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Controlled release of terbinafine hydrochloride from pH sensitive poly(acrylamide/maleic acid) hydrogels

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Abstract

Adsorption and controlled release of terbinafine hydrochloride (TER-HCl) to and from pH sensitive poly(acrylamide/maleic acid) (P(AAm/MA)) hydrogels were investigated. P(AAm/MA) hydrogels were prepared by irradiating the ternary mixtures of AAm/MA/and water by γ-rays at ambient temperature. Antifungal drug, TER-HCl containing hydrogels, at different drug to polymer ratios, was prepared by direct adsorption method. The influence of MA content in the gel on the adsorption capacities of hydrogel and the effect of pH on the releasing behavior of TER-HCl from gel matrix were investigated. Terbinafine adsorption capacity of hydrogels are found to increase from 2 to 38 mg TER-HCl per g dry gel with increasing amount of MA in the gel system. In vitro drug release studies in different buffer solutions show that the basic parameters affecting the drug release behavior of hydrogel are the pH of the solution and MA content of hydrogel.

Keywords: Terbinafine hydrochloride; Poly(acrylamide/maleic acid); Hydrogel; pH sensitive

1. Introduction

During the last couple of decades many different kind of polymeric systems are proposed as drug carrier systems. One of the these systems is poly-electrolyte polymers which contain relatively ionizable groups at levels ranging from a few mol to 100% of the repeating units (Karadağ et al., 1995; Saraydın et al., 1995; Güven et al., 1999; Şen et al., 1999a). Poly-electrolytes may be anionic, cationic or amphophilic, and may be synthetic or naturally occurring. Poly-electrolyte type hydrogels undergo controllable volume changes in response to small variation in solution conditions (Tanaka, 1987; Siegel and Firestone, 1988; Ichijo et al., 1995) such as temperature, pH, and electric signal which are also employed the solution variables in typical physiological, biological and chemical systems (Peppas and Mikos, 1986; Kudela, 1987; Kaetsu, 1993, 1995; Kaetsu et al., 1999).

The sensitivity of poly-electrolyte hydrogels on pH with a certain interval makes this system suitable for change in the pH of the skin. The pH sensitivity also imparts additional advantages to these systems by causing an overall retardation in the release of drug as compared with non-electrolyte gels.

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Yoshida et al. (1999) synthesized the thermo and pH responsive acryloyl-L-proline ether ester (A-ProOEt) copolymers with methacryloyl-glycine (MA-Gly) and methacryllic acid as a novel biofunctional gel for application in colon delivery systems. The release of 2-(3-benzoylphenyl) propionic acid(ketoprofen) was studied in different buffer solutions. It was found that the copolymeric gel obtained by introducing 60 mol% MA-Gly or MA-Ac, the gel adopted a collapsed state at pH 3.0 for A-ProOEt/MA-Gly gel and pH 5.5 for A-ProOEt/MAAc gel and the release of ketoprofen from these copolymer gels is closely related to swelling of the gels in response to pH changes. The cumulative amount of ketoprofen released from A-ProOEt/MA-Gly copolymer reached 100% in 1.5 h after start of the experiment in pH 7.5 buffer solution and 4 h after in pH 5.5 buffer solution. However, at pH 3 the cumulative amount of released drug was only 14% even after 6 h had passed due to gel shrinkage. They also observed a correlation between gel swelling and drug release due to changes in pH of the medium.

Recently, Nakamae et al. (1996) synthesized phosphate group containing metacryloyloxyethyl dihydrogen phosphate/*N*-isopropyl acrylamide copolymeric hydrogels for the delivery of positively charged enzymes. They investigated the influence of negatively charged phosphate group content in the gel on the positively charged lysozyme enzyme uptake capacity of hydrogel and pH of the medium on the release properties of network structure. It was found that negatively charged phosphate groups bind ionically to positively charged lysozyme. It was also observed that the ratio of phosphate groups per one lysozyme molecule is 18, which is apparently equal to the number of positive charges on lysozyme. Increasing pH from 1.4 to 7.4 increased the degree of ionization of anionic polymer thus increased the enzyme release rate from gel system. They also recommended that this type of pH sensitive hydrogels should be ideal for delivering drugs to the small intestines, while avoiding release in the stomach.

Terbinafine or terbinafine hydrochloride (TER-HCl) is a topically and orally active allylamine antifungal agent which appears to act by preventing fungal ergesterol biosynthesis via specific and selective inhibition of fungal squale oxidase (Balfour and Faulds, 1992). In standard in vitro susceptibility tests terbinafine has demonstrated activity against a wide range of dermatophyte filamentous, dimorphic and dematiaceous fungi as well as yeasts.

The usual duration of treatment for fungal or yeast skin infection has been 2–4 weeks (topical therapy) or 3–6 weeks (oral therapy) but shorter courses of topical terbinafine (1–2 weeks) were as effective as standard-duration therapy in dermatomycoses (Balfour and Faulds, 1992).

Higher affectivity of topical terbinafine than other topical antifungal drugs for many fungal or yeast skin infection and lower drug requirement are the main advantages of this drug for using in transdermal drug delivery systems (TDDS).

The hydrogels used in this work were synthesized by γ-irradiation of respective aqueous solution. The advantages of using radiation in the synthesis of these hydrogels and their characterization have been described in detail in our previous publications (Güven and Şen, 1991; Güven et al., 1999; Saraydın et al., 1995; Şen et al., 1999b).

The results of our previous study (Şen and Güven, 1999) indicated that polydiprotic acid containing hydrogel systems can be considered as potential carriers for the drug delivery systems and may be considered for local therapeutic applications of cationic drugs. In this study, the usability of an anionic polymer prepared from acrylamide (AAm) and maleic acid (MA) for the controlled release of cationic drug TER-HCl has been investigated. Drug adsorption and release capacities of hydrogel systems and influence of MA content and pH of the medium on the release properties were examined.

2. Experimental

2.1. Chemicals

The two monomers used in this study, namely AAm and MA were obtained from BDH. Pure TER-HCl was obtained from its commercial drug form Lamisil of Novartis Company. In order to

obtain pure terbinafine firstly lamisil was dissolved in distilled water, after removing undissolved part the solution was dried in a vacuum oven at 315 K to constant weight. The chemical formula of TER-HCl is shown in Scheme 1.

2.2. Preparation of hydrogels

Aqueous solutions of monomers of 1 g AAm and 20, 40, 60 and 90 mg MA were prepared in 1 ml of distilled water (AAm/MA mol ratios, 100:0.0, 98.8:1.2, 97.6:2.4, 96.5:3.5, 94.8:5.2). Monomer solutions thus prepared were placed in polyvinylchloride (PVC) straws of 4 mm diameter and irradiated to 25 kGy in air at ambient temperature in Gammacell 220 type γ-irradiator at a fixed dose rate of 0.17 kGy/h.

2.3. Composition of gels

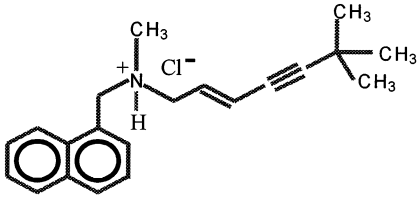
Irradiated mixtures were dried in a vacuum oven at 315 K to constant weight and subjected to Soxhlet extraction with water as solvent. Uncrosslinked polymer and/or residual monomer were removed with this extraction from the gel structure. Extracted gels were dried again in vacuum oven at 315 K to constant weight. The amount of uncrosslinked MA was determined by titration of extract against NaOH (0.05 mol/l) to phenolphthalein end point.

2.4. Swelling studies

Dried hydrogels (3–4 min thickness, 4 mm diameter) were left to swell in a solution of desired pH (2–9), ionic strength $I = 0.1$ mol/l in buffer and TER-HCl solutions at 25 and 4°C. Swollen gels removed from the swelling medium at regular intervals were dried superficially with filter paper, weighed and placed in the same bath. The measurements were continued until a constant weight was reached for each sample. This weight was used to calculate the volume fraction v_{2m} of polymer and equilibrium degree of swelling (EDS) Q of gel in a given gel sample swollen to equilibrium in water as given below (Tong and Liu, 1994).

$$v_{2m} = \left[1 + \frac{\rho}{\rho_w}(w^{-1} - 1)\right]^{-1} \quad (1)$$

where ρ and ρ_w are the densities of dry gel and water, and w is the weight fraction of the polymer in the swollen gel. The EDS was defined as $Q = 1/v_{2m}$.



Scheme 1.

2.5. Loading of drug

The drug to be loaded into hydrogels was firstly dissolved in distilled water and dry copolymer discs (2 mm thickness, 4 mm diameter) were loaded with TER-HCl by immersion into aqueous solutions of drug (0.16–0.80 mg/ml) at 4°C for 2 days. Preliminary tests showed that 2 days is the minimum time to ensure complete swelling of gel and maximum loading of drug.

2.6. Controlled release of TER-HCl from hydrogels

The controlled release of TER-HCl from hydrogel matrices was measured after TER-HCl loaded, swollen gel was placed in a vessel containing 50 ml of phosphate buffer solution (0.1 mol/l) at 37°C under continuous shaking. At various times aliquots of 3 ml were drawn from the medium to follow the TER-HCl release and placed again into the same vessel so that the liquid volume was kept constant. TER-HCl release was determined spectrophotometrically using a Philips 8715 spectrophotometer at 222 nm. The calibration tests made with UV absorption measurements of pure TER-HCl at pHs studied in this work showed no changes in the spectra of drug. The controlled release of non-specifically adsorbed TER-HCl was followed at pH 7.0. pH 6.1, 5.5, and 4.4 were used for the controlled release of specifically adsorbed terbinafine from

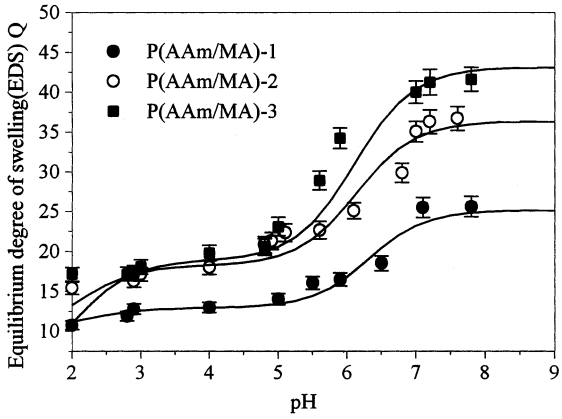


Fig. 1. Effect of pH on the EDS of PAAm and P(AAm/MA) hydrogels (solid curves are theoretical predictions).

hydrogels. After the completion of release at pH 4.4, the hydrogels were immersed in pH 3.0 buffer solution and than 0.1 mol/l, HCl for 2 days to remove any remaining terbinafine in the gel system. Every data point shown on the release figures is the average of tripled measurements.

3. Results and discussion

3.1. Composition of hydrogels

When pure AAm monomer is irradiated with γ-rays, polymerization and cross-linking reactions take place simultaneously (Saraydın et al., 1995). Because of its high tendency of polymerization it can also easily copolymerize with monomer otherwise difficult to homo, polymerize, MA being such a typical monomer. The considerations for selecting the particular feed compositions are firstly the solubility of MA in aqueous AAm solution and the shape stability of obtained hydrogels in their fully swollen state. The maximum solubility of MA was found to be 90 mg in 1 g AAm per 1 ml water mixture. So only hydrogels with four compositions were investigated in this study. For the preparation of mechanically stable hydrogels, the ternary mixtures of AAm/MA/H_2O were irradiated to 25 kGy with γ-rays. Mol percentages of MA in the P(AAm/MA)-1, P(AAm/MA)-2, P(AAm/MA)-3, and P(AAm/MA)-4 hydrogels are 1.1, 2.2, 3.1 and 4.5, respectively.

3.2. Swelling properties

One of the most important properties to be characterized of pH sensitive drug delivery systems is EDS and its variation with solution pH. Fig. 1 represents the EDS of PAAm and P(AAm/MA) hydrogels at 25°C in phosphate buffer solution from pH 2 to 9 at fixed ionic strength of $I = 0.1$ M. Consistent with poly-anionic behavior, swelling of hydrogels was found to increase with pH. The solid curves in these figures represent the theoretical swelling curves of hydrogels. The construction of theoretical swelling curves are explained in detail in our previous work (Şen and Güven, 1998). In all compositions maximum extent of swelling were reached at pH 7, this being due to the complete dissociation of acidic groups of MA at this pH value. The first and second dissociation constants of MA are $pK_{a1} = 1.85$, $pK_{a2} = 6.06$, respectively (Weast, 1972). Due to large difference in pK_a values, swelling takes place in stepwise manner as shown in Fig. 1. The swelling shows sudden increases at the pH values around corresponding pK_a values. P(AAm/MA)-4 hydrogel disintegrated into small parts in buffer solutions before reaching equilibrium so the effect of pH on the EDS could not be investigated for this system.

For the investigation of effect of drug on the EDS, hydrogels were also swollen in TER-HCl solution. Percentage mass swelling values of hydrogels in distilled water and in 0.80 mg/ml TER-HCl solution at pH 4.0 is given in Fig. 2. It is seen from this figure increase of ionic strength of the solution and adsorption of terbinafine in the gel system, exclusion of water molecules, the EDS values show a sharp decrease and this effect becomes more pronounced at higher MA containing systems. When the concentration of drug decreased from 0.80 to 0.32 mg/ml slight increase in the swelling values has been observed. An increase in ionic strength generally decreased the swelling because the difference in concentration of mobile ions between the gel and solution is reduced causing a decrease in the osmotic swelling pressure of these mobile ions inside the gel. The effect of external stimuli such as pH, ionic strength and the presence of metal ions on the swelling properties

of diprotic acid hydrogel systems are well evaluated in our previous studies (Kantoğlu et al., 1999; Şen et al., 1999a,b).

EDS of hydrogels after drug loading and release at pH 7.0, 6.1, 5.5 and 4.4 are given in Fig. 3. Slightly increase of swelling at pH 7.0 and decrease again at low pH values was attributed pH sensitive swelling and deswelling of hydrogels as observed in buffer solutions (Fig. 1).

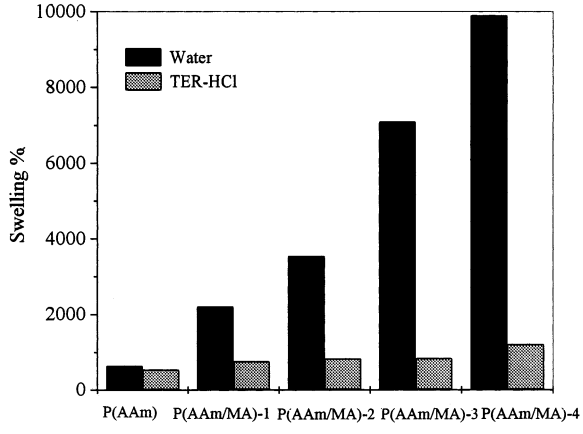


Fig. 2. Effect of TER-HCl on the equilibrium mass swelling of PAAm and P(AAm/MA) hydrogels (concentration of TER-HCl, 0.80 mg/ml).

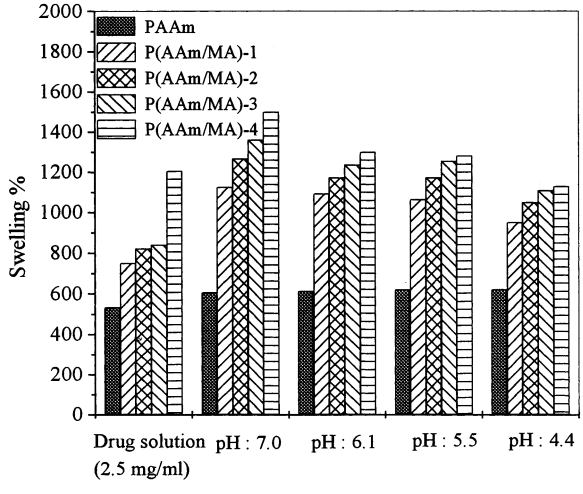


Fig. 3. Effect of pH on the equilibrium mass swelling of drug adsorbed PAAm and P(AAm/MA) hydrogels.

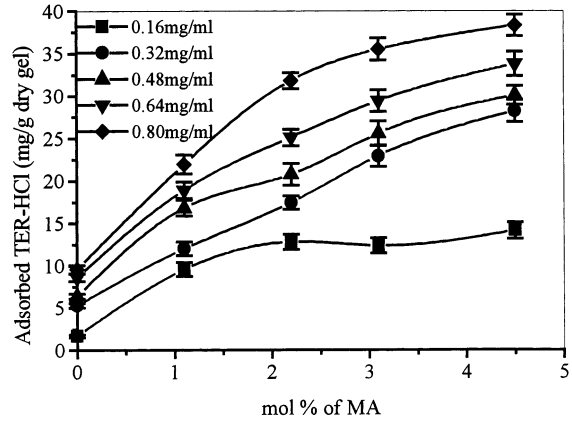


Fig. 4. Effect of MA content and drug concentration on the adsorption capacities of PAAm and P(AAm/MA) hydrogels.

3.3. Terbinafine hydrochloride loading

For the investigation of cationic drug adsorption behavior of PAAm and P(AAm/MA) hydrogels prepared in this study, hydrogels were firstly swollen in TER-HCl solution at pH 4.0 in concentration range 0.16–0.80 mg/ml. The consideration for selecting the particular drug concentration and pH is the solubility of TER-HCl in aqueous solution. The maximum solubility of TER-HCl was found to be 0.8 mg/ml water and the pH of this solution was 4.0. So the drug loading into hydrogels was investigated in this concentration range and pH value.

The total amount of (specific and non-specific) TER-HCl adsorbed into 1 g of dry gel at different initial drug concentrations is given in Fig. 4. As can be seen from the figure the amount of total TER-HCl taken increased with increasing MA content and initial drug concentration. The reason of this increase was attributed to the increase of free volume available for diffusion and specific bonding of positively charged drug to partially ionized hydrogel.

The effect of initial concentration of TER-HCl solution on the adsorption capacities of hydrogels are also shown in Fig. 4. As can be seen from figure increase in the drug concentration in the swelling medium increased the amount of adsorbed drug as observed in many adsorption studies (Saraydın et al., 1994; Akkaş et al., 1999). In

order to obtain adsorption isotherms of hydrogels the mass of adsorbate per unit mass of adsorbent (q_e) was plotted versus equilibrium concentration of drug (C). q_e Values are calculated from the following equation

$$q_e = \left(\frac{C_i - C}{m}\right) V_t$$

where q_e is in mg adsorbate per g dry adsorbent, C_i and C are the initial and equilibrium concentration of solution of adsorbate in mg/ml, V_t the volume of solution treated in ml, and m is the mass of dry adsorbent in g. As can be seen from Fig. 5 increase in the content of ionic comonomer

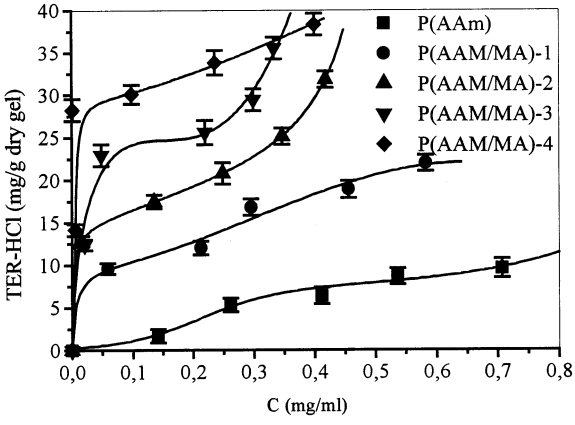


Fig. 5. TER-HCl adsorption isotherms of PAAm and P(AAm/MA) hydrogels.

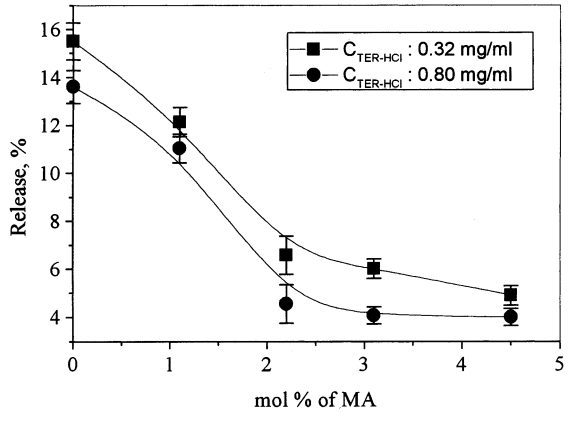


Fig. 6. Effect of MA content on the percentage release of non-specific adsorbed TER-HCl.

MA in the gel system increased q_e values at all initial drug concentrations due to the specific interactions between the ionized polymer and drug molecules and also increase of swelling. The L and S type curves in PAAm and P(AAm/MA) hydrogels, respectively, indicate that the type of the isotherm change from monomoleculer to multimoleculer adsorption (Giles et al., 1960).

3.4. Release behavior of hydrogels

For the investigation of drug release behavior of AAm and AAm/MA hydrogels, first drug loading experiments were conducted in 0.32 and 0.80 mg/ml TER-HCl solutions. In order to determine the amount of non-specifically adsorbed TER-HCl, hydrogels were first placed in pH 7.0 phosphate buffer solution. Fig. 6 shows the percentage release of non-specifically adsorbed TER-HCl from AAm and P(AAm/MA) hydrogels. The non-specifically adsorbed TER-HCl was assessed by measuring its concentration upon reaching equilibrium release conditions. While 15.5% of drug was released from AAm hydrogels this value decreased to 4.9 with increasing MA content in the gel when initial drug concentration was 0.32 mg/ml. As can be seen from the figure increasing drug concentration decreased the extent of non-specific release from gel systems.

The percentage release of TER-HCl at pH 7 was calculated from the following equation

$$\%\text{Release} = \frac{w}{w_{\text{total}}} \times 100 \qquad (2)$$

where w is the weight of released TER-HCl at pH 7.0 and w_{total} is the total weight of specific and non-specific adsorbed TER-HCl in the gel system.

The incomplete release of TER-HCl from hydrogels at pH 7 was expected to be due to binding of the cationic TER-HCl to the polymer. The difference between the total and non-specific adsorbed TER-HCl is therefore taken to be equal to the amount of specific adsorbed TER-HCl in the hydrogel.

The controlled release of specific adsorbed TER-HCl from P(AAm/MA) hydrogels was investigated primarily at pH 6.0. The drug release was followed until equilibrium and then hydrogel

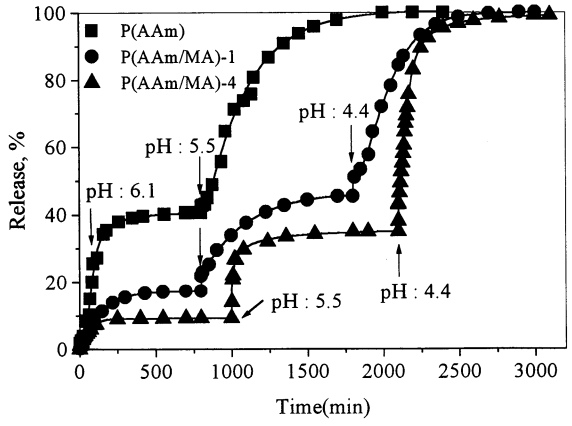


Fig. 7. Release of specific adsorbed TER-HCl from PAAm and P(AAm/MA) hydrogels.

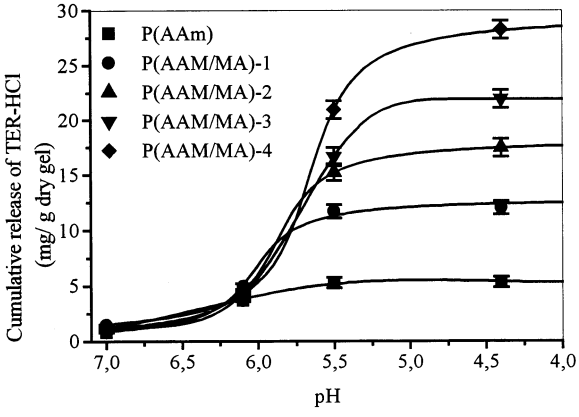


Fig. 8. Effect of pH on the cumulative release of TER-HCl from PAAm and P(AAm/MA) hydrogels when the adsorption achieved from 0.32 mg/m TER-HCl solution.

was transferred into TER-HCl free buffer at pH 5.5. After reaching new equilibrium at 5.5 it was again transferred into another buffer solution at pH 4.4. The percent release of TER-HCl with time for AAm, P(AAm/MA)-2 and P(AAm/MA)-4 hydrogel systems are given in Fig. 7. The percentage release of specific adsorbed TER-HCl at pH 6.1, 5.5 and 4.4 were calculated from the following equation

$$\%\text{Release of specific adsorbed TER-HCl} = \frac{w_{\text{pH}}}{w_{\text{sp}}} \times 100 \quad (3)$$

where w_{pH} is the weight of released TER-HCl at any pH value and w_{sp} is the total weight of specific adsorbed TER-HCl in the gel system.

As can be seen from figure the release rate and percentage release decreased at pH 6.1 with increasing MA content in the gel system due to the increase of specific adsorption of drug to hydrogel structure. Approximately 40, 15 and 9.0% drug release was observed in equilibrium release of PAAm, P(AAm/MA)-1 and P(AAm/MA)-4 hydrogels at pH 6.1, respectively. While 100% of TER-HCl was released from AAm hydrogels at pH 5.5, only 40 and 30% of drug released from P(AAm/MA)-1 and P(AAm/MA)-4 hydrogels when the system reached equilibrium, respectively. The release of TER-HCl from P(AAM/MA)-4 hydrogels was opposite in trend than P(AAm/MA)-1 at pH 5.5 and 4.4. Very fast release rates were observed for P(AAm/MA) hydrogels at these pH values may be due to higher drug content of the hydrogel.

The overall (specific and non-specific) cumulative release of drug from all hydrogel systems depending on the pH of the solution are given in Figs. 8 and 9. As can be seen from those figures, while all adsorbed drug was released at pH 5.5 for P(AAm) hydrogels in 0.32 and 0.80 mg/ml initial drug concentrations, this pH shifted to 4.5 with increasing MA content in the gel system. This can be explained again by the increase of specific interactions between drug and hydrogel with in-

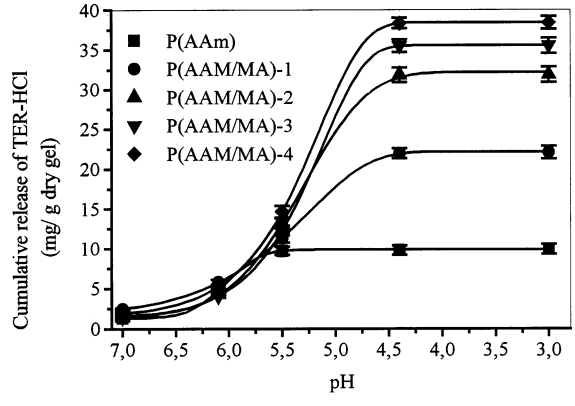


Fig. 9. Effect of pH on the cumulative release of TER-HCl from PAAm and P(AAm/MA) hydrogels when the adsorption achieved from 0.80 mg/ml TER-HCl solution.

creasing drug adsorption and may be due to changes of the dissociation constant of MA in the gel–drug–phosphate buffer system.

4. Conclusion

In this study, the preparation of P(AAm/MA) hydrogels and their cationic drug TER-HCl release behaviors have been investigated. It has been found that the specific adsorption capacity of hydrogels increases with increasing MA content in the gel system. This has been explained due to the incorporation of more specific acidic groups into the network and an almost higher swelling capacity of gels. The release studies show that one of the basic parameters affecting the drug release behavior of P(AAm/MA) hydrogels is the pH of the solution. Consequently, the hydrogels prepared in this study can be considered as potential carriers for the drug delivery systems and may be used especially as local therapeutic trans dermal delivery applications of cationic drugs.

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