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The release dynamics of salicylic acid and tetracycline hydrochloride from the psyllium and polyacrylamide based hydrogels (II)

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Abstract

Psyllium, a medicinally active natural polysaccharide, has been modified with polyacrylamide to develop the hydrogels; those can act as the potential candidate for novel drug delivery systems. In the present studies, the release dynamics of model drugs (salicylic acid and tetracycline hydrochloride) from the drug-loaded hydrogels have been discussed, for the evaluation of the drug release mechanism and diffusion coefficients. It has been observed that diffusion exponent 'n' have 0.68 and 0.74 values and gel characteristic constant 'k' have 1.625×10^{-2} and 1.272×10^{-2} values, respectively, for the release of salicylic acid and tetracycline hydrochloride in distilled water from the drug loaded hydrogels. Therefore, drug release from the drug loaded hydrogels through Non-Fickian or Anomalous diffusion mechanism where the rate of drug diffusion and rate of polymer relaxation were comparable. The effect of pH on the release pattern of tetracycline has been studied by varying the pH of the release medium. However, in each release medium, the Initial diffusion coefficient was observed to be more than the late time diffusion coefficient.

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

1. Introduction

A number of drug delivery devices have been proposed to deliver the drug for efficient therapy (Chourasia & Jain, 2003). Among them, hydrogels, specially based on polysaccharides, have attracted considerable attention as an excellent candidates for controlled release devices or targetable devices of the therapeutic agents (Chourasia & Jain, 2004). The in vitro release of salicylic acid from the polymers increased with the increase of monomer content in the polymers, the increase of pH value of degradation buffer solution and the rat cecal contents (Bajpai, Bajpai, Shukla, & Kulkarni, 2004; Cai, Zhu, & Zhang, 2005; Cai, Zhu, Chen, & Gao, 2003; Rubinstein, 1995).

The release rate of drugs from hydrogels was primarily determined by the swelling extent, which further enhanced by addition of enzyme in the buffer solutions (Chiu, Hsiue, Lee, & Huang, 1999) whereas swelling of polymeric networks was depended on composition of copolymer and pH of the surrounding medium (El-Hag Ali Said, 2005). Colonic delivery of drugs is associated with the local delivery of salicylate derivatives to the large intestine for the topical treatment of ulcerative colitis and sometimes the local treatment of irritable bowel syndrome (Rubinstein, 1995). From the release dynamics of diclofenac sodium, propranolol hydrochloride and vitamin B_6 hydrochloride, as hydrophilic model drugs from the gels, it was observed that the drug concentrations was more in the large intestine as compare to the upper part of the gastrointestinal tract (Orienti, Trere, & Zecchi, 2001). It indicates, gels exhibit a sharp pH-dependent release behavior. With increasing concentration of cross-linker in the gel, the drug released was found to decrease.

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Moreover, with low content of cross-linker in the polymeric networks, 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 $t^{1/2}$. The in vitro release studies of riboflavin, vitamin B_{12} and vitamin B_2 from pH-sensitive co-polymeric hydrogels were carried out at the physiological temperature 37 °C by Bajpai and co-workers (Bajpai & Mishra, 2004; Bajpai & Saxena, 2004; Bajpai & Dubey, 2004, 2005).

The controlled release of active anti-microbial agents-amoxicillin (Risbud & Bhonde, 2000), metronidazole (Portero, Remunan-Lopez, Criado, & Alonso, 2002), oxytetracycline (Mi, Wong, & Shyu, 1997) and tetracycline-HCl (Bittner, Mader, Kroll, Borchert, & Kissel, 1999) from the polymeric matrix have been well reported in literature. Freeze-dried membranes could serve as potent candidates for antibiotic delivery in an acidic environment. Increased swelling of hydrogels, under acidic conditions, was due to the protonation of a primary amino group on chitosan. Freeze-dried membranes released around 73% of the amoxicillin (33% by air-dried) in 3 h at pH 1.0 and, thus, have superior drug-release properties to air-dried hydrogels (Cerchiara et al., 2003; Risbud, Hardikar, Bhat, & Bhonde, 2000).

Psyllium is the common name used for several members of the plant genus *Plantago*; its seeds are used commercially for the production of mucilage. Gel-forming fraction of mucilage is alkali-extractable polysaccharides, composed of arabinose, xylose and traces of other sugars (Fischer, Nanxiong, Ralph, Andersond, & Marletta, 2004). Psyllium is medicinally important polysaccharide, it has been used for the treatment of constipation (Leung & Foster, 1996), to improved blood sugar levels in some people with diabetes (Florholmen, Arvidsson-Lenner, Jorde, & Burhol, 1982) and lowering the cholesterol levels in children as well in adults (Davidson, Dugan, & Burns, 1996; Oson, Anderson, & Becker, 1997). Psyllium has also 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). In a double-blind trial, people with ulcerative colitis had a reduction in symptoms such as bleeding and remained in remission longer when they have taken 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) Also, the combination of the two was slightly more effective than either alone.

Modification of the psyllium to develop the hydrogels is not much reported in the literature. Singh and co-workers have first time modified the psyllium to prepare the hydrogels (Singh, Chauhan, Bhatt, & Kumar, 2006; Singh, Chauhan, Dhiman, & Chauhan, in press). Keeping in view, the pharmacological importance of these polysaccharides, an attempt has been made to explore the potential of the psyllium and poly(AAM) based hydrogels for the use as the novel drug delivery device. Therefore, the present study is an attempt, to synthesize psyllium and poly(AAm) based hydrogels by using *N*,*N*-MBAAm as crosslinker and ammonium persulfate (APS) as initiator and thereafter utilization of these hydrogels to study the release dynamics of the model drugs (salicylic acid and tetracycline hydrochloride) from the drug loaded samples. The observations thus obtained, were utilized to describe the releases mechanism and diffusion coefficient of the model drugs, from these polymeric matrix.

2. Experimental

2.1. Materials and method

Plantago psyllium mucilage (psy) was obtained from an Sidpur Sat Isabgol factory (Gujrat, India), acrylamide (AAm) was obtained from the Merck-Schuchardt, Germany, ammonium persulphate (APS), *N*,*N*-methylenebisacrylamide (NN-MBAAm) and salicylic acid from *SD*. Fine Mumbai India were used as received. Tetracycline hydrochloride was obtained from the Ind-Swift Limited, Chandigarh, India.

2.2. Synthesis of Psy-cl-poly(AAm)

The optimum reaction conditions for the modification of psyllium to hydrogels has been discussed somewhere else (Singh et al. (2006, in press)). Reaction was carried out with 1 g of psyllium husk, 1.095×10^{-2} mol/L of APS, 7.03×10^{-1} mol/L of AAm, 16.20×10^{-3} mol/L of *N*,*N*-MBAAm in the aqueous reaction system at 65 °C temperature for 2 h. Polymers thus formed were stirred for two hours in distilled water and for two hours in ethanol to remove the soluble fraction and then were dried in air oven at 40 °C. The resultant polymeric network Psy-*cl*-poly(AAm), were used to study the release dynamics of the model drugs from the drug loaded hydrogels.

2.3. 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).

2.4. Drug loading to the polymer matrix

The loading of a drug onto hydrogels was carried out by swelling equilibrium method. The hydrogel was allowed to

swell in the drug solution of known concentration for 24 h at 37 °C and than dried to obtain the release device. The concentration of the rejected solution was measured to calculate percent entrapment of the drug in the polymer matrix.

2.5. 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 tetracycline released was measured spectrophotometrically and amount of salicylic acid was measured by standard acid base titration method. The release studies for tetracycline were done in distilled water, 2.2 pH buffer and 7.4 pH buffer and in case of salicylic acid the release studies were done in distilled water. The drug release was measured after fixed interval of time and release dynamics of model drugs were calculated.

2.6. 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. 0.2 M KCl solution was prepared by dissolving 14.911 g of KCl in distilled water to make the volume 1000 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. 0.2 M KH_2PO_4 was prepared by dissolving 27.218 g. KH_2PO_4 in distilled water to make volume 1000 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 NN-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(AAm) These will resultant into the formation of three-dimensional networks i.e. Psy-*cl*-poly(AAm), which were used to study the in vitro release of the model drugs.

3.1. Characterization

Psyllium and Psy-*cl*-poly(AAm) were characterized by SEM, FTIR and TGA techniques and discussed in detailed in our earlier studies (Singh et al.).

3.2. 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. 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 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 water in hydrogels was 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 profiles from the swelling polymer (Peppas & Korsmeyer, 1987). They are:

3.2.1. 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).

3.2.2. 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).

3.2.3. 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).

3.3. 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 (Bamba, Puisieus, Marty, & Carstensen, 1979; Brannon-Peppas & Peppas, 1989; Korsmeyer, Meerwall, & Peppas, 1986; Lee, 1980; Peppas, Gurny, Doelker, & Buri, 1980).

Fickian, Non-Fickian and Case II diffusion mechanism of the drugs from the polymeric matrix can be calculated from the following equation

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

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. For Normal Fickian diffusion the value of $n = 0.5$, Case II diffusion $n = 1.0$ and Non-Fickian $n = 0.5$–1.0 (Alfrey et al., 1966; Ritger & Peppas, 1987a, 1987b).

Initial diffusion coefficient, average diffusion coefficient and late diffusion coefficient can be calculated from the Eqs. (2)–(4) (Ritger & Peppas, 1987a, 1987b).

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

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

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

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 1 is the thickness of the sample. The values of 'n', 'k' and D have been evaluated for the release studies of salicylic acid and tetracycline from the Figs. 1–8 and result thus obtained have been presented in Table 1.

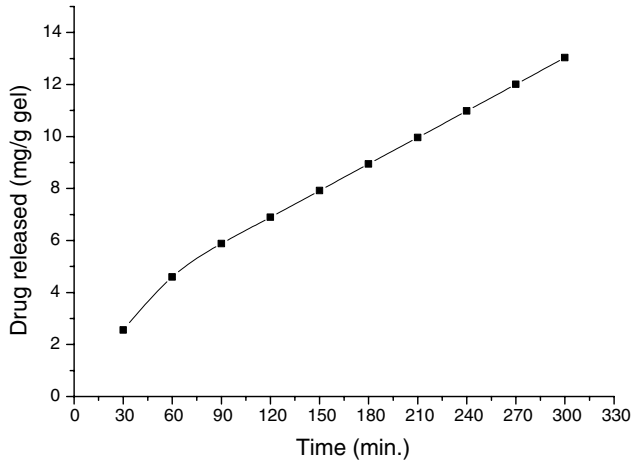

Fig. 1. Release dynamics of salicylic acid from drug loaded sample of Psy-*cl*-poly(AAm) in 20 mL distilled water at 37 °C.

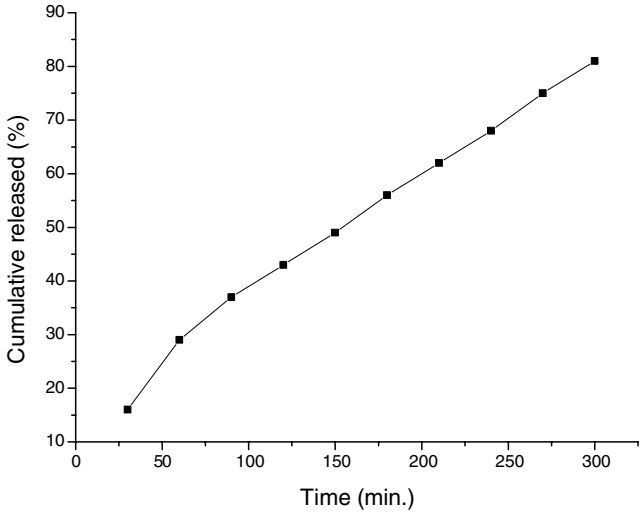

Fig. 2. Percentage of cumulative released of salicylic acid from drug loaded sample of Psy-*cl*-poly(AAm) in distilled water.

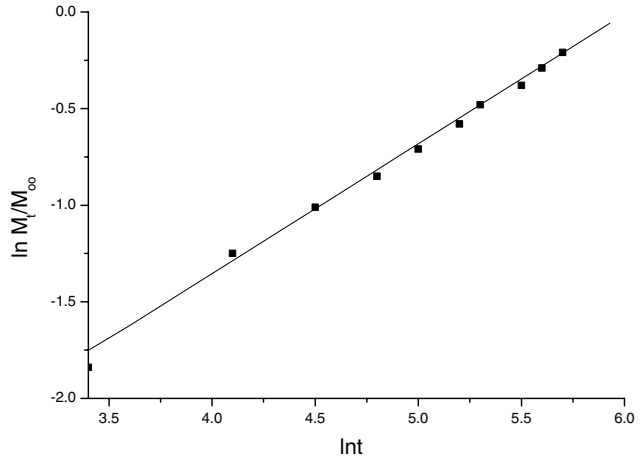

Fig. 3. Plot of $\ln M_t/M_\infty$ versus $\ln t$ for the release dynamics of salicylic acid from the loaded hydrogel samples of Psy-*cl*-poly(AAm) in distilled water at 37 °C.

3.4. 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 salicylic acid and tetracycline hydrochloride from per grams of the drug loaded hydrogels has been shown in the Figs. 1 and 5, respectively. The amount of drug release in pH 7.4 buffer was higher than the release medium of 2.2 pH buffer and distilled water. The swelling of hydrogels [psy-*cl*-poly(AAm)], increased when the pH of the medium changed from acidic to basic. At lower pH values the $-CONH_2$ groups does not ionized and keep

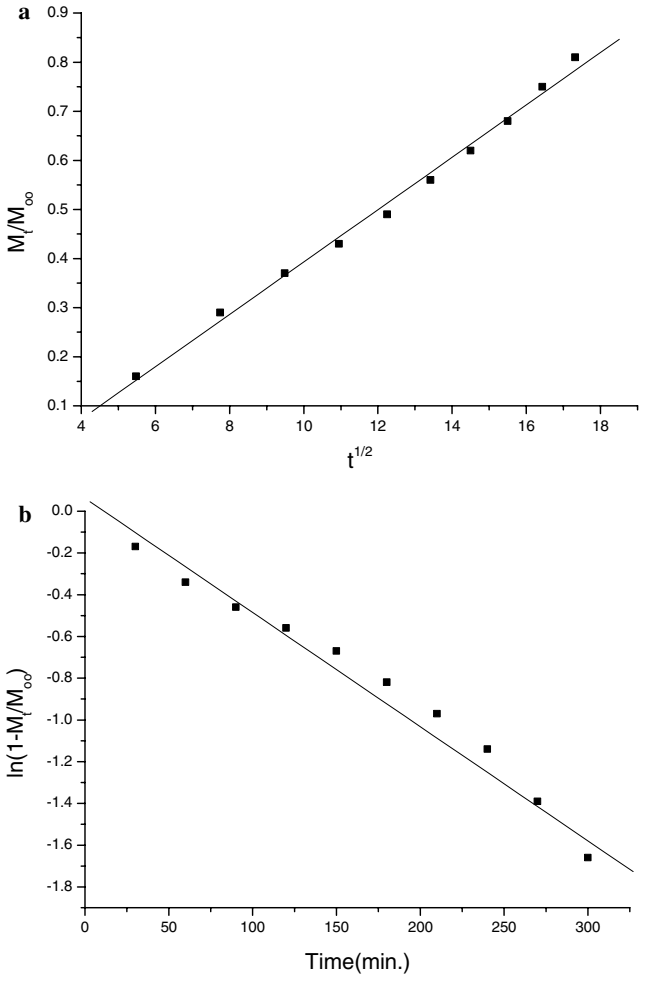

Fig. 4. (a) Plot of M_t/M_∞ versus $t^{1/2}$ for the fractional released of the salicylic acid from the drug loaded hydrogel samples of Psy-*cl*-poly(AAm) in distilled water at 37 °C. (b) Plot of $\ln(1 - M_t/M_\infty)$ versus time for the release dynamics of the salicylic acid from the drug loaded hydrogel samples of Psy-*cl*-poly(AAm) in distilled water at 37 °C.

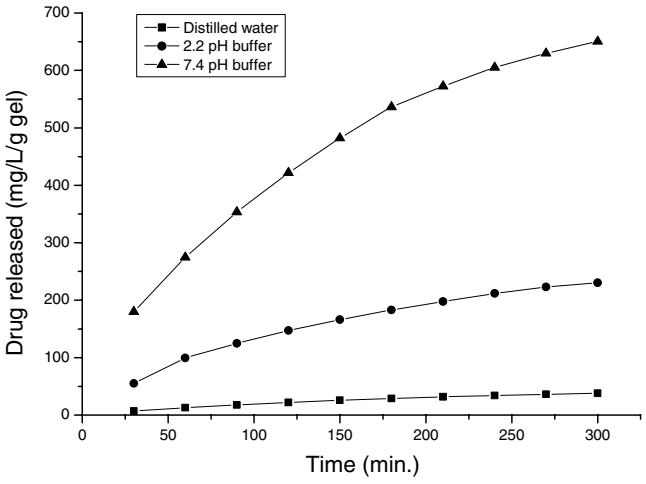

Fig. 5. Release dynamics of tetracycline from drug loaded sample of Psy-*cl*-poly(AAm) in different medium at 37 °C.

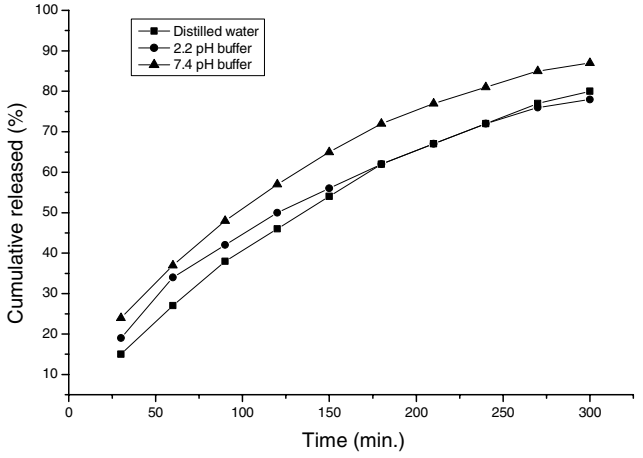

Fig. 6. Percentage of cumulative released of tetracycline from drug loaded sample of Psy-*cl*-poly(AAm) in different medium at 37 °C.

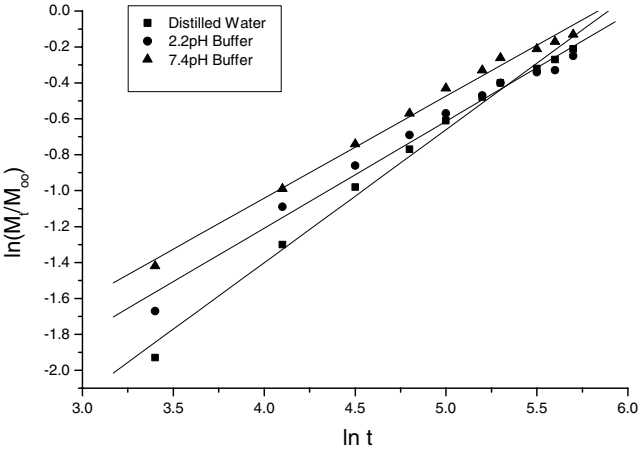

Fig. 7. Plot of $\ln M_t/M_\infty$ versus $\ln t$ for the release dynamics of tetracycline from the loaded hydrogel samples of Psy-*cl*-poly(AAm) in different release medium at 37 °C.

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 to more drug release. The release of drug was observed to be faster in pH 7.4. This observation is also supported from the figures of percent cumulative release (Fig. 6). From the percent cumulative release studies of salicylic acid it was observed that first 50% of the total release occurred in 150 min (Fig. 2), whereas in case of tetracycline the 50% of the total release of drug occurred in 90, 120 and 135 min in releasing medium of pH 7.4 buffer, pH 2.2 buffer and distilled water, respectively (Fig. 6).

From the slope and intercept of the plot (Fig. 3) of $\ln M_t/M_\infty$ versus $\ln t$, the diffusion exponent '*n*' and gel characteristic constant '*k*' was calculated to be 0.68 and 1.626×10^{-2}, respectively, for the salicylic acid release from the polymeric matrix. Hence non-Fickian or anomalous diffusion occurs where the rate of diffusion of salicylic acid

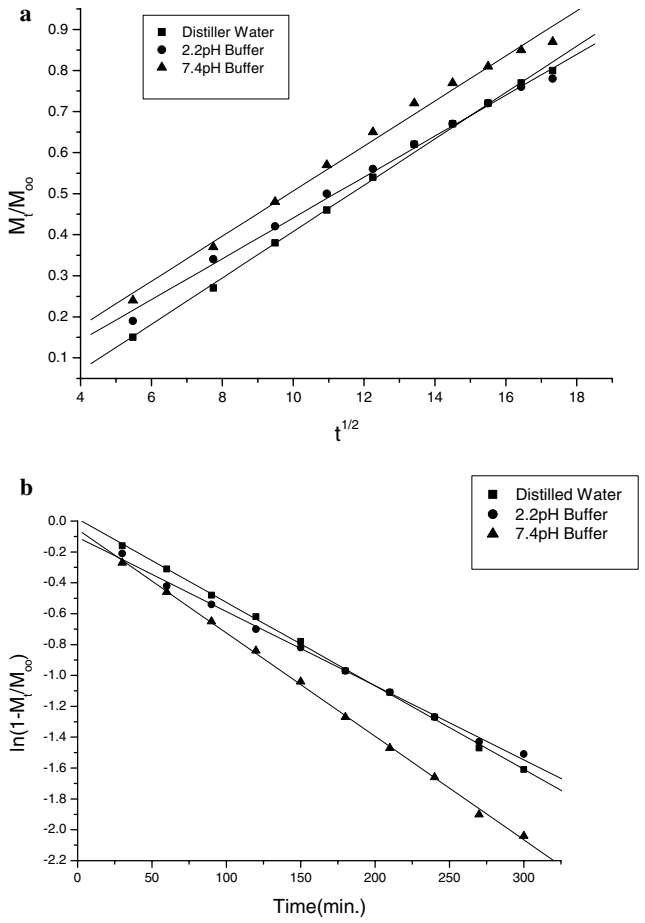

Fig. 8. (a) Plot of M_t/M_∞ versus $t^{1/2}$ for the fractional released of the tetracycline from the drug loaded hydrogel samples of Psy-*cl*-poly(AAm) in different release medium at 37 °C. (b) Plot of $\ln(1 - M_t/M_\infty)$ versus time for the release dynamics of the tetracycline from the drug loaded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

and rate of relaxation of polymeric chains are comparable. Drug release depends on two simultaneous rate processes, water migration into the devices and drug diffusion through continuously swelling hydrogels. However, initial diffusion coefficient, average diffusion coefficient and late time diffusion coefficient was observed to be 9.74×10^{-4}, 8.84×10^{-4} and 1.42×10^{-4} (cm^2/min) respectively, for the release of salicylic acid from polymeric matrix (Fig. 4a and b).

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. It is clear from the Table 1 that diffusion exponent '*n*' have 0.74, 0.60 and 0.56 values and gel characteristic constant '*k*' have 1.272×10^{-2}, 2.754×10^{-2} and 3.639×10^{-2} values in distilled water, 2.2 pH buffer and 7.4 pH buffer, respectively, for the tetracycline release from the hydrogels and these values were obtained from the slope and intercept of the plot between $\ln M_t/M_\infty$ versus $\ln t$. It means non-Fickian or anomalous diffusion occurs for the tetracycline release from the hydrogels. However in each release medium the initial diffusion coefficient was observed to more than late time diffusion coefficient (Fig. 8a and b).

Similar release behavior has been reported for guar gum based hydrogels (Soppimath, Kulkarni, & Aminabhavi, 2001). 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.

4. Conclusion

It is concluded from the foregone discussion that psyllium and polyacrylamide based hydrogels have potential to be act as drug delivery devices, that to colon targeted, indicated from the drug release profile in different release medium. It has also been concluded from the drug release dynamics that the drug released through the polymeric matrix follows non-Fickian diffusion mechanism, for which, 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. In each release medium the Initial diffusion coefficient was more than late time diffusion coefficient.

Table 1
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(AAm)

Drug in releasing medium	Thickness of the samples (cm)	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 in distilled water	0.470	0.68	1.626	9.74	8.84	1.42
Tetracycline hydrochloride						
Distilled water	0.660	0.74	1.272	21.44	19.5	2.95
pH 2.2 buffer	0.440	0.6	2.754	7.60	8.70	1.16
pH 7.4 buffer	0.580	0.56	3.639	15.97	17.37	2.81

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