characteristic constant '*k*' have been evaluated from the slope and the intercept of the plot $\ln(M_t/M_\infty)$ versus $\ln t$ (Fig. 3b) and results are presented in Table 1. The results show that the values of diffusion exponent '*n*' are between 0.5 and 1 which indicate that Non-Fickian type diffusion mechanism has occurred for the diffusion of water molecules in the polymer matrix prepared with different monomer concentration. This diffusion mechanism occurs when the diffusion of water molecules into the polymer matrix and relaxation rates of polymer chains are comparable. The values of initial diffusion coefficients D_i and late diffusion coefficient D_L are observed less as compared to the values of average diffusion coefficient D_A, which reflects that during initial and late stages of the swelling, the rate of uptake of water by hydrogels is slow (Table 1).

3.2.2. Swelling as a function of temperature

Swelling was taken at 25 and 37 °C, to study the effect of temperature on swelling kinetics (Fig. 4). The swelling

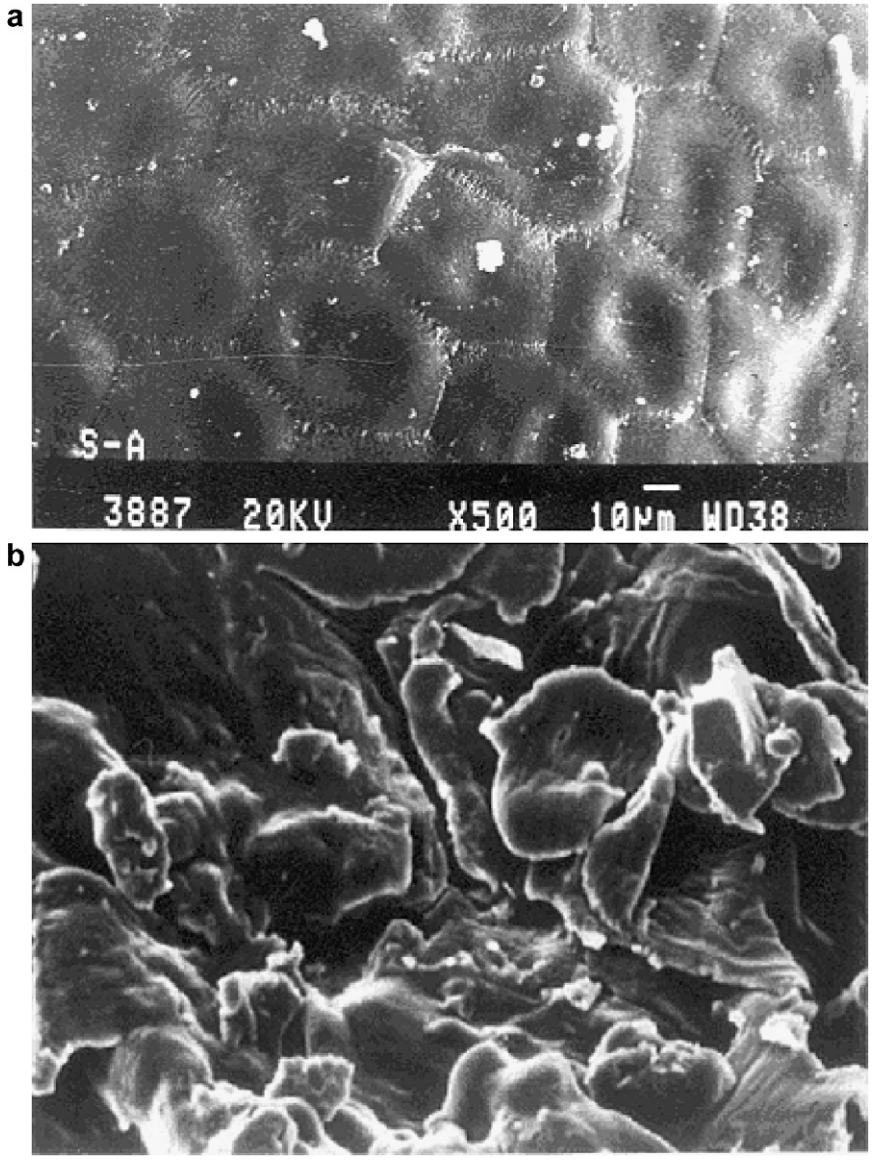

Fig. 1. (a) Scanning electron micrograph of psyllium. (b) Scanning electron micrograph of psy-*cl*-poly(AAc). [Magnification 3000×].

of the hydrogels increases with increase in temperature of the swelling medium. This is due to increase in kinetic energy of water molecules and increase in rate of diffusion of water molecules with increase in temperature of the swelling medium. The maximum swelling (10.20 ± 1.24) g/g of gel and (3.48 ± 0.16) g/g of gel has been observed, respectively, at 37 and at 25 °C. The values of diffusion exponent '*n*' have been observed 0.46 and 0.57, respectively, at 25 and 37 °C (Fig. 4b). At 25 °C the rate of diffusion of water into the hydrogels is much less than the rate of relaxation of polymer chains (Fickian diffusion mechanism) but at 35 °C, rate diffusion of water molecules in to the polymer chains and relaxation of polymer chains are comparable (Non-Fickian diffusion mechanism). From the values of the diffusion coefficients, it has been observed that in the initial stages the rate of diffusion of water molecules into the polymer matrix is less at 25 °C as compared to the 37 °C but in latter stages this order become reversed (Table 1).

3.2.3. Swelling as a function of pH

In order to study the effect of pH on water uptake of the psy-*cl*-poly(AAc) hydrogels, the swelling studies of the polymers were carried out in distilled water, pH 2.2 buffer and pH 7.4 buffer solutions at 37 °C. It has been observed from the Fig. 5 that swelling of polymer matrix increases with increase in pH of swelling medium. After 24 h maximum water uptake (13.65 ± 1.62) g/g of gel, (10.20 ± 1.24) g/g of gel and 4.63 ± 0.15 g/g of gel in pH 7.4 buffer, distilled water and pH 2.2 buffer have been observed, respectively. This is due to the reason that at lower pH values, the —COOH groups do not ionize and keep the network at its collapsed state. At higher pH values, the —COOH groups ionize and the charged —COO^-

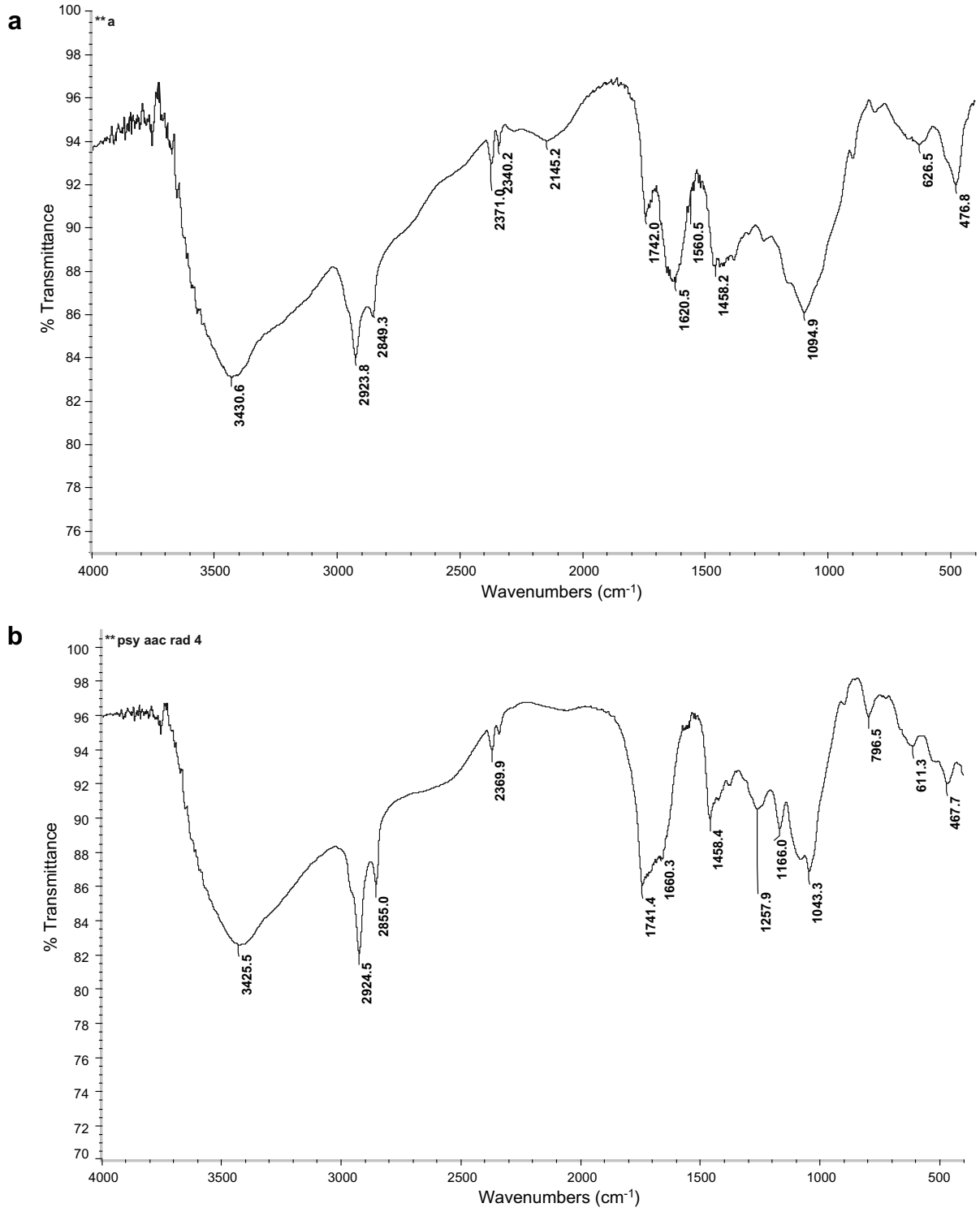

Fig. 2. (a) FTIR of psyllium. (b) FTIR of psy-*cl*-poly(AAc).

groups repel each other, resulting in the swelling of the polymer. From the values of the diffusion exponent '*n*', it has been observed that the Non-Fickian type diffusion mechanism has occurred for the diffusion of water molecules in polymer matrix in distilled water and pH 7.4 buffer (Fig. 5b). The values of the average diffusion coefficient (D_A) has been observed more than initial (D_i) and late diffusion coefficients D_L (Table 1).

3.2.4. Swelling as a function of [NaCl]

Effect of the salt concentration on swelling has been observed by taking the swelling of the hydrogels in 0.9%

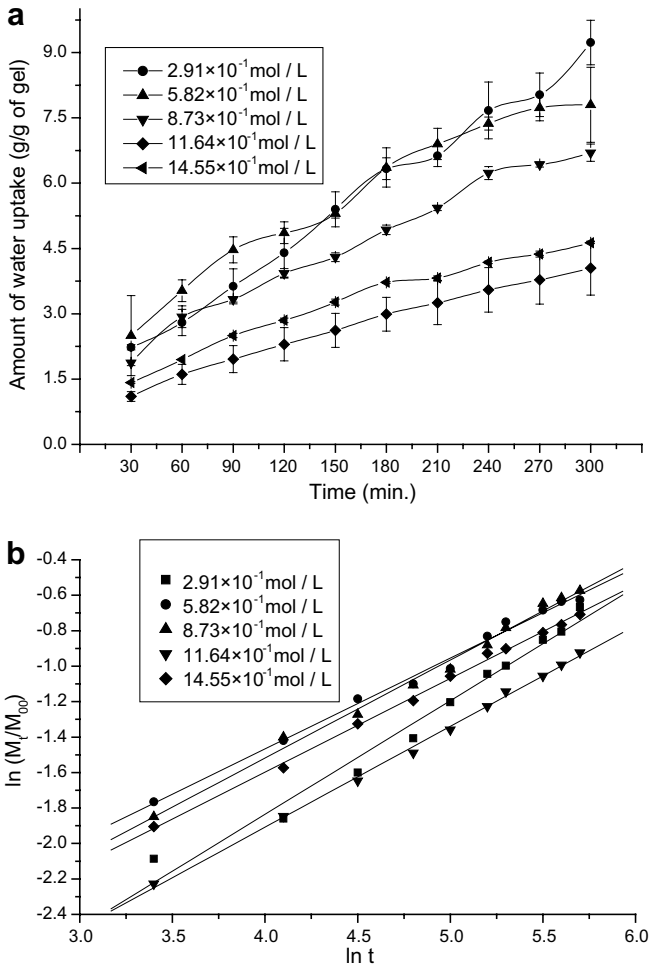

Fig. 3. (a) Effect of monomer concentration on swelling kinetics of psy-*cl*-poly(AAc) hydrogels in distilled water at 37 °C. (b) Plot of $\ln(M_t/M_\infty)$ versus ln t for the evaluation of diffusion exponent 'n' and gel characteristic constant 'k' for the swelling of psy-*cl*-poly(AAc) hydrogels at 37 °C.

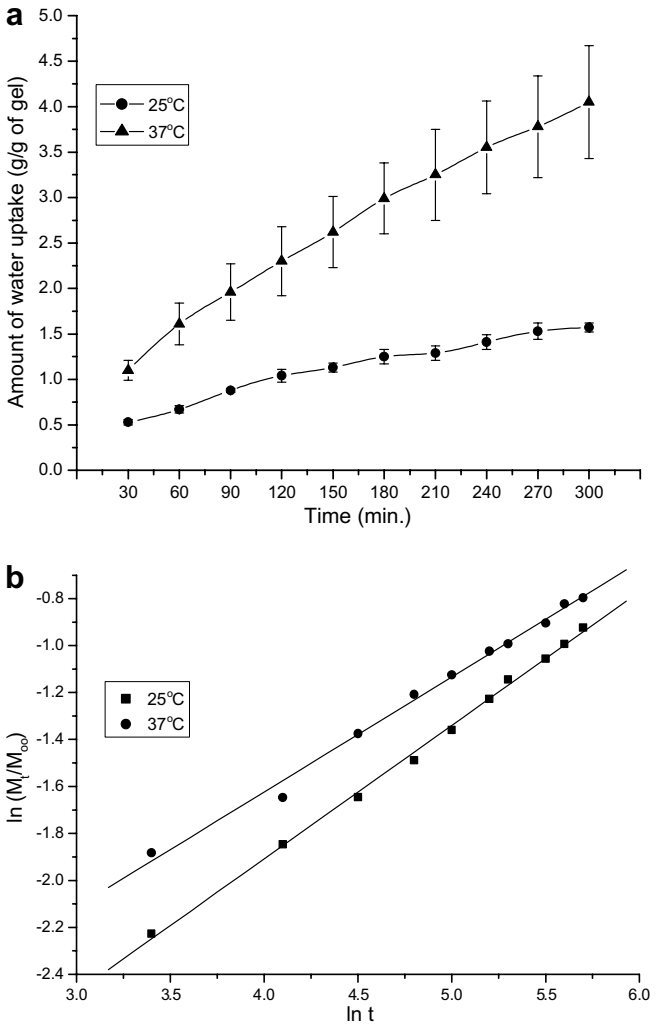

Fig. 4. (a) Swelling kinetics of psy-*cl*-poly(AAc) hydrogels at different temperatures. (b) Plot for the evaluation of diffusion exponent 'n' and gel characteristic constant 'k' for the swelling of psy-*cl*-poly (AAc) hydrogels at different temperatures.

NaCl and results are presented in Fig. 6. It has been observed from the figures that the amount of water uptake by per gram of gel decreases in solution of NaCl. Maximum water uptake after 24 h has been observed (10.21 ± 1.24) g/g of gel and (4.53 ± 0.076) g/g of gel in distilled water and salt solution, respectively. Hydrogels do not swell appreciably in the presence of electrolytes salts due to ex-osmosis and even the swollen hydrogels shrink dramatically in the presence of salts. The 50% of total swelling has been occurred in 474 and 353 min in distilled water and salt solution, respectively. The values of diffusion exponent 'n', gel characteristic constant 'k' (Fig. 6b) and diffusion coefficient D_i, D_A and D_L have been shown in the Table 1.

3.3. Release dynamics of the drugs

In the present study the effect of pH on the release profile of 5-fluorouracil has been studied by varying the pH of the release medium. The release pattern of drug from per gram of the drug-loaded hydrogels has been shown in Fig. 7. It has been observed from the figure that the amount of drug released in the pH 7.4 buffer and in distilled water is more as compared to the pH 2.2 buffer. In the initial 300 min the rate of release of drug in distilled water, pH 2.2 buffer and pH 7.4 buffer has been observed 3.89, 3.30 and 4.21 μg per minute, respectively. This observation is corresponding to swelling trends observed in different pH medium. After 24 h the total amount of drug release in distilled water, pH 2.2 and pH 7.4 buffer solution has been observed (2.081 ± 0.014), (1.643 ± 0.019) and (2.247 ± 0.037) mg/10 mL per g gel, respectively. The 50% of the total release has occurred in 454, 374 and 423 min in distilled water, pH 2.2 buffers and pH 7.4 buffer, respectively. For the release of drug from the polymeric matrix diffusion exponent 'n' have 0.69, 0.79 and 0.70 values and gel characteristic constant 'k' have 9.13×10^{-3}, 6.22×10^{-3} and 9.01×10^{-3} values, respectively, in dis-

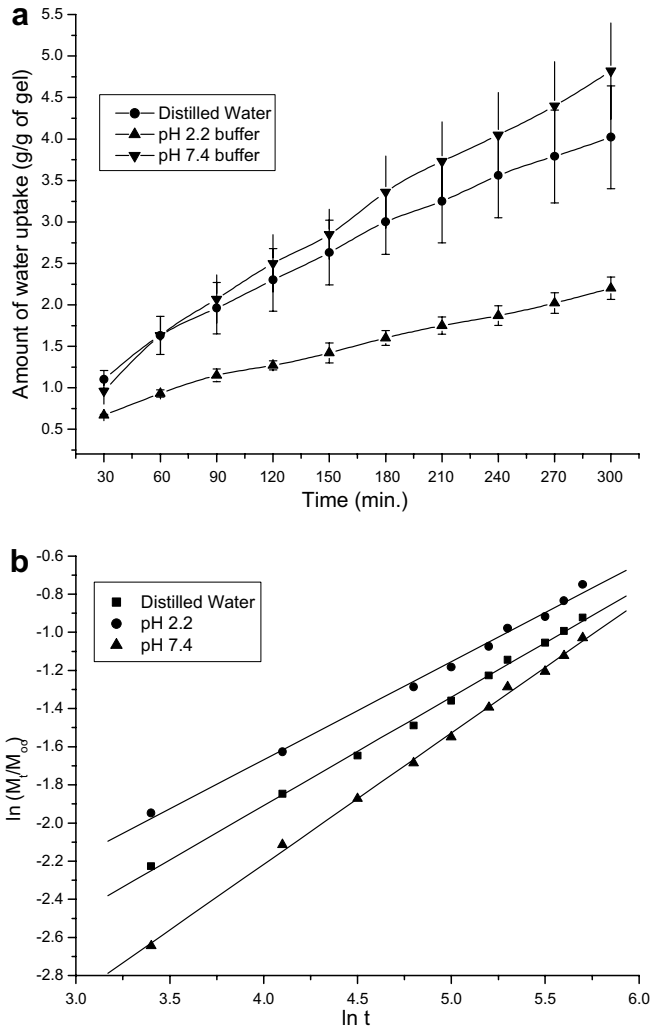

Fig. 5. (a) Swelling kinetics of psy-*cl*-poly(AAc) hydrogels in different pH solution at 37 °C. (b) Plot of the evaluation of diffusion exponent '*n*' and gel characteristic constant '*k*' for the swelling of psy-*cl*-poly(AAc) hydrogels.

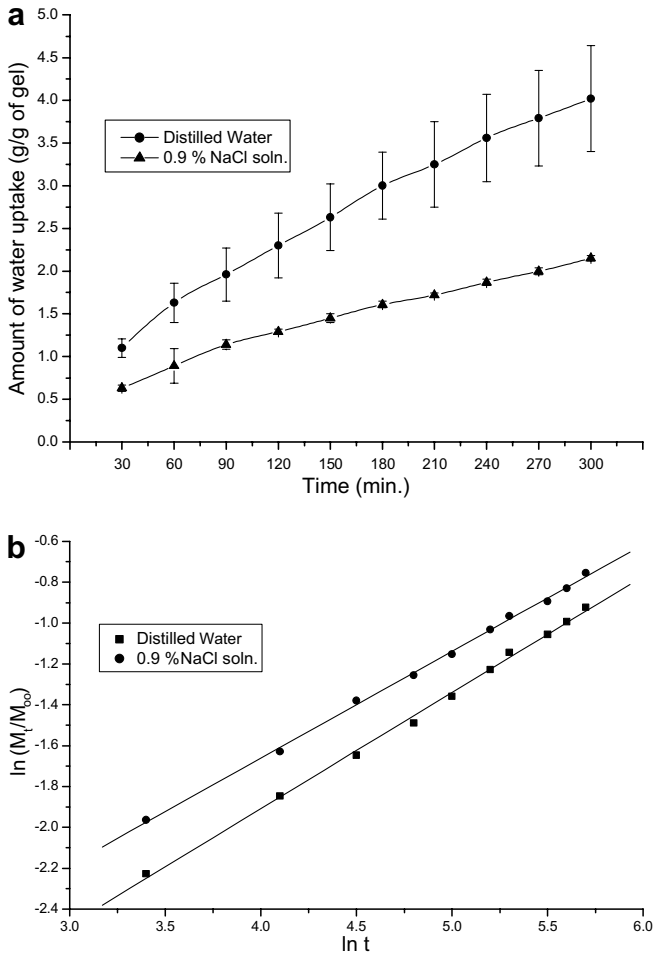

Fig. 6. (a) Swelling kinetics of psy-*cl*-poly(AAc) hydrogels in different salt solution at 37 °C. (b) Plot for the evaluation of diffusion exponent '*n*' and gel characteristic constant '*k*' for the swelling of psy-*cl*-poly (AAc) hydrogels.

tilled water, pH 2.2 buffer and pH 7.4 buffer, respectively, (Fig. 7b). The values of '*n*' are between 0.5 and 1.0 in all the releasing mediums which indicate a Non-Fickian or Anomalous diffusion mechanism for the release of drugs from the polymer matrix. In this release mechanism, the rate of polymer chain relaxation and the rate of drug diffusion from these hydrogels are comparable. The values of initial diffusion coefficients D_i and late diffusion coefficient D_L have been obtained less than the value of average diffusion coefficient D_A, which reflect that during initial and late stages, the rate of release of 5-fluorouracil into the solution is slow (Table 2).

4. Conclusion

It is concluded from the foregone discussion that composition of polymer and nature of swelling medium affect the swelling of hydrogels. The hydrogels developed from the modification of psyllium with acrylic acid through radiation method are pH responsive and have shown good degree of swelling in the pH 7.4 buffer. It is also reflected in the release behavior of anticancer drug in this pH solution. Hence, these hydrogels have potential to deliver the drug in the colon that too in the controlled and sustained manner. It is further concluded that hydrogels developed from psyllium can act as double potential drug delivery devices because psyllium itself has therapeutic importance for its anticancer action. It is also concluded from the drug release dynamics that release of drug from the polymeric matrix has occurred through Non-Fickian diffusion mechanism, in this mechanism, the rate of drug diffusion and rate of polymer chain relaxation are comparable. Therefore, drug release depends on two simultaneous rate processes, water migration into the device and drug diffusion through continuously swelling hydrogels.

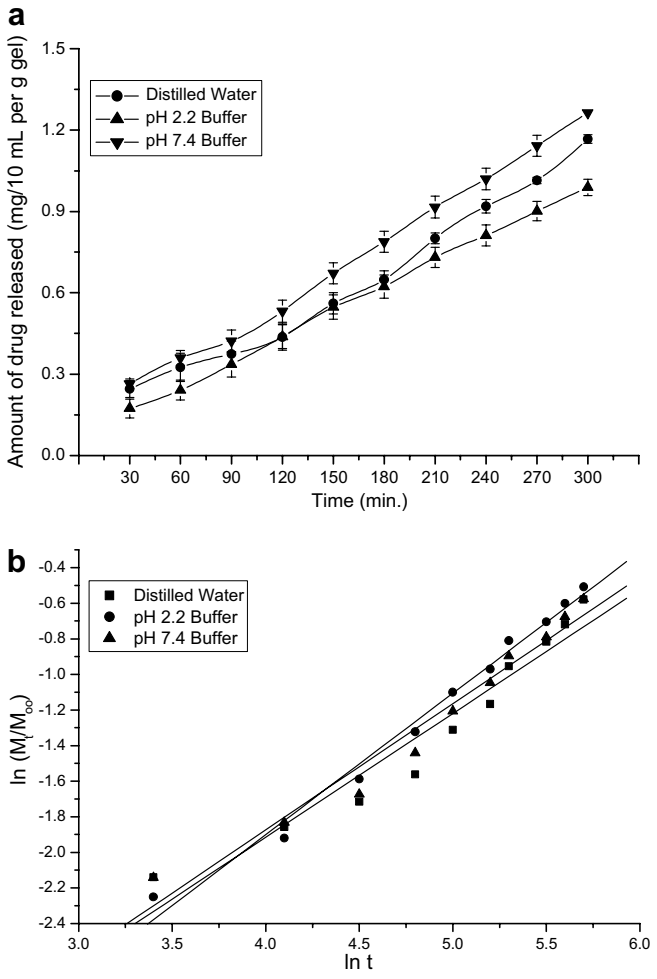

Fig. 7. (a) Release profile of 5-fluorouracil from drug-loaded psy-*cl*-poly(AAc) hydrogels in different medium at 37 °C. (b) Plot for the evaluation of diffusion exponent '*n*' and gel characteristics constant '*k*' for the release of 5-fluorouracil from drug-loaded psy-*cl*-poly(AAc) hydrogels in different medium at 37 °C.

References

Abdel-Aal, S. E., Gad, Y. H., & Dessouki, A. M. (2006). Use of rice straw and radiation-modified maize starch/acrylonitrile in the treatment of wastewater. *Journal of Hazardous Materials, 129*(1–3), 204–215.

Alabaster, O., Tang, Z. C., Frost, A., & Shivapurkar, N. (1993). Potential synergism between wheat bran and psyllium: Enhanced inhibition of colon cancer. *Cancer Letters, 75*(1), 53–58.

Alabaster, O., Tang, Z., & Shivapurkar, N. (1996). Dietary fiber and the chemopreventive modelation of colon carcinogenesis. *Mutation Research, 350*(1), 185–197.

Alfrey, T., Gurnee, E. F., & Lloyd, W. G. (1966). Diffusion in glassy polymers. *Journal of Polymer Science. Part C, 12*, 249–261.

Bufill, J. A. (1990). Colorectal cancer: Evidence for distinct genetic categories based on proximal or distal tumor location. *Annals of Internal Medicine, 113*, 779–788.

Cummings, J. H. (1981). Short chain fatty acids in the human colon. *Gut, 22*, 763–795.

Cummings, J. H., Beatty, E. R., Kingman, S. M., Bingham, S. A., & Englyst, H. N. (1996). Digestion and physiological properties of resistant starch in the human large bowel. *British Journal of Nutrition, 75*, 733–747.

Cummings, J. H., & Englyst, H. N. (1987). Fermentation in the human large intestine and the available substrates. *The American Journal of Clinical Nutrition, 45*, 1243–1255.

El-Hag Ali, A., Abd El-Rehim, H. A., Hegazy El-Sayed, A., & Ghobashy, M. M. (2006). Synthesis and electrical response of acrylic acid/vinyl sulfonic acid hydrogels prepared by γ-irradiation. *Radiation Physics and Chemistry, 75*(9), 1041–1046.

Fischer, H. M., Nanxiong, Y., Ralph, R. G. J., Andersond, L., & Marletta, J. A. (2004). The gel-forming polysaccharide of psyllium husk (Plantago ovata Forsk). *Carbohydrate Research, 339*, 2009–2017.

Holt, P. R., Mokulo, A. O., Distler, P., Liu, T., & Reddy, B. S. (1996). Regional distribution of carcinogenesis induced colonic neoplasia in the rat. *Nutrition and Cancer, 25*, 129–135.

Huang, M., Shen, X., Sheng, Y., & Fang, Y. (2005). Study of graft copolymerization of *N*-maleamic acid–chitosan and butyl acrylate by gamma-ray irradiation. *International Journal of Biological Macromolecules, 36*(1–2), 98–102.

Karadag, E., Saraydin, D., & Güven, O. (2001). Radiation Induced super adsorbent hydrogels: Acrylamide/itaconic acid hydrogels. *Macromolecular Material and Engineering, 286*, 34–42.

Khan, F. (2005). Characterization of methyl methacrylate grafting onto preirradiated biodegradable lignocellulose fiber by gamma-radiation. *Macromolecular Bioscience, 5*(1), 78–89.

Kim, Y. S., Tsao, D., Siddiqui, B., Whitehead, J. S., Arnstein, P., Bennet, J., et al. (1980). Effects of sodium butyrate and dimethylsulfoxide on biochemical properties of human colon cancer cell. *Cancer, 45*, 1185–1192.

Morita, T., Kasaoka, S., Hase, K., & Kiriyama, S. (1999). Oligo-L-methionine and resistant protein promote cecal butyrate production in rats fed resistant starch and fructooligosaccharide. *The Journal of Nutrition, 129*, 1333–1339.

Morita, T., Kasaoka, S., Oh-hashi, A., Ikai, M., Numasaki, Y., & Kiriyama, S. (1998). Resistant proteins alter cecal short-chain fatty acid profiles in rats fed high amylose cornstarch. *The Journal of Nutrition, 128*, 1156–1164.

Mostafa, K. M., & Morsy, M. S. (2004). Modification of carbohydrate polymers via grafting of methacrylonitrile onto pregelled starch using potassium monopersulfate/Fe^{+2} redox pair. *Polymer International, 53*(7), 885–890.

Peppas, N. A., & Korsmeyer, R. W. (1987). Dynamically swelling hydrogels in controlled release applications, in hydrogels in medicines and pharmacy. In N. A. Peppas (Ed.). *Properties and applications* (Vol. III, pp. 118–121). Boca Raton, FL: CRC Press Inc.

Pharmacopoeia of India (1985). 3rd ed., Vol II. Controller of publications, Delhi, Appendix-7, p. A-142.

Pouillart, P. R. (1998). Role of butyric acid and its derivatives in the treatment of colorectal cancer and hemoglobinopathies. *Life Sciences, 63*(20), 1739–1760.

Ritger, P. L., & Peppas, N. A. (1987a). A simple equation for description of solute release I. Fickian and non-Fickian release from non-swellable devices in the form of slabs, spheres, cylinders or Discs. *Journal of Controlled Release, 5*, 23–36.

Ritger, P. L., & Peppas, N. A. (1987b). A simple equation for description of solute release I. Fickian and non-Fickian release from swellable devices. *Journal of Controlled Release, 5*, 37–42.

Rosiak, J., Burczak, K., Czolozynska, T., & Pekala, W. (1983). Radiation-crosslinked hydrogels from acrylamide water solutions. *Journal of Radiation Physics and Chemistry, 22*, 917–928.

Saraydin, D., Karadag, E., & Güven, O. (1995a). Highly swollen hydrogels: Crosslinked acrylamide–crotonic acid copolymers. *Turkish Journal of Chemistry, 19*, 179–187.

Saraydin, D., Karadag, E., & Güven, O. (1995b). Acrylamide/maleic acid hydrogels. *Polymer Advance Technolology, 6*, 719–726.

Saraydin, D., Karadag, E., & Güven, O. (1997). Super water-retainer hydrogel: Crosslinked acrylamide/succinic acid copolymers. *Polymer Journal, 29*, 631–636.

Singh, B. (2007). Psyllium as therapeutic and drug delivery agent. *International Journal of Pharmaceutics, 334*, 1–14.

Soppimath, K. S., Kulkarni, A. R., & Aminabhavi, T. M. (2000). Controlled release of antihypertensive drug from the interpenetrating network poly(vinyl alcohol)-guar gum hydrogel microspheres. *Journal of Biomaterial Science. Polymer Edition, 11*(1), 27–43.

Soppimath, K. S., & Aminabhavi, T. M. (2002). Water transport and drug release study from cross-linked polyacrylamide grafted guar gum hydrogel microspheres for the controlled release application. *European Journal of Pharmaceutics and Biopharmaceutics, 53*(1), 87–98.

Taşdelen, B., Kayaman-Apohan, N., Güven, O., & Baysal, B. M. (2005). Anticancer drug release from poly(*N*-isopropylacrylamide/itaconic acid) copolymeric hydrogels. *Radiation Physics and Chemistry, 73*(6), 340–345.

Weaver, G. A., Krause, J. A., Miller, T. L., & Wolin, M. J. (1988). Short chain fatty acid distributions of enema samples from a sigmoidoscopy population: An association of high acetate and low butyrate ratios with adenomatous polyps and colon cancer. *Gut, 29*, 1539–1543.

Whitehead, R. H., Young, G. P., & Bhathal, P. S. (1986). Effects of short chain fatty acids on a new human colon carcinoma cell line (LM 1215). *Gut, 27*, 1457–1463.

Wilson, J. K. V. (1989). Biology of large bowel cancer. *Hematology/Oncology Clinics of North America, 3*, 19–34.