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Synthesis, characterization and swelling studies of pH responsive psyllium and methacrylamide based hydrogels for the use in colon specific drug delivery

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Abstract

In order to utilize the psyllium husk a medicinally important natural polysaccharide and to develop the novel hydrogels meant for the colon specific drug delivery, we have prepared psyllium and methacrylamide based polymeric networks by using *N*,*N*′-methylenebisacrylamide (NN-MBAAm) as crosslinker and ammonium persulfate (APS) as initiator. To study various structural aspects of the polymeric networks thus formed psy-*cl*-poly(MAAm), these were characterized with SEMs, FTIR, TGA and swelling studies. The swelling studies of networks were carried out as a function of time, temperature, pH and [NaCl]. Equilibrium swelling has been observed to depend on both composition of the polymer and nature of swelling medium. Maximum percent swelling 1262 was observed for the polymeric network prepared with 19.45×10^{-3} mol/L of [NN-MBAAm] at 40 °C in 0.5 M NaOH solution. This article also discusses the release dynamics of tetracycline hydrochloride from the hydrogels, for the evaluation of the drug release mechanism and diffusion coefficients of drug from the polymer matrix. The effect of pH on the release pattern of tetracycline hydrochloride has been studied by varying the pH of the release medium. It has been observed from the release dynamics of drug from the hydrogels that the diffusion exponent '*n*' have 0.477, 0.423 and 0.427 values and gel characteristic constant '*k*' have 5.07×10^{-2}, 6.34×10^{-2} and 6.38×10^{-2} values, respectively, in distilled water, pH 2.2 buffer and pH 7.4 buffer solution. The values the '*n*' indicated that the Fickian type diffusion mechanism occurred for the release of tetracycline hydrochloride from drug loaded psy-*cl*-poly(MAAm) polymers in different release mediums. In Fickian type diffusion mechanism, the rate of polymer chain relaxation is more as compare to the rate of drug diffusion from these hydrogels and release behavior follows Fick's law of diffusion. In each release medium, the values of the initial diffusion coefficient 'D_i' for the release of tetracycline hydrochloride was higher than the values of late time diffusion coefficient 'D_L' indicating that in the start, the diffusion of drug from the polymeric matrix was faster as compare to the latter stages.

Keywords: Drug delivery devices; Hydrogels; Psyllium; Release dynamics

1. Introduction

High colonic concentration of drugs is required for the treatment of the diseases associated with the colon. Therefore, a versatile approach is needed to deliver drugs to the colon for effective therapy. Hydrogels, specially based on the polysaccharides, have attracted considerable attention to act as a smart candidate for the controlled release of therapeutic agents to the specific sites in the GI tract. The rationale for the development of polysaccharide based delivery systems for colon is the presence of large amount of polysaccharidases in the human colon, as the colon is inhabited by a large number and variety of bacteria, which secrete many enzymes (Chourasia & Jain, 2003, 2004). The controlled release of active anti-microbial agents such as amoxicillin (Risbud & Bhonde, 2000; Risbud, Hardikar, Bhat, & Bhonde, 2000; de la Torre, Torrado, & Torrado, 2003), metronidazole (Portero, Remunan-Lopez, Criado, & Alonso,

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2002), oxytetracycline (Mi, Wong, & Shyu, 1997), vancomycin (Cerchiara et al., 2003) and tetracycline-HCl (Bittner, Mader, Kroll, Borchert, & Kissel, 1999; Hejazi & Amiji, 2002, 2003) from the polymeric matrix to the GI tract have been carried out successfully by various workers.

Polymeric networks were found to have potential to act as vehicle for the controlled delivery of tetracycline. Fractional release of tetracycline from the polymeric networks was greatly influenced by the chemical architecture of the gel (Bajpai, Bajpai, & Shukla, 2003). Depending upon the sites specificity, hydrogels were designed to deliver the drug. In one study, diffusion of oxytetracycline entrapped in microbeads of calcium alginate and calcium alginate coacervated with chitosan covered with poly(ethylene glycol) of different molecular mass was carried out at 37 °C, in pH 7.4 and pH 1.2 buffer solutions, to provide the conditions similar to those found in the gastrointestinal system. The microbeads swelling at pH 7.4 and drug diffusion was classically Fickian, suggesting that the drug transport, in this case, was controlled by the exchange rates of free water and relaxation of calcium alginate chains. In case of acid media, it was observed that the phenomenon did not follow Fick's law, owing, probably, to the high solubility of the oxytetracycline in this environment. It was possible to modulate the release rate of drug in several types of microbeads (Cruz et al., 2004). In an another observation, formulation comprising of 3% (w/w) chitosan, 10% (w/w) tetracycline HCl and 9% (w/v) tripolyphosphate, kinetic models revealed that drug release followed Fickian diffusion while textural analysis showed minimal hydration over the test period. Anti-microbial studies showed that the drug concentrations in the in vitro release samples were above the minimum concentration of drug required for inhibition of *Staphylococcus aureus* growth (Govender et al., 2005). For localized antibiotic delivery in the acidic environment of the stomach, for the treatment of *Helicobacter pylori* infection in peptic ulcer disease, cationic hydrogels with pH-sensitive swelling behavior were developed. The release behavior of two common antibiotics, moxicillin and metronidazole, entrapped in freeze-dried chitosan–poly(ethylene oxide) polymer networks were evaluated in enzyme-free simulated gastric fluid (SGF; pH 1.2) and simulated intestinal fluid (SIF; pH 7.2). More than 65% and 59% of the entrapped amoxicillin and metronidazole, respectively, were released from the hydrogels after 2 h in SGF with higher swelling ratio (Patel & Amiji, 1996). Release of the drug from the polymeric networks of gelatin–poly(ethylene oxide) further enhanced with the presence of the enzyme solution in the release medium (Amiji, Tailor, Ly, & Goreham, 1997). Different polysaccharides based colon specific drug delivery devices has been reported (Chourasia & Jain, 2003, 2004) but potential of psyllium has not been explored so for.

Psyllium is the common name used for several members of the plant genus *Plantago*. Its seeds are used commercially for the production of mucilage, which is obtained from the seed coat by mechanical milling/grinding of the outer layer of the seeds and yield amounts to approximately 25% of the total seeds yield. Mucilage is a white fibrous material that is of hydrophilic nature and forms the clear colorless mucilaginous gel by absorbing water. The gel nature and composition of the polysaccharides extracted from the seeds of the *Plantago ovata* has been reported in literature (Kennedy, Sandhu, & Southgate, 1979; Laidlaw & Purcival, 1950; Sandhu, Hudson, & Kennedy, 1981). Gel-forming fraction of the alkali-extractable polysaccharides composed of arabinose, xylose and traces of other sugars (Fischer, Nanxiong, Ralph, Andersond, & Marletta, 2004). Psyllium has been reported as a medicinally active natural polysaccharide has been used for cholesterol-lowering in children (Davidson, Dugan, & Burns, 1996), as well as in adults (Oson, Anderson, & Becker, 1997). Psyllium supplementation has also improved blood sugar levels in some people with diabetes. The soluble fiber component of psyllium is believed to account for this effect (Anderson, Allgood, & Turner, 1999; Rodriguez-Moran, Guerrero-Romero, & Lazcano-Burciaga, 1998). In a double-blind trial, people with ulcerative colitis had a reduction in symptoms such as bleeding and remained in remission longer when they took 20 g of ground psyllium seeds twice daily with water compared to the use of the medication mesalamine alone (Fernandez-Banares, Hinojosa, & Sanchez-Lombrana, 1999). In addition, the combination of the two was slightly more effective than alone. Psyllium has been reported to inhibit lactulose-induced colonic mass movements and to benefit patients with irritable bowel syndrome, improving both constipation and diarrhea (Washington, Harris, Mussell White, & Spiller, 1998).

Keeping in view, the pharmacological importance of psyllium polysaccharides and need to develop the colon specific drug delivery devices, psyllium, if suitably tailored to prepare the hydrogels, can act as the potential candidate for the novel drug delivery systems. Modification of the psyllium to develop the hydrogels is not much reported in the literature. Singh and coworkers have first time modified the psyllium to prepare the hydrogels for the use in metal ion sorption and drug delivery systems (Singh, Chauhan, Bhatt, & Kumar, 2006, 2007). Therefore, the present study is an attempt, to synthesize psyllium and poly (MAAm) based hydrogels by using NN-MBAAm as cross-linker and ammonium persulfate (APS) as initiator. The polymeric networks [psy-*cl*-poly(MAAm)], thus formed were characterized by SEMs, FTIR, TGA, and swelling response of the hydrogels were studied as a function of time, temperature, pH and [NaCl]. The release dynamics of tetracycline hydrochloride from hydrogels have also been discussed, for the evaluation of the release mechanism and diffusion coefficients.

2. Experimental

2.1. Materials and methods

Plantago psyllium mucilage was obtained from Sidpur Sat Isabgol factory, Gujrat-India, methacrylamide

(MAAm) was obtained from the Merck-Schuchardt, Germany, Ammonium persulphate (APS) and *N*,*N*′-methylenebisacrylamide (NN-MBAAm) was obtained from S.D. Fine, Mumbai, India and were used as received. Tetracycline hydrochloride was obtained from the Ind-Swift Limited, Chandigarh, India.

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

Optimum reaction conditions for the synthesis of polymer networks were discussed somewhere else (Singh et al., 2006). Reaction was carried out with 1 g of psyllium husk, 1.095×10^{-2} mol/L of APS, known concentration of monomer and crosslinker in the aqueous reaction system at 65 °C temperature for 2 h. Polymers thus formed were stirred in distilled water and ethanol for 2 h each to remove the soluble fraction and then were dried in air oven at 40 °C. Different polymeric networks [psy-*cl*-poly(MAAm)] were synthesized by varying [NN-MBAAm] (from 6.45×10^{-3}–32.40×10^{-3} mol/L) to study the effect of crosslinker variation on the structure of network and swelling of the polymers.

2.3. Characterization

Psyllium and psy-*cl*-poly(MAAm) polymer were characterized by the following techniques:

2.3.1. Scanning electron micrography (SEM)

To investigate and compare the surface morphology of psyllium and psy-*cl*-poly(MAAm), SEMs were taken on Jeol Steroscan 150 Microscope.

2.3.2. Fourier transform infrared spectroscopy (FTIR)

FTIR spectra of psyllium and psy-*cl*-poly(MAAm) were recorded in KBr pellets on Perkin Elmer RXI FTIR SYSTEM to study the modified nature of psyllium.

2.3.3. Thermogravimetric analysis (TGA)

Thermogravimetric analysis of psyllium and psy-*cl*-poly(MAAm) was carried out on a Schimatdzu DT-40 TG-DTA Analyzer in air at a heating rate of 20 °C/min to examine the thermal properties of the polymers.

2.4. Swelling studies

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

$$P_s = \left(\frac{W_s - W_d}{W_d}\right) \times 100$$

where W_s is weights of swollen polymers and W_d is the weight of dried polymers.

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

2.5. 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–vis spectrophotometer (Cary 100 Bio, Varian) and calibration graph was constructed. The concentration of the drug in the sample solution read from the graph as the concentration corresponding to the absorbance of the solution. Three calibration graphs of tetracycline HCl were made to determine the amount of drug release from the drug loaded polymer matrix in different medium (distilled water, pH 2.2 buffer and pH 7.4 buffer).

2.6. 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.

2.7. Drug release from polymer matrix

In vitro release studies of the drug have been carried out by placing dried and loaded sample in definite volume of releasing medium at 37 °C temperature. The amount of tetracycline–HCl released was measured spectrophotometrically by taking the absorbance of the solution after every 30 min at wavelength 357, 361 and 356 nm, respectively, for release in distilled water, pH 2.2 buffer and pH 7.4 buffer. The drug release was measured after fixed interval of time and release dynamics of model drugs were studied.

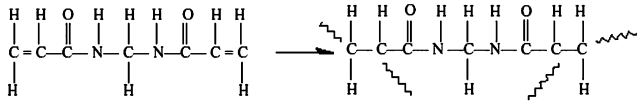
2.8. Preparation of buffer solution

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).

3. Results and discussion

Polymeric networks were synthesized by chemically induced polymerization through free radical mechanism. APS has generated the reactive sites, on both the psyllium and monomer, leading to the propagation of the reaction.

In the presence of crosslinker NN-MBAAm (CH_2=CHCO $NHCH_2$ $NHCOCH$=CH_2), because of its poly-functionality, a new macro-radical get formed that has four reactive sites and these sites can be linked both with the radical on the psyllium and the poly(AAm). Those will resultant into the formation of three-dimensional networks. In order to study the effect crosslinker concentration on structure of three-dimensional networks and thereafter on percent swelling, polymeric networks of different [NN-MBAAm] were prepared and characterized. The chemical structure of the polymer affects the swelling ratio of the hydrogels, which is directly related to loading of drug to the polymers and release of drug from the polymeric matrix. The chemical structure depended upon composition of the polymeric matrix i.e. the crosslinking ratio. The higher the crosslinking ratio, the more crosslinking agent is incorporated in the hydrogels structure. Highly crosslinked hydrogels have a tighter structure, and will swell less as compared to the same hydrogels with lower crosslinking ratios. Crosslinking hinders the mobility of the polymer chain, hence lowering the swelling ratio. Swelling of environmentally sensitive hydrogels can be affected by specific stimuli. In the hydrogels system, absorption of water from the environment changes the dimensions and physicochemical properties of the system and thus the drug release kinetics.



N,N′-methylenebisacrylamide

3.1. Characterization

Psyllium and psy-*cl*-poly(MAAm) were characterized by SEMs, FTIR and TGA studies.

3.1.1. Scanning electron micrography

The morphology of psyllium and psy-*cl*-poly(MAAm) were examined by SEMs and presented in Fig. 1a and b, respectively. It was observed that psyllium has smooth and homogeneous morphology whereas modified psyllium has structural heterogeneity. Zhang and Peppas have used Scanning electron microscopy in the morphological studies of the poly(methacrylic acid)/poly(*N*-isopropylacrylamide) interpenetrating polymeric networks (IPN) with both conventional SEM and cryogenic SEM experiments. In order to visualize the IPN morphological behavior in its swollen state, a new approach, cryogenic SEM, was used on the IPN samples. IPN samples were frozen in their swollen state by liquid nitrogen and investigated on a cold stage in the SEM column. The pH and temperature influence on the IPN morphology was studied. The results showed that a decrease in pH and increase in temperature resulted in a drastic decrease in the pore size of the IPNs (Zhang & Peppas, 2002).

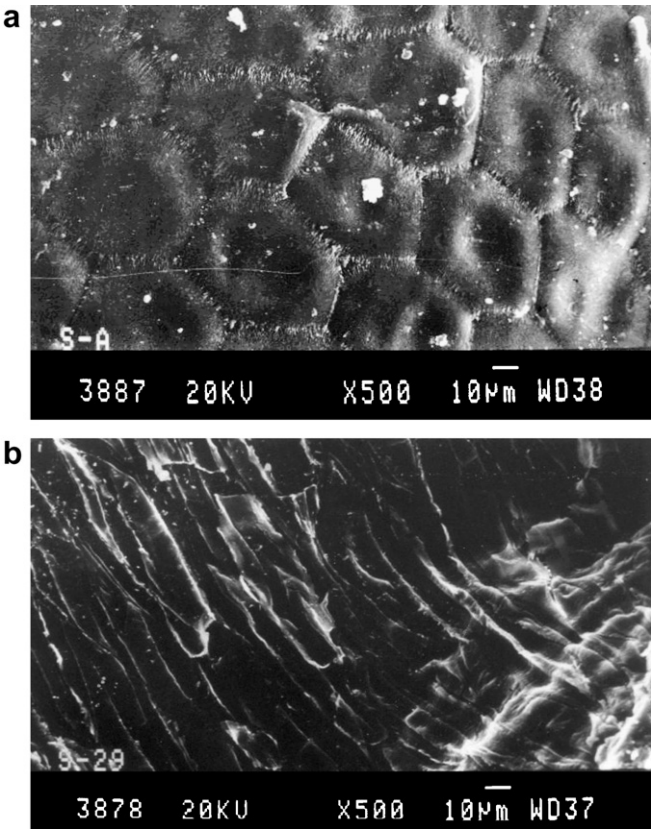


Fig. 1. (a) Scanning electron micrograph of psyllium. (b) Scanning electron micrograph of psy-*cl*-poly(MAAm).

3.1.2. Fourier transform infrared spectroscopy

FTIR spectra of psyllium and polymeric networks were recorded to study the modification of the psyllium and presented in Fig. 2a and b, respectively. The broad absorption bands at 3405.0 cm^{-1} and at 3422.1 cm^{-1} are due to –OH stretching indicate association in the psyllium and modified psyllium. In case of crosslinked polymer IR absorption bands due to C=O stretching at 1656.3 cm^{-1} and CN stretching at 1460.6 cm^{-1} were observed apart from usual peaks in psyllium.

3.1.3. Thermogravimetric analysis (TGA)

TGA of psyllium and psy-*cl*-poly(MAAm) showed that the mechanism of decomposition were different in both the cases (Fig. 3a and b). The initial decomposition temperature (IDT) of the psyllium and psy-*cl*-poly(MAAm) were recorded at 245.7 and 205.3 °C, respectively. Final decomposition temperature (FDT) of the psy-*cl*-poly(MAAm) 662.9 °C was observed higher than that of the psyllium (539.28 °C). It was observed that the difference in decomposition temperature (DT) for the crosslinked polymer was more as compared to psyllium; hence the rate of decomposition with respect to temperature was slower in case of psy-*cl*-poly(MAAm). It was thus understandable that thermal degradation starts earliest in case of psy-*cl*-poly(MAAm) but it becomes stable at higher temperature.

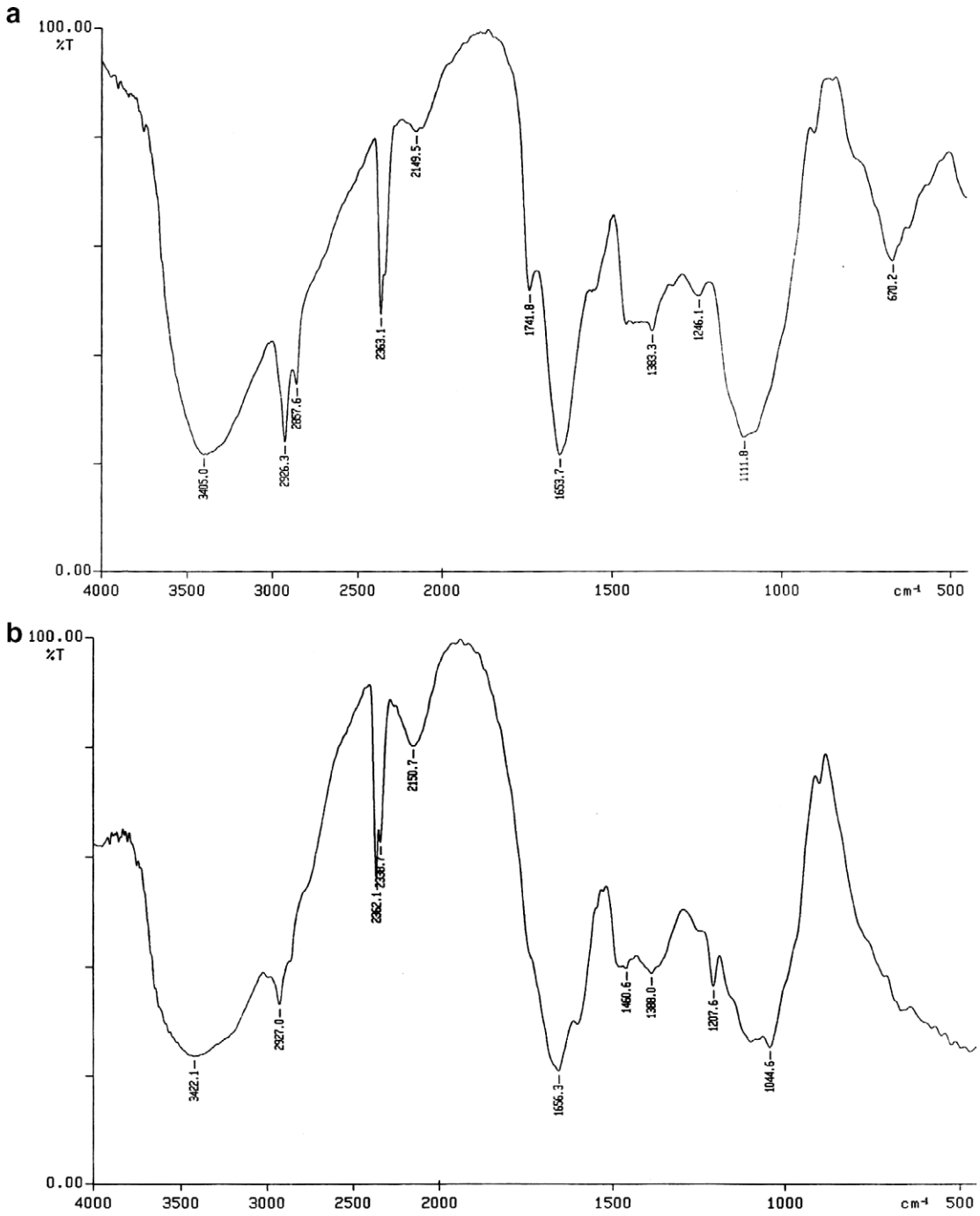


Fig. 2. (a) FTIR spectra of psyllium. (b) FTIR spectra of psy-*cl*-poly(MAAm).

It is further supported by the fact that first 50% decomposition occur at 316.2 °C in psyllium and at 392.42 °C in crosslinked polymer (Table 1). Such thermal behavior of these networks are explained by fact that $–CONH_2$ groups in psy-*cl*-poly(MAAm) degrade easily by dehydration and generating more stable groups as –CN those are thermally very stable and can undergo cyclization reactions at higher temperature. Differential thermal analysis (DTA) of these polymers showed that decomposition process was fast in the psyllium than psy-*cl*-poly(MAAm). Exothermic peaks were observed at higher temperature in crosslinked polymer. These all results point to the change in thermal properties of the modified psyllium.

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

Swelling behavior of psy-*cl*-poly(MAAm) prepared with different [NN-MBAAm] was studied as a function of time, temperature, pH and [NaCl] of the swelling medium.

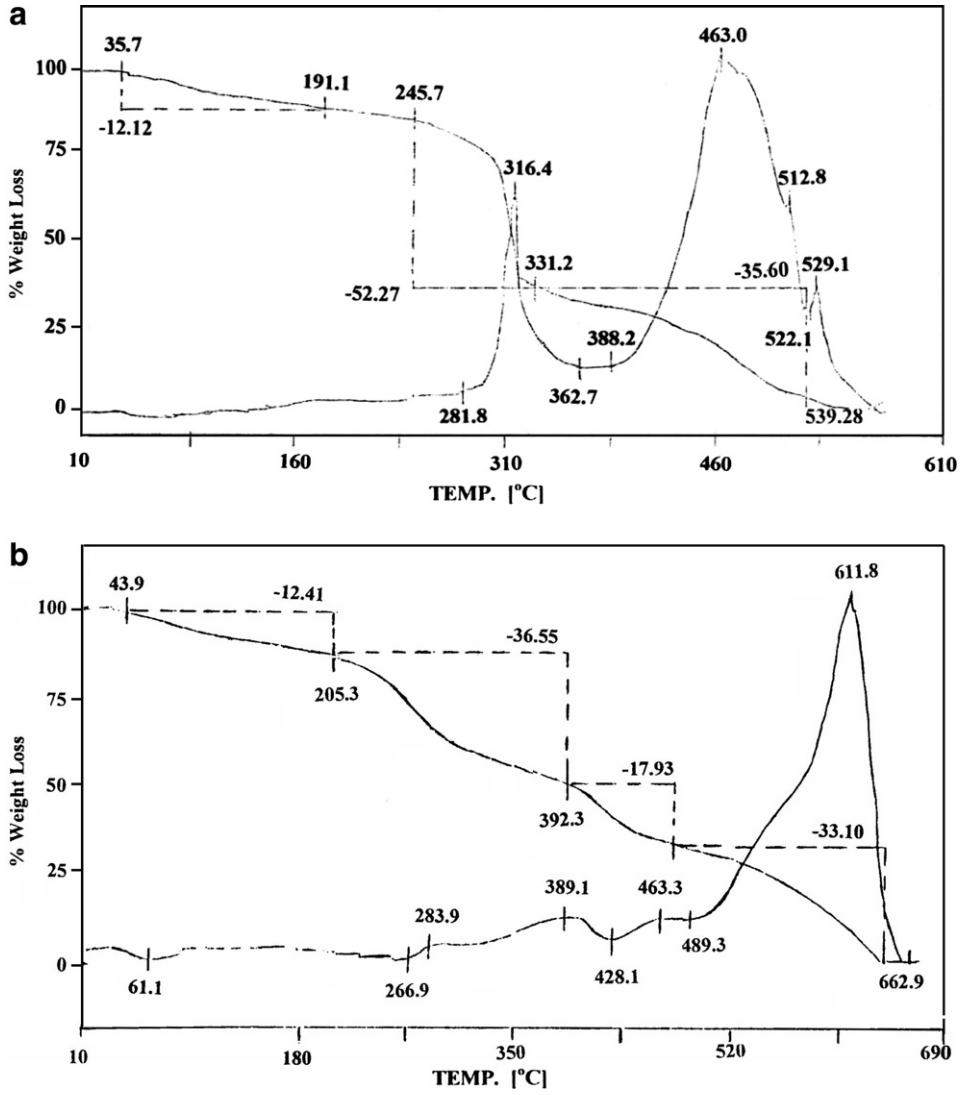


Fig. 3. (a) Primary thermogram of psyllium. (b) Primary thermogram of psy-*cl*-poly(MAAm).

3.2.1. Percent swelling as a function of time

The swelling behaviors of polymeric networks were studied at time interval of 10 min, 30 min, 1 h, 2 h, and 24 h. The effect of different [NN-MBAAm] (Fig. 4) on the equilibrium swelling was studied in the swelling medium at 40 °C and it was observed from the figure that P_s decreases with increase in the crosslinker concentration in the polymeric networks with some irregular trends up to 2 h. However, after 2 h swelling, it has been observed that swelling first increases and than decreases with the increase in crosslinker concentration in the polymer networks. It is also observed that swelling increases with increase in swelling time for the each concentration of the crosslinker in the polymers. Similar observations have been reported by Singh and coworkers for the hydrogels based on psyllium and poly(AAc) (Singh et al., 2006).

3.2.2. Percent swelling as a function of temperature

To study the effect of temperature on swelling equilibrium, P_s was studied at different temperature i.e. 25, 30, 35, 40 and 45 °C (Fig. 5). At each fixed concentration of the crosslinker in the polymer networks the increase in

Table 1
Thermogravimetric analysis of psyllium and psy-*cl*-poly(MAAm)

Sample	IDT (°C)	FDT (°C)	DT (°C) at every 10% weight loss									
			10	20	30	40	50	60	70	80	90	100
Psyllium	245.7	539.28	155.7	284.2	305.72	310.0	316.2	320.7	410.6	464.28	494.28	539.28
Psy-cl-poly(MAAm)	205.3	662.9	135.5	246.66	273.08	323.58	342.42	430.8	515.8	572.52	607.02	662.9

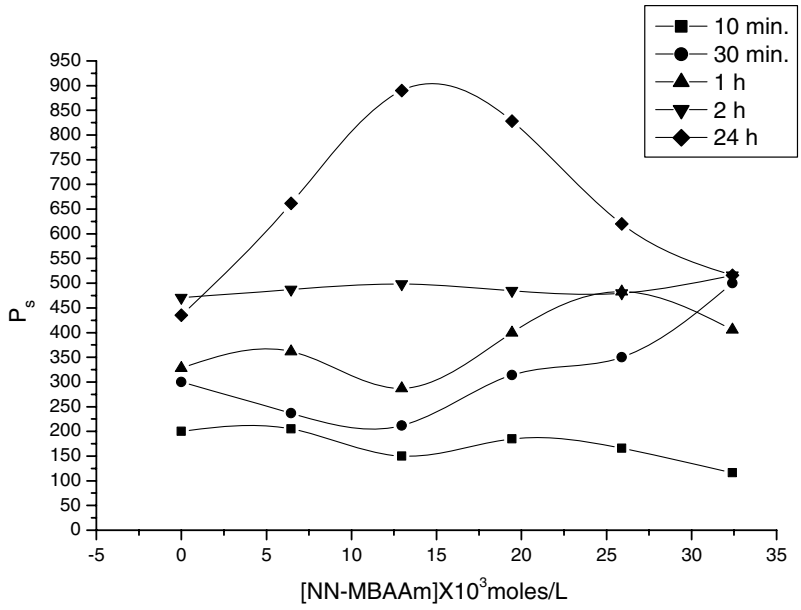


Fig. 4. Effect of time on P_s of psy-*cl*-poly(MAAm) prepared with different [NN-MBAAm]. [Swelling temp. = 40 °C. (Reaction time = 2 h, temperature = 65 °C, [APS] = 1.095×10^{-2} mol/L, [MAAm] = 5.85×10^{-1} mol/L and psyllium = 1 g)].

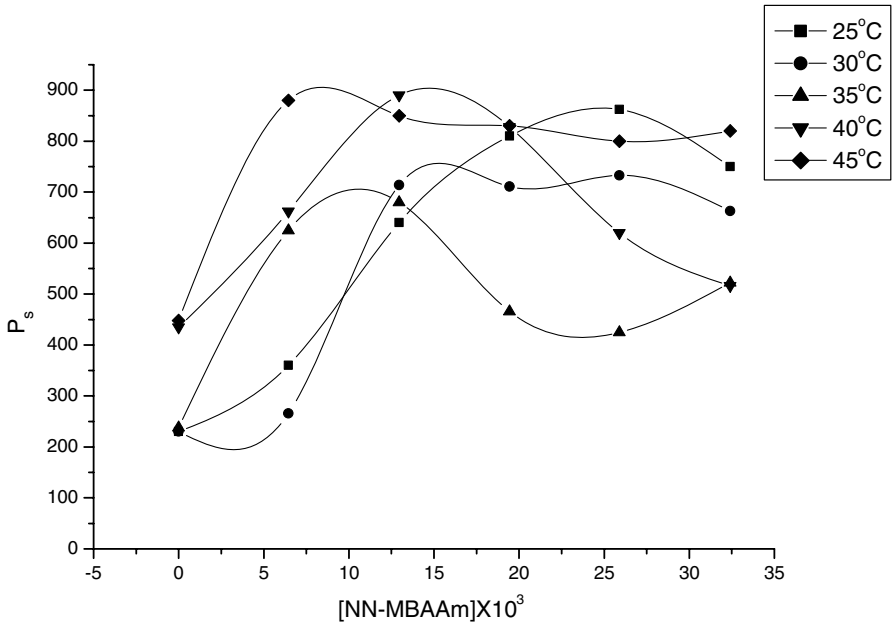


Fig. 5. Effect of temperature on P_s of psy-*cl*-poly(MAAm) prepared with different [NN-MBAAm]. [Swelling time = 24 h. (Reaction time = 2 h, temperature = 65 °C, [APS] = 1.095×10^{-2} mol/L, [MAAm] = 5.85×10^{-1} mol/L and psyllium = 1 g)].

swelling observed as the temperature rises in the swelling medium. This may be attributed due to the increase in kinetic energy of the solvent molecule and increase in rate of diffusion of water molecule with increase in temperature. P_s first increases and than decreases with leveling off with increase in [NN-MBAAm] from 6.45×10^{-3}–32.4×10^{-3} mol/L. Maximum P_s 890 was obtained at 12.95×10^{-3} mol/L [NN-MBAAm] at 40 °C. The crosslinking density increased with increase of crosslinker concentration and pore size of the crosslinked network decrease that was responsible for decrease in P_s.

3.2.3. Percent swelling as a function of pH

The pH of swelling medium has a significant effect on water uptake of these hydrogels. Effect of pH on P_s of hydrogels prepared with different [NN-MBAAm] is presented in the Fig. 6. It has been observed from the figure that Ps of psy-*cl*-poly(MAAm) at higher pH swelling medium was

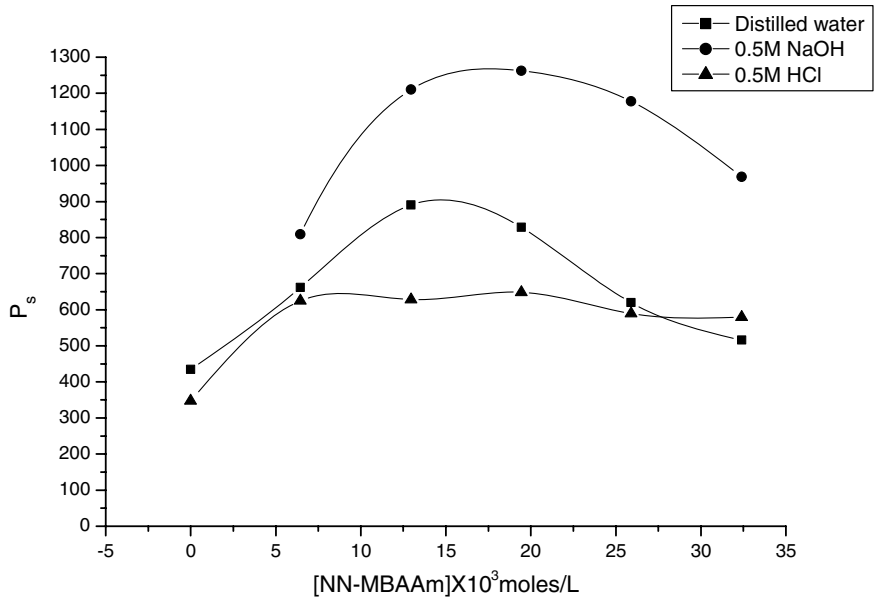


Fig. 6. Effect of pH on P_s of psy-*cl*-poly(MAAm) prepared with different [NN-MBAAm]. [Swelling time = 24 h and temp. = 40 °C. (Reaction time = 2 h, temperature = 65 °C, [APS] = 1.095×10^{-2} mol/L, [MAAm] = 5.85×10^{-1} mol/L and psyllium = 1 g)].

higher than that of the swelling media of lower pH. This is attributed to the reason that partial hydrolysis leads to the generation of new water interaction centers and especially new ion dipole interactions in the polymer chins, leading to the significant changes in the water uptake of these hydrogels. At lower pH the $-CONH_2$ groups does not ionized and keep the network at its collapsed state while at high pH it gets partially ionized, and the charged COO^- groups repel each other, leading to swelling of the polymer. Further, it was observed from the figure that polymer without cross-linker dissolved in 0.5 M NaOH solution. P_s first increases and than decrease with increase in [NN-MBAAm] in the networks in distilled water and 0.5 M NaOH solution. Maximum percent swelling 1262 was observed in the polymeric network having 19.45×10^{-3} mol/L of [NN-MBAAm] at 40 °C in 0.5 M NaOH. These observations indicate that these polymers are pH sensitive and have potential for use in colon specific drug delivery.

3.2.4. Percent swelling as a function of [NaCl]

In the present study, the percent swelling for the polymers, prepared with different [NN-MBAAm] was studied

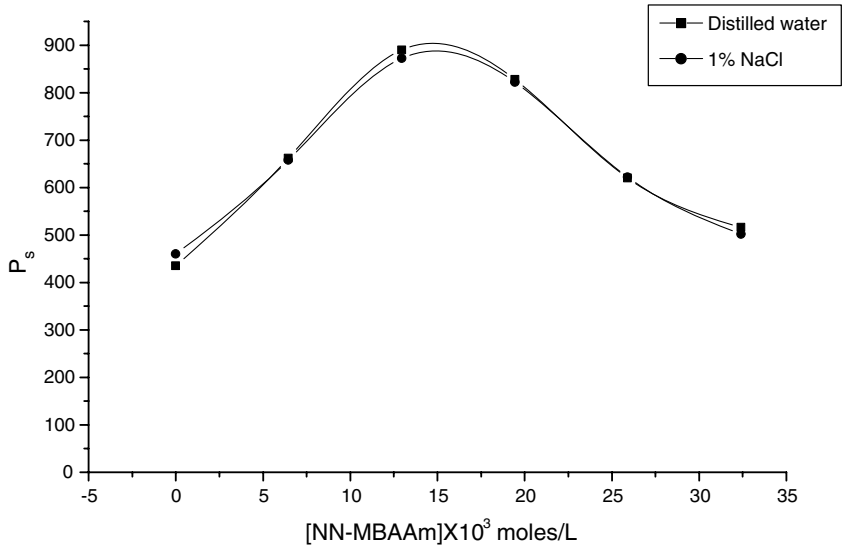


Fig. 7. Effect of [NaCl] on P_s of psy-*cl*-poly(MAAm) prepared with different [NN-MBAAm]. Swelling time = 24 h and temp. = 40 °C. (Reaction time = 2 h, temperature = 65 °C, [APS] = 1.095×10^{-2} mol/L, [MAAm] = 5.85×10^{-1} mol/L and psyllium = 1 g)].

in distilled water and 1% NaCl solution and results are shown in Fig. 7. Decrease in P_s has been observed in the brine solution as compare to distilled water at 40 °C. Hydrogels do not swell appreciably in the presence of electrolyte salts due to ex-osmosis as even the swollen hydrogels shrink dramatically in the presence of salts. The swelling ratios 2451 and 119 g/g of gel, have been reported in distilled water and in 0.9% NaCl solution, respectively, for the polymers prepared in an aqueous solution using acrylamide and 2-acrylamido-2-methyl-propanesulfonic acid (Liu, Xie, Zhu, & Zhang, 2004). Also the swelling ratio of the IPN hydrogels composed of poly(AAc) and poly(AN) decreased with an increasing [NaCl] in an aqueous solution (Kim, Lee, & Kim, 2004).

4. Mechanism and mathematical modeling for drug release from polymer matrix

4.1. Mechanism for drug release

In the hydrogels system, absorption of water from the environment changes the dimensions and physicochemical properties of the system and thus the drug release kinetics. A model based on the work of Alfrey et al. describes the swelling membrane, which consists of three zones. Adjacent to the bulk water is a layer of completely swollen gel. Then there is a thin layer in which the polymer chains are slowly hydrating and relaxing. The third zone is a matrix of unswollen, completely dried, rigid polymer. The diffusion of water in hydrogels is classified into three different types based on the relative rates of diffusion and polymer relaxation (Alfrey, Gurnee, & Lloyd, 1966). This classification of the diffusion of water in hydrogels can also be used to classify the drug release profile from the swelling polymer. Three type of diffusion mechanism of drug from polymeric matrix have been proposed: Fickian diffusion, non-Fickian diffusion and Case II diffusion (Peppas & Korsmeyer, 1987).

4.1.1. Case I or simple Fickian diffusion

Case I or Fickian diffusion occurs when the rate of diffusion is much less than that of relaxation. When the drug is loaded into the hydrogels by equilibrium swelling in the drug solution, drug release from the swollen gel follows Fick's law. Thus, the rate of drug release from the equilibrated slab device can be described by Eq. (1) and drug release from Case I systems is dependent on $t^{1/2}$ (Ritger & Peppas, 1987a, 1987b).

4.1.2. Case II diffusion

Case II diffusion (relaxation-controlled transport) occurs when diffusion is very rapid compared with the relaxation process. In Case II systems, diffusion of water through the previously swollen shell is rapid compared with the swelling-induced relaxation of polymer chains. Thus, the rate of water penetration is controlled by the polymer relaxation. For film specimens, the swelling zone moves into the membrane at a uniform rate and the weight gain increases in direct proportion to time. If the hydrogels contain a water-soluble drug, the drug is essentially immobile in a glassy polymer, but being a diffuse out as the polymer swells by absorbing water (Alfrey et al., 1966; Peppas & Korsmeyer, 1987).

4.1.3. Non-Fickian or anomalous diffusion

Non-Fickian or Anomalous diffusion occurs when the diffusion and relaxation rates are comparable. Drug release depends on two simultaneous rate processes, water migration into the device and drug diffusion through continuously swelling hydrogels is highly complicated (Ritger & Peppas, 1987a, 1987b).

4.2. Mathematical modeling for drug release

Although there are a number of reports dealing with mathematical modeling of drug release from swellable polymeric systems, no single model successfully predicts all the experimental observations (Bamba, Puisieus, Marty, & Carstensen, 1979; Brannon-Peppas & Peppas, 1989; Korsmeyer, Meerwall, & Peppas, 1986; Lee, 1980; Peppas, Gurny, Doelker, & Buri, 1980). Since most complex models do not yield a convenient formula and require numerical solution techniques, the generalized empirical equations have been widely used to describe both the water uptake through the swellable glassy polymers and the drug release from these devices. In the case of water uptake, the weight gain, M_s, is described by the following empirical equations:

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

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.

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

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. When the plot is drawn between $\ln M_t/M_\infty$ and $\ln t$, the slope of the plot gives the value of 'n' and intercept will inform about value of 'k'. This equation applies until 60% of the total amount of drug is released. It predicts that the fractional release of drug is exponentially related to the release time and it adequately describes the release of drug from slabs, spheres, cylinders and discs

from both swellable and non-swellable matrices. The values of '*n*' and '*k*' have been evaluated for the release studies of tetracycline from the plot drawn (Fig. 8a–c) and results are presented in Table 2.

4.3. Diffusion coefficients

Fick's first and second laws of diffusion adequately describe the most diffusion processes. For cylindrical

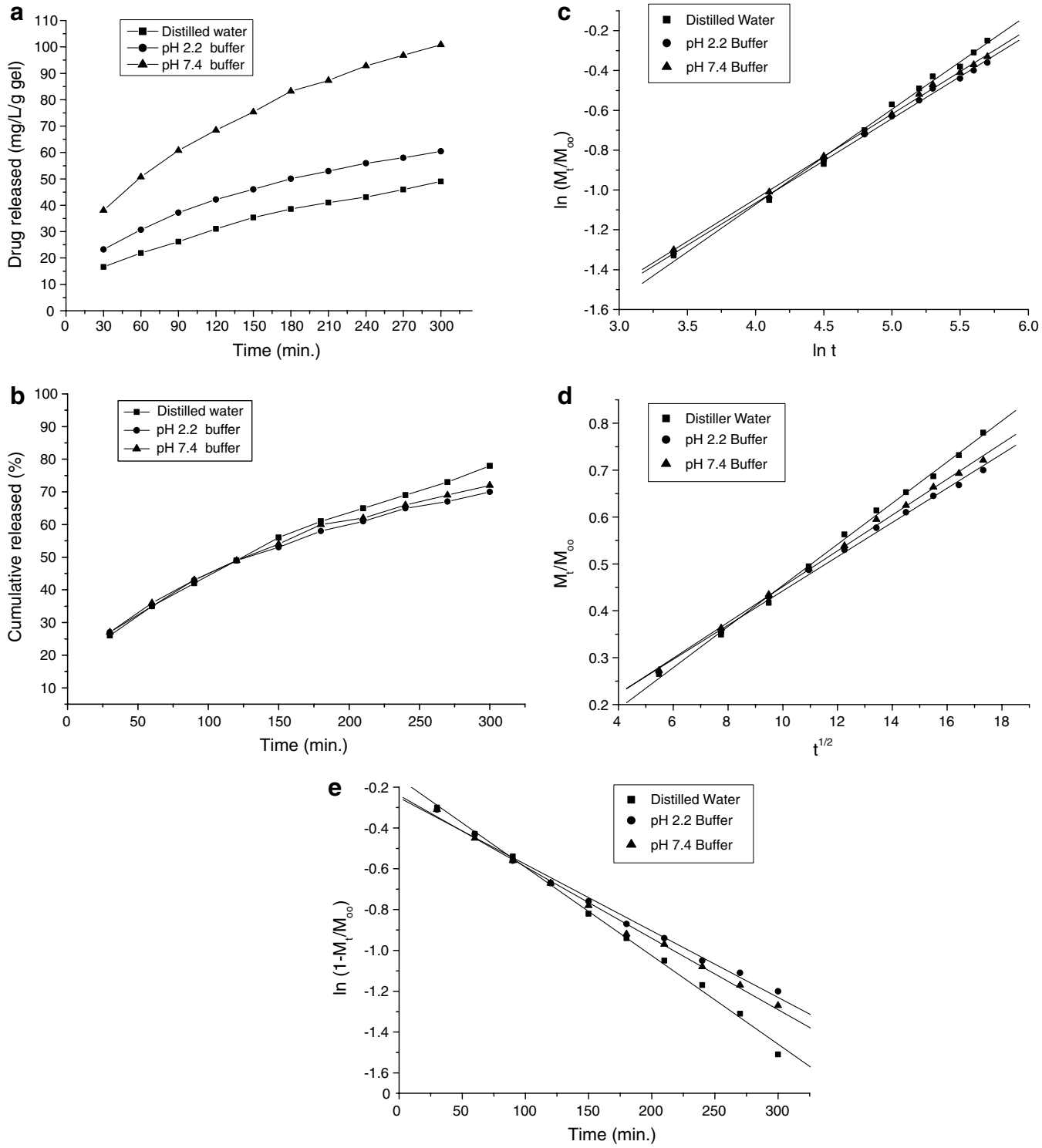


Fig. 8. (a) Release dynamics of tetracycline from drug loaded sample of psy-*cl*-poly(MAAm) in different medium at 37 °C. (b) % Cumulative released of tetracycline from drug loaded sample of psy-*cl*-poly(MAAm) in different medium at 37 °C. (c) Plot of $\ln M_t/M_\infty$ versus $\ln t$ for the release dynamics of tetracycline from the loaded hydrogel samples of psy-*cl*-poly(MAAm) in different release medium at 37 °C. (d) Plot of M_t/M_∞ versus $t^{1/2}$ for the fractional released of the tetracycline from the drug loaded hydrogel samples of psy-*cl*-poly(MAAm) in different release medium at 37 °C. (e) Plot of $\ln M_t/M_\infty$ versus time for the release dynamics of the tetracycline from the drug loaded hydrogel samples of psy-*cl*-poly(MAAm) in different release medium at 37 °C.

Table 2
Results of diffusion exponent '*n*', gel characteristic constant '*k*' and various diffusion coefficients for the release of tetracycline hydrochloride from drug loaded hydrogels samples of psy-*cl*-poly(MAAm)

Drug in releasing medium	Diffusion exponent '*n*'	Gel characteristic constant '*k*' $\times 10^2$	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	0.477	5.07	12.84	18.91	2.30
pH 2.2 buffer	0.423	6.34	8.02	16.71	1.52
pH 7.4 buffer	0.427	6.38	9.29	18.33	1.79

shaped hydrogels the integral diffusion is given in simple Eq. (3) (Ritger & Peppas, 1987a, 1987b)

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

where (M_t/M_∞) is the fractional release and M_t and M_∞ is drug released at time '*t*' and at equilibrium respectively, D is the diffusion coefficient and l is the thickness of the sample. In Eq. (3) the slope of linear plot between (M_t/M_∞) and $t^{1/2}$ yield initial diffusion coefficient D. Therefore, initial diffusion coefficient D_i was evaluated from the slope of the plot, as given below.

$$D_i = \left(\frac{(\text{slope})\ell^2\pi}{2}\right) \tag{4}$$

The plot of M_t/M_∞ versus $t^{1/2}$ has been shown in Fig. 8d drawn for the release tetracycline and values of initial diffusion coefficient D_i are presented in Table 2.

The average diffusion coefficient D_A can be calculated for 50% of the total release by putting $M_t/M_\infty = 0.5$ in the Eq. (3), which finally yields (5)

$$D_A = \frac{0.049\ell^2}{t^{1/2}} \tag{5}$$

where $t^{1/2}$ is the time required for 50% release of drug.

Late diffusion coefficients were calculated using the late time approximation in Eq. (6) (Ritger & Peppas, 1987a, 1987b)

$$\frac{M_t}{M_\infty} = 1 - \left(\frac{8}{\pi^2}\right)\exp\left[\frac{(-\pi^2 Dt)}{\ell^2}\right] \tag{6}$$

The slope of the plot between $\ln(1 - M_t/M_\infty)$ and t was used for the evaluation of D_L.

$$D_L = -\left[\frac{(\text{slope})\ell^2}{8}\right] \tag{7}$$

The values of D_L have been evaluated for the release studies of tetracycline in different release medium from the Fig. 8e and have been presented in Table 2.

4.4. Release dynamics of the drugs

The release of water-soluble drugs, entrapped in a hydrogels, occur only after water penetrates the polymeric networks to swell and dissolve the drug, followed by diffusion along the aqueous pathways to the surface of the device. The release of drug is closely related to the swelling characteristics of the hydrogels, which in turn, is a, key function of chemical architecture of the hydrogels. The release profile of tetracycline hydrochloride from per gram of the drug loaded hydrogels has been shown in the Fig. 8a and b. In the present study, the effect of pH on the release pattern of tetracycline has been studied by varying the pH of the release medium. It has been observed from the release profile that the 50% of the total release in each release medium occur in 120 min. However, amount of drug release in pH 7.4 buffer solution was higher than the pH 2.2 buffer and distilled water. The swelling of hydrogels [psy-*cl*-poly(MAAm)], increased when the pH of the medium changed from acidic to basic. At lower pH values the $-CONH_2$ groups of the polymeric matrix does not ionized and keep the polymeric networks at its collapsed state. At high pH values, it gets partially ionized, and the charged $-COO^-$ groups repel each other, leading to the higher swelling of the polymer and resultant into increase in drug diffusion from the polymeric network, which otherwise is immobilized in the glassy polymer. The diffusion exponent '*n*' have 0.477, 0.423 and 0.427 values and gel characteristic constant '*k*' have 5.07×10^{-2}, 6.34×10^{-2} and 6.38×10^{-2} values, respectively, in distilled water, pH 2.2 buffer and pH 7.4 buffer solution for the release of tetracycline hydrochloride from the hydrogels (Table 2). These values were obtained from the slope and intercept of the plot between $\ln M_t/M_\infty$ versus $\ln t$ (Fig. 8c). The values of the n indicated that the Fickian type diffusion mechanism occurs for the release of tetracycline from drug loaded psy-*cl*-poly (MAAm) networks in different release mediums and in Fickian mechanism the rate of diffusion of drug from the polymer is much less than that of rate of relaxation of polymer chains. In each release medium the values initial diffusion coefficient was observed to be more than the values of late time diffusion coefficient for the release of tetracycline from the drug loaded hydrogels, which indicates that in the start, the diffusion of drug from the polymeric matrix was faster than the latter stages (Table 2). Similar release behavior has been reported for guar gum based hydrogels. The pH-sensitive microgels, prepared with grafting of polyacrylamide onto guar gum, were loaded with diltiazem hydrochloride and nifedipine (both antihypertensive drugs) and their release studies were performed in both the simulated gastric and intestinal pH conditions. The release was relatively

quicker in pH 7.4 buffer than observed in 0.1 N HCl; the release followed non-Fickian transport in almost all the cases (Soppimath, Kulkarni, & Aminabhavi, 2001).

5. Conclusion

It is concluded from the foregone discussion that psyllium and methacrylamide based hydrogels have potential to be act as drug delivery devices, that to colon targeted, indicated from swelling responses of the hydrogels in the different swelling medium. Swelling of the hydrogels abruptly changes by changing the swelling medium from distilled water to the solution of high pH, indicating the pH sensitive nature of the polymers. It has also been concluded from the drug release dynamics that the drug released through the polymer matrix followed Fickian diffusion mechanism in different release mediums, for which, the rate of polymer chain relaxation was more as compare to the rate of drug diffusion from these hydrogels and it follows Fick's law of diffusion. In each release medium, the initial diffusion coefficient was more than late time diffusion coefficient.

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