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The release dynamics of model drugs from the psyllium and *N*-hydroxymethylacrylamide based hydrogels

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Abstract

In order to utilize the psyllium husk, a medicinally important natural polysaccharide, for developing the novel hydrogels for the controlled drug delivery device, we have prepared psyllium and *N*-hydroxymethylacrylamide based polymeric networks by using *N*,*N*′-methylenebisacrylamide (*N*,*N*′-MBAAm) as crosslinker. The polymeric networks thus formed were characterized with scanning electron micrography (SEM), FTIR and thermogravimetric analysis (TGA) techniques to study various structural aspects of the networks and also with the swelling response of the polymeric networks as a function of time, temperature, pH and [NaCl]. Equilibrium swelling has been observed to depend on both structural aspects of the polymers and environmental factors. Maximum P_s 748.3 was observed at 13.0×10^{-3} mol/L of [*N*,*N*′-MBAAm] in 0.5 M NaOH solution. The release dynamics of model drugs (salicylic acid and tetracycline hydrochloride) from hydrogels has also been discussed, for the evaluation of the release mechanism and diffusion coefficients. The effect of pH on the release pattern of tetracycline has been studied by varying the pH of the release medium. In release medium of pH 7.4 buffer the release pattern of tetracycline drastically changes to the extent that mechanism of drug diffusion shifted from non-Fickian diffusion to Fickian diffusion. It has been observed that diffusion exponent '*n*' have 0.71, 0.67 and 0.52 values and gel characteristic constant '*k*' have 1.552×10^{-2}, 2.291×10^{-2} and 5.309×10^{-2} values in distilled water, pH 2.2 buffer and pH 7.4 buffer, respectively, for tetracycline release. In solution of pH 7.4 buffer, 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. The value of the initial diffusion coefficient for the release of tetracycline hydrochloride was higher than the value of late time diffusion coefficient in each release medium indicating that in the start, the diffusion of drug from the polymeric matrix was fast as compare to the latter stages.

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

1. Introduction

Recently, an increasing number of studies suggested the use of polysaccharide hydrogels as colon-specific drug delivery device. An example of the colonic delivery of drugs is the local delivery of salicylate derivatives for the topical treatment of ulcerative colitis and sometimes the local treatment of irritable bowel syndrome. Some recent examples include bypassing small intestine metabolism, achieving constant absorption rates for some molecules and delivering cationized antioxidant enzymes to the colonic epithelium (Rubinstein, 1995). The release rate of drugs from hydrogels was primarily determined by the swelling extent which further enhanced by addition of enzyme in buffer solutions (Chiu et al., 1999) whereas swelling was depended on composition of copolymer and pH of the surrounding medium (El-Hag Ali Said, 2005). The in vitro release of salicylic acid from the poly[bi(*o*-carboxyphenyl)adipate-polyethylene glycol] anhydrides polymers increased with the increase of polyethylene glycol content in the polymers, the increase of pH value of degradation buffer solution and the rat cecal contents in the release media (Cai et al., 2003, 2005).

A semi interpenetrating polymer networks (IPNs) of carboxymethyl cellulose and crosslinked poly(acrylic acid) have been prepared and their water-sorption capacity have been evaluated as a function of chemical architecture of the IPNs, pH, and temperature of the swelling medium (Bajpai and Mishra, 2004). The in vitro release studies of riboflavin, Vitamin B_{12} and Vitamin B_2 from pH-sensitive co-polymeric hydrogels were

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carried out at the physiological temperature 37 °C (Bajpai and Saxena, 2004; Bajpai and Dubey, 2004, 2005). The gels exhibit a sharp pH-dependent release behavior. With increasing concentration of cross-linker in the gel, the drug released was found to decrease. Moreover, with low content of cross-linker a nearly zero-order profile was obtained. The size of the cylindrical devices also affected the release kinetics and a linear dependency was observed between $t^{1/2}$ (i.e., the time required for 50% release) and the square of the diameter, thus supporting the Tanaka–Fillmore theory. The controlled release of active anti-microbial agents such as amoxicillin (Risbud and Bhonde, 2000), metronidazole (Portero et al., 2002), oxytetracycline (Mi et al., 1997) and tetracycline-HCl (Bittner et al., 1999) from the hydrogels have been studied and reported in literature.

Psyllium is the common name used for several members of the plant genus *Plantago* and its seeds have used commercially for the production of mucilage. The 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 (a white fibrous material) hydrophilic nature 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 et al., 2004). Psyllium has been reported as a medicinally active natural polysaccharide. The cholesterol-lowering effect of psyllium has been reported in children (Davidson et al., 1996), as well as in adults (Oson et al., 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 et al., 1999; Florholmen et al., 1982; Rodriguez-Moran et al., 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 et al., 1999). Also, the combination of the two was slightly more effective than either 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 et al., 1998).

Psyllium if suitably tailored to prepare the hydrogels, which can act as the potential candidates for novel drug delivery devices. The chemical modification of mucilage of *Plantago psyllium* (Psy), is not much reported. Some work on the grafting of polyacrylamide and polyacrylonitrile onto psyllium has been reported for the use in flocculation studies (Agarwal et al., 2002; Mishra et al., 2002, 2003, 2004a,b). Singh and coworkers have studied the metal ion sorption and swelling behavior of psyllium and acrylic acid based hydrogels (Singh et al., 2006). Therefore, the present study is an attempt, to synthesize psyllium and *N*-HMAAm based hydrogels, by using *N*,*N*′-MBAAm as crosslinker and ammonium persulfate (APS) as initiator; The polymeric networks [Psy-*cl*-poly(*N*-HMAAm)], thus formed were characterized by SEM, FTIR, TGA, and swelling response of the hydrogels were studied as a function of time, temperature, pH and [NaCl]. The release dynamics of model drugs (salicylic acid and tetracycline hydrochloride) from hydrogels have also been discussed, for the evaluation of the release mechanism and diffusion coefficients.

2. Experimental

2.1. Materials and method

P. psyllium mucilage (Psy) was obtained from Sidpur Sat Isabgol factory (Gujrat, India), *N*-hydroxymethylacrylamide (*N*-HMAAm) (Merck-Schuchardt, Germany), Ammonium persulphate (APS), Salicylic acid and *N*,*N*′-methylenebisacrylamide (*N*,*N*′-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(N-HMAAm)

The optimum reaction parameters were evaluated for the synthesis of Psy-*cl*-poly(*N*-HMAAm) by varying [APS], [*N*-HMAAm] reaction time, amount of solvent from the morphology and swelling behavior of the polymeric networks (Table 1). Reaction carried out with 1 g of psyllium husk, 11×10^{-3} mol/L of APS, definite concentration of monomer and crosslinker in the aqueous reaction system at 65 °C temperature for 2 h. Polymers thus formed were stirred for 2 h in distilled water and for 2 h in ethanol to remove the soluble fraction and then were dried in air oven at 40 °C. At optimum reaction parameters different polymeric networks were synthesized by varying [*N*,*N*′-MBAAm] (from 6.45×10^{-3} to 32.40×10^{-3} mol/L) to study the effect of crosslinker variation on the structure of three dimensional networks and thereafter on the percent swelling of these polymeric networks. The polymer used for the study of release dynamics of model drugs was prepared with 15.0×10^{-3} mol/L of [*N*,*N*′-MBAAm] and 53.45×10^{-3} mol/L of [*N*-HMAAm].

2.3. Characterization

Psyllium and Psy-*cl*-poly(*N*-HMAAm) 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(*N*-HMAAm), SEMs were taken on Jeol Steroscan 150 Microscope.

2.3.2. Fourier transform infrared spectroscopy (FTIR)

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

2.3.3. Thermogravimetric analysis (TGA)

Thermo gravimetric analysis of psyllium and Psy-*cl*-poly(*N*-HMAAm) was carried out on a Schimatdzu Simultaneous Thermal Analyzer in air at a heating rate of 20 °C/min to examine the thermal properties of the polymers.

Table 1
Optimum reaction parameters for the synthesis of Psy-*cl*-poly(*N*-HMAAm)

S. no.	[APS] ($\times 10^3$ mol/L)	Water (mL)	Psyllium (g)	Time (min)	[*N*-HMAAm] ($\times 10^3$ mol/L)	Max. P_s (after 24 h)
1	11	20	1	120	53.45	623.3
2	22	20	1	120	53.45	604.4
3	33	20	1	120	53.45	333.3
4	44	20	1	120	53.45	226.6
5	55	20	1	120	53.45	167.7
6	22	10	1	120	53.45	236.8
7	14.6	15	1	120	53.45	407.6
8	11	20	1	120	53.45	623.3
9	8.8	25	1	120	53.45	793.0
10	7.3	30	1	120	53.45	×
11	11	20	0.2	120	53.45	×
12	11	20	0.4	120	53.45	×
13	11	20	0.6	120	53.45	×
14	11	20	0.8	120	53.45	780.0
15	11	20	1	120	53.45	623.3
16	11	20	1	30	53.45	×
17	11	20	1	60	53.45	924.8
18	11	20	1	90	53.45	436.7
19	11	20	1	120	53.45	623.3
20	11	20	1	150	53.45	602.8
21	11	20	1	180	53.45	338.0
22	11	20	1	120	10.7	×
23	11	20	1	120	21.4	×
24	11	20	1	120	32.1	268.7
25	11	20	1	120	42.75	325.8
26	11	20	1	120	53.45	623.3

[*N*,*N*′-MBAAm] = 15.0×10^{-3} mol/L; temperature of synthesis = 65 °C. '×' indicates uncrosslinked samples.

2.4. Swelling behavior

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 Spectronic 20D 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 of tetracycline hydrochloride were made to determine the amount of drug release from the drug loaded polymeric 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 released was measured spectrophotometrically by taking the absorbance of the solution after every 30 min at 370 nm and salicylic acid was measured by standard acid base titration method. The release studies for tetracycline were carried out in distilled water, pH 2.2 buffer and pH 7.4 buffer and in case of salicylic acid; it was done in distilled water. The drug release was measured after fixed interval of time and release dynamics of model drugs were studied.

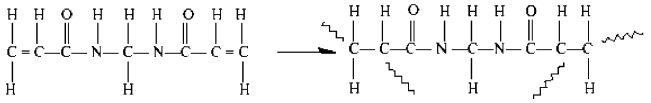
2.8. Preparation of buffer solution

Buffer solution of pH 2.2 was prepared by taking 50 mL of 0.2 M KCl and 7.8 mL of 0.2N 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 0.2N NaOH in volumetric flask to make volume 200 mL with distilled water.

3. Results and discussion

Polymeric networks were synthesized by chemically induced polymerization through free radical mechanism. APS has generated the reactive sites, both on the psyllium and monomer, leading to the propagation of the reaction. In the presence of crosslinker *N*,*N*′-MBAAm (CH_2=CHCONHCH$_2$ 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(*N*-HMAAm). These will resultant into the formation of three-dimensional networks. In order to study the effect of crosslinker concentration on structure of three-dimensional networks and thereafter on percent swelling, polymeric networks of different [*N*,*N*′-MBAAm] were prepared and characterized.



N,*N*′-methylenebisacrylamide

Linking sites of N, N'-methylenebisacrylamide

3.1. Characterization

Psyllium and Psy-*cl*-poly(*N*-HMAAm) were characterized by SEM, FTIR and TGA studies.

3.1.1. Scanning electron micrography

The morphology of psyllium and Psy-*cl*-poly(*N*-HMAAm) were examined by SEMs and presented in Fig. 1a and b, respectively. It was observed that psyllium has smooth and homogeneous morphology whereas Psy-*cl*-poly(*N*-HMAAm) has showed structural heterogeneity.

3.1.2. Fourier transform infrared spectroscopy

FTIR spectra of polymeric networks synthesized were studied to investigate incorporation of monomer in the network. The broad absorption bands at 3405.0 cm^{-1} due to –OH stretching indicate polymeric association. IR absorption bands due to C=O stretching has been prominently witnessed at 1653.7 because of substituted amide, i.e., –CONHCH$_2$OH– of poly(*N*-HMAAm) in Psy-*cl*-poly(*N*-HMAAm), and bands at 2926.3 and 2857.6 cm^{-1} represent asymmetric and symmetric C–H stretching vibrations of CH_2 group in crosslinked polymer. N–H out of plane bending at 670.2 cm^{-1} and C–O stretching of the N substituted group at 1111.8 cm^{-1} were observed apart from usual peaks in the psyllium. FTIR of psyllium and Psy-*cl*-poly(*N*-HMAAm) are shown in Fig. 2a and b, respectively.

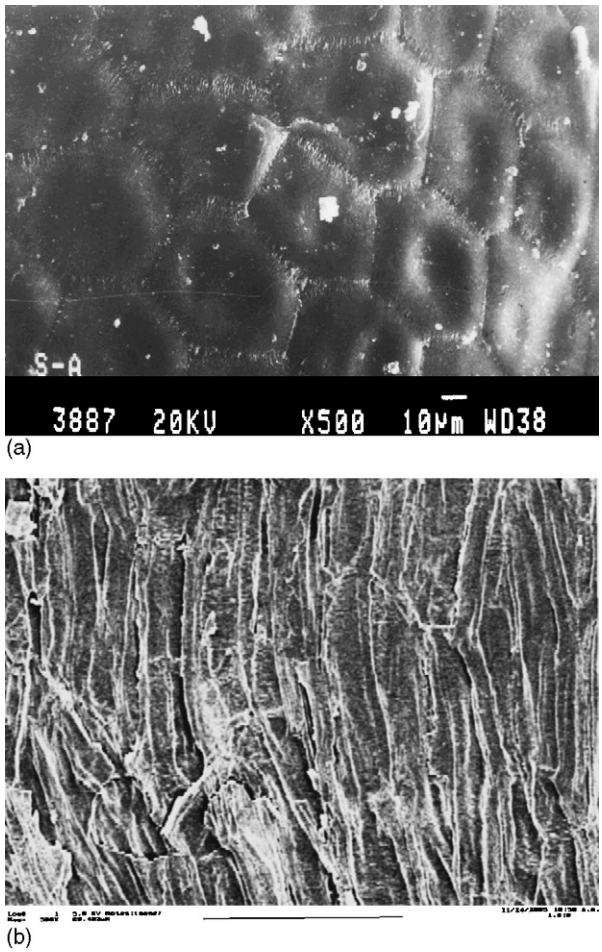


Fig. 1. (a) Scanning electron micrograph of psyllium. (b) Scanning electron micrograph of psyllium-*cl*-poly(*N*-HMAAm).

3.1.3. Thermo gravimetric analysis (TGA)

TGA of psyllium and Psy-*cl*-poly(*N*-HMAAm) illustrated that the mechanism of decomposition were different in both the cases (Fig. 3a and b). It was single stage decomposition in case of psyllium and two stage decomposition in crosslinked product. The initial decomposition temperature (IDT) of the psyllium and Psy-*cl*-poly(*N*-HMAAm) were observed at 230 and 144 °C, respectively. Final decomposition temperature (FDT) of the Psy-*cl*-poly(*N*-HMAAm) (580 °C) was observed higher than the psyllium (560 °C). It has been observed from Table 2 that the difference in decomposition temperature (DT) for the crosslinked polymeric networks was more as compared to psyllium; hence, the rate of decomposition with respect to temperature was slower in polymeric networks. It was thus understandable that thermal degradation started faster in case of Psy-*cl*-poly(*N*-HMAAm) but it becomes stable at higher temperature. Such thermal behavior of these networks are explained by fact that –CONH– groups Psy-*cl*-poly(*N*-HMAAm) degrade easily by dehydration and deformylation, and generating more stable groups as –CN those are thermally very stable and can undergo cyclization reactions at higher temperature. This observation was further supported by the decomposition temperature corresponding to the 10% weight loss (Table 2).

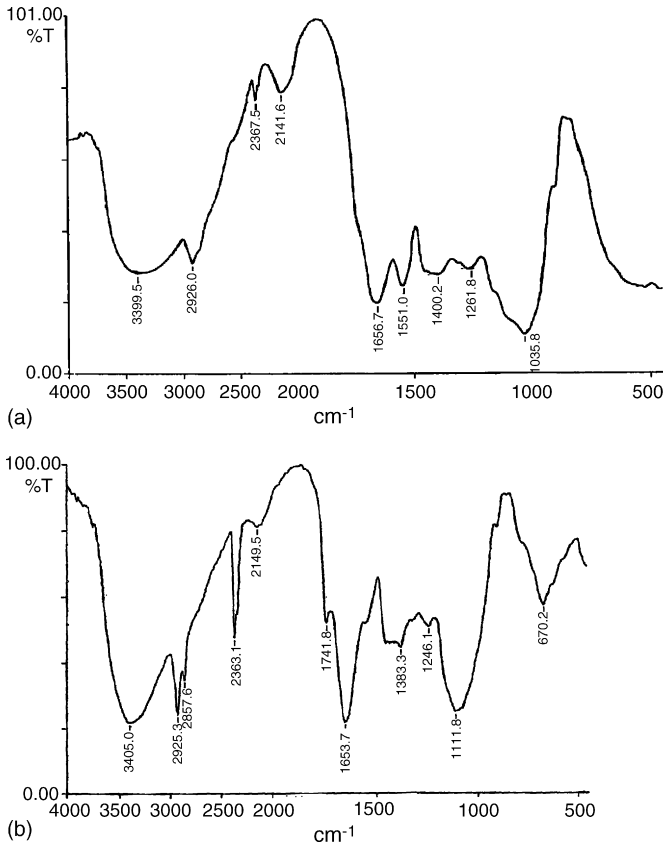


Fig. 2. (a) FTIR spectra of psyllium. (b) FTIR spectra of Psy-*cl*-poly(*N*-HMAAm).

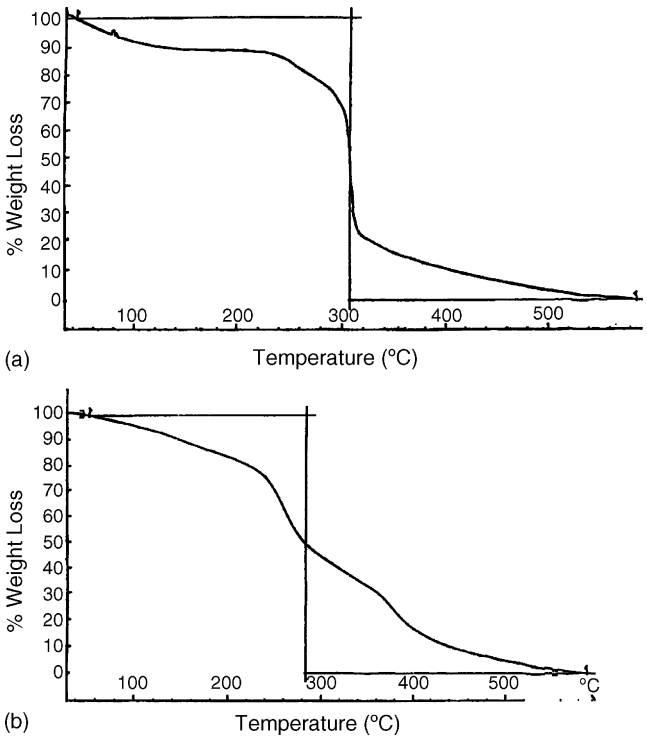


Fig. 3. (a) TGA of psyllium. (b) TGA of Psy-*cl*-poly(*N*-HMAAm).

3.2. Swelling studies

Swelling behavior of Psy-*cl*-poly(*N*-HMAAm) prepared with different [*N*-MBAAm] was studied as a function of time, temperature, pH and [NaCl].

3.2.1. P_s as a function of time

The swelling behavior of polymeric networks was studied at time interval of 10 min, 30 min, 1 h, 2 h, and 24 h to determine the time for equilibrium swelling. The effect of different crosslinker concentration on the percent swelling has been shown in Fig. 4. It has been observed from the figure that P_s increases with increase in swelling time until the equilibrium attained and for each polymeric network and percent swelling decreases with increase in [*N*,*N*′-MBAAm] in the polymer. Maximum P_s 538 was obtained for the polymeric matrix prepared with 13.0×10^{-3} mol/L [*N*,*N*′-MBAAm].

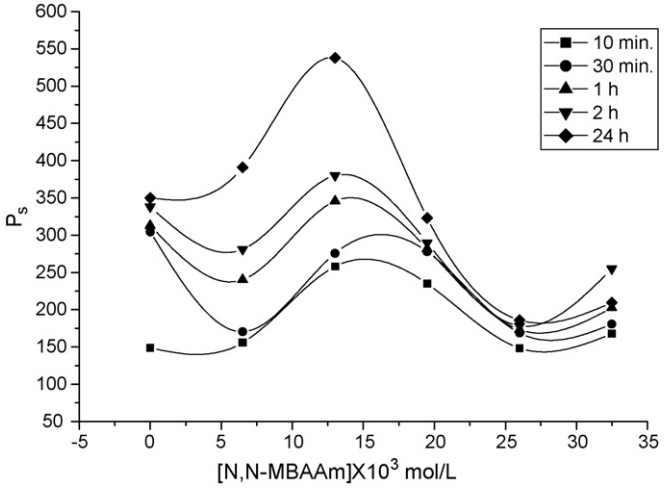


Fig. 4. Effect of time on P_s of Psy-*cl*-poly(*N*-HMAAm) prepared with different [*N*,*N*′-MBAAm] (swelling temperature = 37 °C) (reaction time = 2 h, temperature = 65 °C, [APS] = 1.095×10^{-2} mol/L, [*N*-HMAAm] = 5.35×10^{-1} mol/L and psyllium = 1 g).

Table 2
Thermogravimetric analysis of psyllium and Psy-*cl*-poly(*N*-HMAAm)

Sample	IDT (°C)	FDT (°C)	DT (°C) at every 10% weight loss									
			10	20	30	40	50	60	70	80	90	100
Psyllium	230	560	230	274	295	300	305	305	315	320	395	560
Psy-*cl*-poly(*N*-HMAAm)	144	580	144	226	250	265	284	328	362	390	435	580

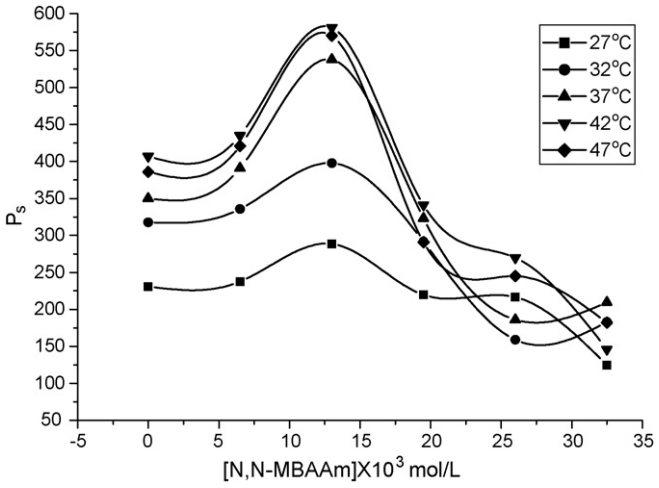


Fig. 5. Effect of temperature on P_s of Psy-*cl*-poly(*N*-HMAAm) prepared with different [*N*,*N*′-MBAAm] (swelling time = 24 h (reaction time = 2 h, temperature = 65 °C, [APS] = 1.095 × 10^{-2} mol/L, [*N*-HMAAm] = 5.35 × 10^{-1} mol/L and psyllium = 1 g).

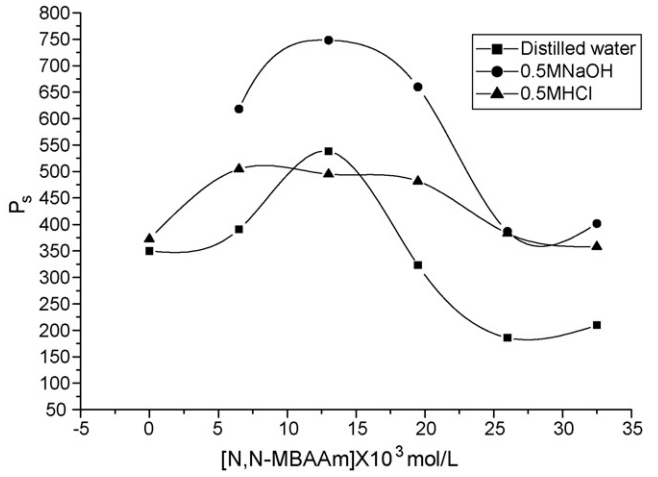


Fig. 6. Effect of pH on P_s of Psy-*cl*-poly(*N*-HMAAm) prepared with different [*N*,*N*′-MBAAm] (swelling time = 24 h and temperature = 37 °C) (reaction time = 2 h, temperature = 65 °C, [APS] = 1.095 × 10^{-2} mol/L, [*N*-HMAAm] = 5.35 × 10^{-1} mol/L and psyllium = 1 g).

3.2.2. P_s as a function of temperature

To study the effect of temperature on swelling equilibrium, percent swelling of hydrogels has been carried out at different temperature (i.e. 27, 32, 37, 42 and 47 °C) and results are shown in Fig. 5. It has been observed from the figure that the percent swelling decreases with increase in [*N*,*N*′-MBAAm] from 6.5 × 10^{-3} to 32.5 × 10^{-3} mol/L in the polymeric networks at each temperature and maximum P_s 538 was obtained at 13.0 × 10^{-3} mol/L [*N*,*N*′-MBAAm] at 37 °C. It is because of the reason that the crosslinking density increases with increase of crosslinker concentration and pore size of the crosslinked network decrease in the networks. It has also been observed that a very small concentration of cross-linker brings abrupt transition from liquid to gel state during synthesis of hydrogels. P_s increased with increase in temperature of the swelling medium till the swelling equilibrium occur. The Kim et al. have reported similar observation. They have observed that the swelling ratio increased with increasing temperature in polyelectrolyte complex hydrogels composed of various weight ratios of chitosan and hyaluronic acid (Kim et al., 2004a,b).

3.2.3. P_s as a function of pH

In order to observe the effect of pH on the swelling equilibrium, percent swelling has been carried out in solution 0.5 M NaOH, 0.5 M HCl and in distilled water and results are shown in Fig. 6. It has been observed from the figure that percent swelling of Psy-*cl*-poly(*N*-HMAAm) in 0.5 M NaOH solution was higher than the swelling in the distilled water and swelling in 0.5 M HCl solution. At lower pH values the –CONH-groups do not ionized and keep the network at its collapsed state. At high pH values, it is partially ionized, and the charged COO^- groups repel each other, leading to swelling of the polymer. Further, it has been observed from the figure that polymer without crosslinker dissolved in 0.5 M NaOH solution. Maximum P_s 748.3 was observed in the polymers prepared with 13.0 × 10^{-3} mol/L of [*N*,*N*′-MBAAm] after that the P_s decreases with increase in [*N*,*N*′-MBAAm] in the polymeric networks. Similar observation has been reported by Chauhan et al. (2003).

3.2.4. P_s as a function of salt

It is important to understand the osmotic and structural changes of hydrogels induced by addition of salts with respect to many physical and chemical processes in biological systems. Hydrogels do not swell appreciably in the presence of electrolyte salts due to ex-osmosis and even the swollen hydrogels shrink dramatically in the presence of salts. Hydrogels shriveling results from the loss of hydrophilic–hydrophobic balance of the networks in the presence of electrolyte salts. Thus, the pre-swollen gels shrink quickly and regain their original shape and weight by de-swelling when they are subjected to electrolyte salt solutions. In the present study, P_s swelling was carried out in 0.9% NaCl solution for the polymers prepared with different crosslinker concentration and shown in Fig. 7. It was observed that percent solvent uptake decreases in saline solution of 0.9% and also it decreases with increase in crosslinker concentration. The swelling ratio of the IPN hydrogels composed of poly(AAc) and poly(AN) were decreased with an increasing [NaCl] in an aqueous solution (Kim et al., 2004a,b).

3.3. Mechanism for drug release from polymer matrix

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. described the swelling membrane, which consists of three zones. Adjacent to the bulk water is a layer of completely swollen gel. Then there is a fairly 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 permeant (i.e., water in hydrogels) was classified into three different types based on the relative rates of diffusion and polymer relaxation (Alfrey

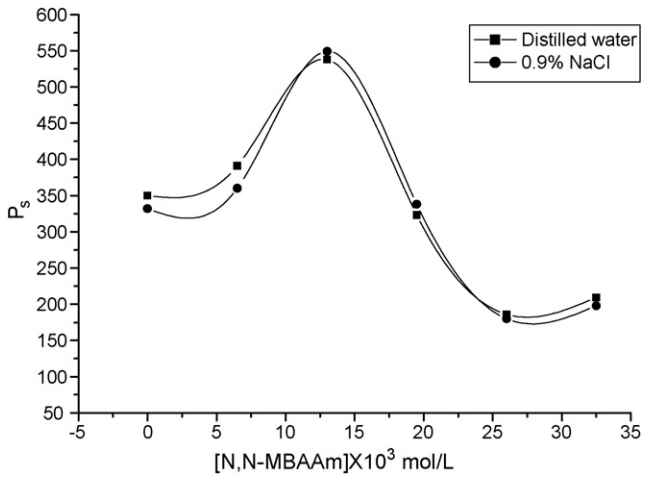


Fig. 7. Effect of [NaCl] on P_s of Psy-*cl*-poly(*N*-HMAAm) prepared with different [*N*,*N*′-MBAAm] (swelling time = 24 h and temperature = 37 °C) (reaction time = 2 h, temperature = 65 °C, [APS] = 1.095×10^{-2} mol/L, [*N*-HMAAm] = 5.35×10^{-1} mol/L and psyllium = 1 g).

et al., 1966). This classification of the diffusion of permeant can also be used to classify the drug release profiles from the swelling polymer (Peppas and Korsmeyer, 1987). This classification of diffusion of drug from the polymeric matrix is as follows.

3.3.1. 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. (2) and drug release from Case I systems is dependent on $t^{1/2}$ (Ritger and Peppas, 1987a,b).

3.3.2. 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 and Korsmeyer, 1987).

3.3.3. 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 and Peppas, 1987a,b).

3.4. Mathematical modeling of 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 (Brannon-Peppas and Peppas, 1989; Korsmeyer et al., 1986; Lee, 1980; Peppas et al., 1980).

Since most complex models do not yield a convenient formula and require numerical solution techniques, the generalized empirical equations has 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 and Peppas, 1987a,b). In this case, M_t/M_∞ replace M_s in above equation to give

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

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 tell about 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 (Figs. 8 and 9). The values of 'n' and 'k' have been evaluated for the release studies of salicylic acid and tetracycline from the plot drawn (Figs. 8c and 9c), respectively, and results are presented in Table 3.

3.5. Diffusion coefficients

Fick's first and second laws of diffusion adequately describe the most diffusion processes. For cylindrical shaped hydrogels the integral diffusion is given in simple Eq. (3) (Ritger and Peppas, 1987a,b)

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

where (M_t/M_∞) is the fractional release and M_t and M_∞ is drug released at time 't' and at equilibrium, respectively, D 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 diffusion coefficient D. Therefore, initial diffusion coefficient D_i for sali-

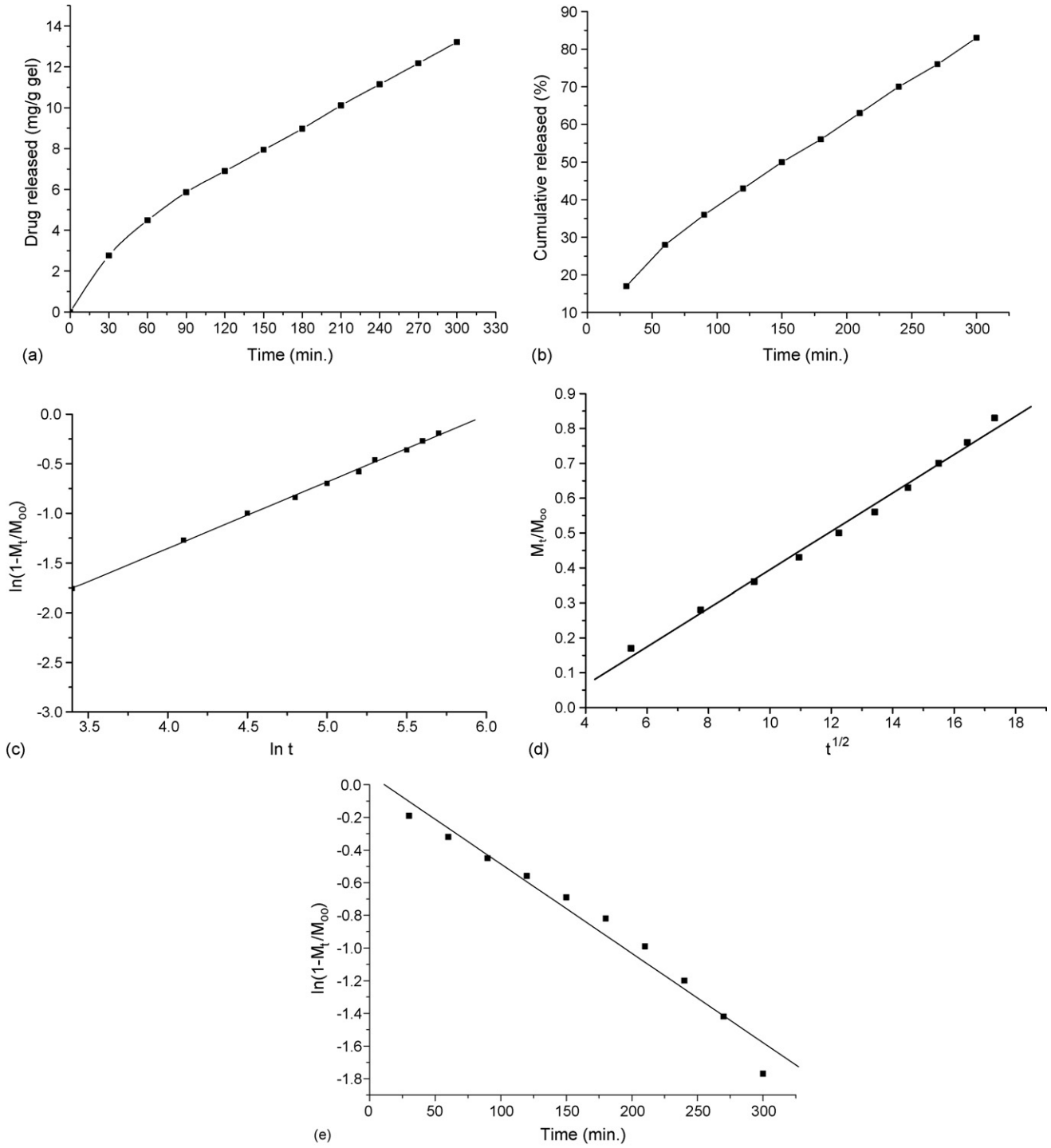


Fig. 8. (a) Release dynamics of salicylic acid from drug loaded sample of Psy-*cl*-poly(*N*-HMAAm) in distilled water at 37 °C. (b) %Cumulative released of salicylic acid from drug loaded sample of Psy-*cl*-poly(*N*-HMAAm). (c) Plot of $\ln M_t/M_\infty$ vs. $\ln t$ for the release dynamics of salicylic acid from the loaded hydrogel samples of Psy-*cl*-poly(*N*-HMAAm) in distilled water at 37 °C. (d) Plot of M_t/M_∞ vs. $t^{1/2}$ for the fractional released of the salicylic acid from the drug loaded hydrogel samples of Psy-*cl*-poly(*N*-HMAAm) in distilled water at 37 °C. (e) Plot of $\ln(1 - M_t/M_\infty)$ vs. time for the release dynamics of the salicylic acid from the drug loaded hydrogel samples of Psy-*cl*-poly(*N*-HMAAm) in distilled water at 37 °C.

cylic acid and tetracycline release was evaluated from the slope of the plot shown in Figs. 8d and 9d, respectively, and results are presented in Table 3.

The average diffusion coefficient D_A may also be calculated for 50% of the total release by putting $M_t/M_\infty = 0.5$ in the Eq. (3), which finally yields (4)

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

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

Table 3
Results of diffusion exponent 'n', gel characteristic constant 'k' and various diffusion coefficients for the release of salicylic acid and tetracycline hydrochloride from drug loaded hydrogels samples of Psy-*cl*-poly(*N*-HMAAm)

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, $D_L \times 10^4$
Salicylic acid	0.67	1.626	4.00	3.364	0.57
Tetracycline hydrochloride					
Distilled water	0.71	1.552	5.01	3.76	0.67
pH 2.2 buffer	0.67	2.291	10.30	9.11	1.71
pH 7.4 buffer	0.52	5.309	6.38	8.52	1.52

Late diffusion coefficients were calculated using the late-time approximation as described by Peppas given in Eq. (5) (Ritger and Peppas, 1987a,b).

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

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

The values of D_L have been evaluated for the release studies of salicylic acid and tetracycline from Figs. 8e and 9e, respectively, and has presented in Table 3.

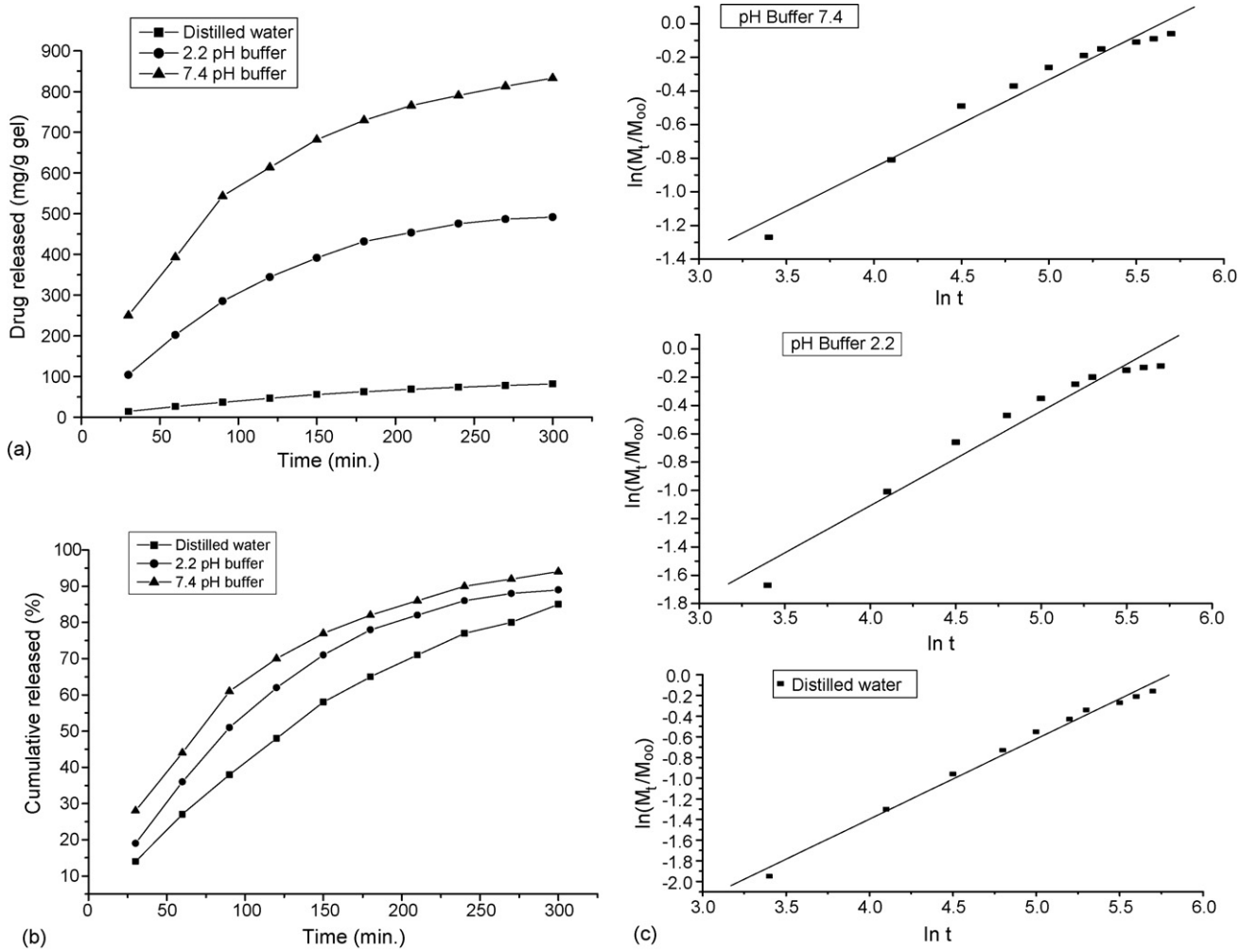


Fig. 9. (a) Release dynamics of tetracycline from drug loaded sample of Psy-*cl*-poly(*N*-HMAAm) in different medium at 37 °C. (b) %Cumulative released of tetracycline from drug loaded sample of Psy-*cl*-poly(*N*-HMAAm) in different medium at 37 °C. (c) Plot of $\ln M_t/M_\infty$ vs. $\ln t$ for the release dynamics of tetracycline from the loaded hydrogel samples of Psy-*cl*-poly(*N*-HMAAm) in different medium at 37 °C. (d) Plot of M_t/M_∞ vs. $t^{1/2}$ for the fractional released of the tetracycline from the drug loaded hydrogel samples of Psy-*cl*-poly(*N*-HMAAm) in different medium at 37 °C. (e) Plot of $\ln(1 - M_t/M_\infty)$ vs. time for the release dynamics of the tetracycline from the drug loaded hydrogel samples of Psy-*cl*-poly(*N*-HMAAm) in distilled water at 37 °C.

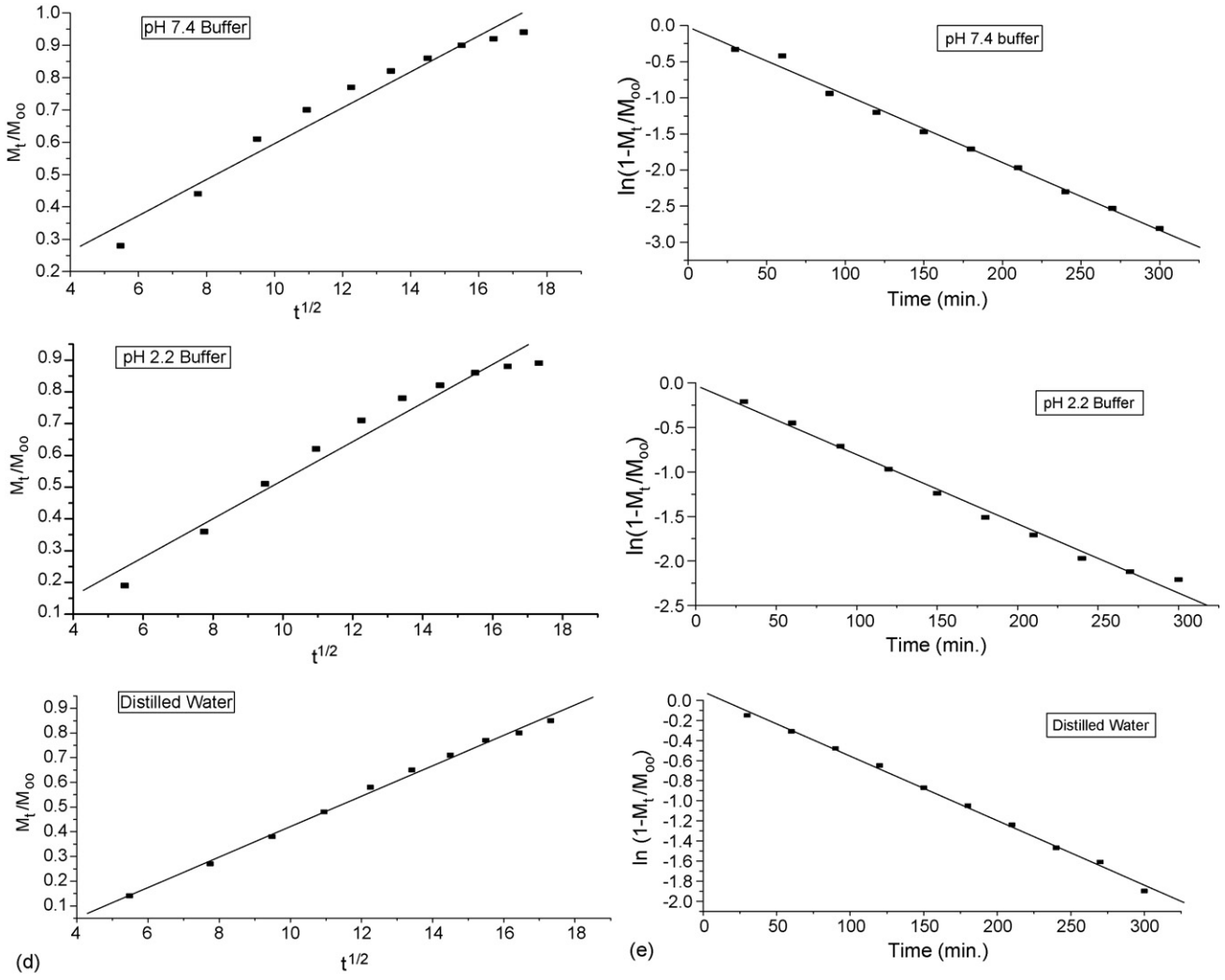


Fig. 9. (*Continued*).

3.6. Release dynamics of the drugs

The release of water-soluble drug, entrapped in a hydrogels, occur only after water penetrates the networks to swell the polymer 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. From the percent cumulative release studies of salicylic acid and tetracycline it has been observed that first 50% of the total release occurred in 150 min (Fig. 8b) whereas in case of tetracycline the first 50% of the total release of tetracycline occurred in 70, 90 and 120 min in releasing medium of pH 7.4 buffer, pH 2.2 buffer and distilled water, respectively (Fig. 9b), which is further supported by the fact that initial diffusion coefficient was more than late diffusion coefficient.

In case of release dynamics of salicylic acid diffusion exponent 'n' and gel characteristic constant 'k' was observed to be 0.67 and 1.626×10^{-2}, respectively. Hence non-Fickian or anomalous diffusion occurs and the diffusion of salicylic acid and relaxation rates of polymeric chains is comparable. Drug release depends on two simultaneous rate processes, water migration into the device and drug diffusion through continuously swelling hydrogels. Initial diffusion coefficient, average diffusion coefficient and late time diffusion coefficient was observed to be 4.0×10^{-4}, 3.364×10^{-4} and 0.57×10^{-4} (cm^2/min), respectively.

In the present study the effect of pH on the release pattern of tetracycline have been studied by varying the pH of the release medium. In release medium of pH 7.4 buffer the release pattern of tetracycline drastically changed. It was observed from Table 3 that mechanism of drug diffusion changes from non-Fickian to Fickian diffusion. It is clear from the table that diffusion exponent 'n' have 0.71, 0.67 and 0.52 values and gel characteristic constant 'k' have 1.552×10^{-2}, 2.291×10^{-2} and 5.309×10^{-2} values in distilled water, pH 2.2 buffer and pH 7.4 buffer, respectively. It means rate of polymer chain relaxation is more as compare to the rate of drug diffusion in pH 7.4 buffer and tetracycline release from the hydrogels follows Fick's law and drug release dependent on $t^{1/2}$. However in each release medium the initial diffusion coefficient was more than late time diffusion coefficient (Table 3).

4. Conclusion

Swelling of the polymeric networks was affected by synthetic conditions [*N*-MBAAm] and also by the environmental factors such as pH of the medium, ionic strength of the solution and swelling temperature. Further, from the observation of water uptake in the different swelling media and from the release dynamics of the tetracycline, it can be concluded that these polymeric networks are pH sensitive and are able to respond to the environmental changes. Therefore, these can act as targeted drug delivery devices. It is also concluded from the drug release dynamics that drug released through the polymeric matrix follows non-Fickian diffusion mechanism in distilled water and Fickian diffusion mechanism in pH 7.4 buffer solution.

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