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Controlled release of antifungal drug terbinafine hydrochloride from poly(*N*-vinyl 2-pyrrolidone/itaconic acid) hydrogels

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Abstract

Adsorption and controlled release of terbinafine hydrochloride (TER-HCl) to and from pH-sensitive poly(*N*-vinyl 2-pyrrolidone/itaconic acid) P(VP/IA) hydrogels were investigated. P(VP/IA) hydrogels were prepared by irradiating the ternary monomer mixtures of *N*-vinyl 2-pyrrolidone/itaconic acid/ethylene glycol dimethacrylate in aqueous solution by γ-rays at ambient temperature. Hydrogels containing antifungal drug TER-HCl, at different drug-to-polymer ratios, were prepared by direct adsorption method. The influence of IA content in the gel on the adsorption capacities of hydrogels and the effect of pH on the releasing behavior of TER-HCl from the gel matrix were investigated. Terbinafine adsorption capacity of hydrogels was found to increase from 6 to 82 mg of TER-HCl per gram of dry gel with increasing drug concentration and amount of IA in the gel system. In-vitro drug-release studies in different buffer solutions showed that the basic parameters affecting the drug-release behavior of hydrogels are the pH of the solution and the IA content of the hydrogel.

Keywords: Terbinafine hydrochloride; Poly(*N*-vinyl 2 pyrrolidone/itaconic acid); Hydrogels; pH-sensitive

1. Introduction

Poly-electrolytes are polymers that contain relatively high concentrations of ionizable groups along the backbone chain. Poly-electrolytes are distinguished from a related class of polymers, ionomers, by the density of ionizable groups. Ionomers contain a relatively low concentration of ionizable groups (less than a few mole% of repeating units), while poly-electrolytes contain ionizable groups at levels ranging anywhere from a few mole % to 100 of the repeating units (Brondsted and Kopecek, 1992; Karadağ et al., 1994; Ende and Peppas, 1997; Siegel and Firestone, 1988; Kou et al., 1988; Sarı, 2000).

The unique properties exhibited by poly-electrolytes have led to their application in biomedical systems. Many biomedical applications of poly-electrolytes ultimately arise from their propensity to bind with oppositely charged surfaces and to associate to form complexes with oppositely charged polymers. For example, cationic poly-

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electrolytes have long been studied for their application in silicosis therapy and immunochemistry due to their ability to bind with negatively charged surfaces, and cationic poly-electrolytes such as poly(vinyl pyridine *N*-oxide) are potent inhibitors of silica hemolysis of red blood cells. Similarly, complexes composed of two oppositely charged poly-electrolytes have been extensively employed as anteric coatings and controlled release devices, and many poly-electrolytes and their complexes have exhibited antithrombogenic character.

Recently, Yau et al. (1994) studied the cross-linked chitosan with glutaraldehyde interpenetrating polyether polymer networks (semi-IPN). The release of chlorohexydine acetals was studied in phosphate buffer, pH 7.8, and hydrochloric acid, pH 1.0, solutions at an ionic strength of 0.1 mol/l. It was found that the gel adopted a collapsed state at pH 7.8, and thus the drug inside the semi-IPN could not be released. However, at pH 1.0, the IPN gel was swollen greatly, leading to the release of the drug.

Hariharan and Peppas (1996) synthesized and characterized cationic polymer networks containing amine and ammonium pendant groups. They investigated the influence of polymer structural characteristics and the molecular weight of the solute, ionizability of the solute, ionic content of the release medium on the transport mechanisms by using oxpronolol HCl, insulin and myoglobin as drugs. It was found that the cross-linking ratio increased due to a decrease in the free volume available for diffusion. An increase in pH decreased the degree of ionization of the cationic polymer, thus decreasing the swelling of the polymer. It was also observed that the release rate of insulin was higher at pH 10 than at pH 6. This was explained by the decrease on the diffusional path at pH 10.

The most commercially successful use of diffusional drug delivery systems is in transdermal applications. In these applications, typically, a polymeric delivery system is held on the skin by an adhesive. The device contains the drug either in a reservoir with a rate-controlling membrane-controlled device (Okano et al., 1994). The sensitivity of poly-electrolyte hydrogels on pH with a certain interval makes these systems 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-electrolytic gels.

Terbinafine hydrochloride (TER-HCl) is a topically and orally active allylamine antifungal agent that appears to act by preventing fungal ergosterol 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 dermotophyte filamentous, dimorphic and dematiaceous fungi as well as yeasts.

The higher effectivity of topical terbinafine than other topical antifungal drugs for many fungal or yeast skin infections and lower drug requirements are the main advantages of this drug for using in transdermal drug-delivery systems (TDDS). Instead of repeated and frequently application of topical creams, it is anticipated that TER-HCl-loaded hydrogels would be more efficiently used for the comfort of the patients.

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; Saraydın et al., 1995; Güven et al., 1999; Şen et al., 1999a).

As a result of our previous studies (Şen and Güven, 1999; Şen et al., 2000), we proposed that the polydiprotic acid containing hydrogel systems can be considered as potential carriers for the drug-delivery systems. Our previous study (Şen et al., 2000) indicated that diprotic maleic acid (MA) containing poly (acryamide/maleic acid) P(AAm/MA) hydrogel systems may be used especially as local therapeutic applications of cationic antifungal drug TER-HCl. However, due to the solubility limitation of MA in the aqueous AAm solution, the drug-uptake capacities of hydrogels could not be improved over 38 mg per gram of dry gel in that study.

In this study, the utility of another anionic polymer prepared from *N*-vinyl 2-pyrrolidone (VP) and itaconic acid (IA) for the controlled

release of cationic drug terbinafine hydrochloride has been investigated. Drug adsorption and release capacities of hydrogel systems and influence of IA 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 *N*-vinyl 2-pyrrolidone (VP) and itaconic acid (IA), were obtained from Aldrich. Cross-linking agent, namely, ethylene glycol dimethacrylate (EGDMA), was obtained from BDH. Pure terbinafine hydrochloride (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 under vacuum at 315 K up to a constant weight. The chemical formula of terbinafine hydrochloride is shown in Fig. 1.

2.2. Preparation of hydrogels

Aqueous solutions of monomers of 2 ml of VP and 60, 120, 180 and 240 mg of IA and 0.25% EGDMA (weight of EGDMA/weight of VP) were prepared in 1 ml of distilled water (VP/IA mol ratios, 97.6:2.4, 95.3:4.7, 93.2:6.8, 91.0:9.0). Monomer solutions thus prepared were placed into 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 0.16 kGy/h.

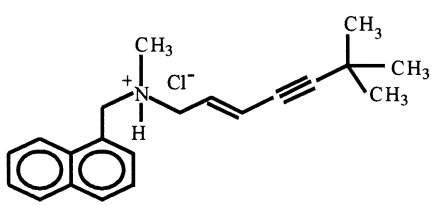

Fig. 1. Chemical structure of terbinafine hydrochloride.

2.3. Composition of gels

Irradiated mixtures were dried under vacuum at 315 K up to a constant weight and subjected to Soxhlet extraction with water as a solvent. Uncross-linked polymer and/or residual monomer were removed with this extraction from the gel structure. Extracted gels were dried again under vacuum at 315 K up to a constant weight. The amount of uncross-linked IA was determined by the titration of extract against 0.01 mol/l NaOH to phenolphthalein end point.

2.4. Swelling studies

Dried hydrogels (3–4 mm 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 superfically 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, ν_{2m}, of the polymer and equilibrium degree of swelling (EDS), Q, of the gel in a given sample swollen to equilibrium in water as given below (Tong and Liu, 1994).

$$\nu_{2m} = [1 + \rho/\rho_w(w^{-1} - 1)]^{-1} \quad (1)$$

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 equilibrium degree of swelling (EDS) was defined as $Q = 1/\nu_{2m}$

2.5. Loading of drug

The drug to be loaded into hydrogels was initially dissolved in distilled water, and 0.05 g dry copolymer discs (2 mm thickness, 4 mm diameter) were loaded with TER-HCl by immersion into aqueous solutions of drug (0.20–3.75 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. The amount of loaded drug was determined spectrophotometrically using a Phillips 8715 Spec-

trophotometer at 222 nm. The calibration curve was prepared through UV absorption measurements of pure TER-HCl at a concentration range of between 0 and 50 μg/ml.

2.6. Controlled release of TER-HC l from hydrogels

The controlled release of TER-HCl from hydrogel matrices was measured after TER-HCl was loaded, swollen gel was placed into a vessel containing 100 ml of phosphate buffer solution (0.1 mol/l), and 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. In order to eliminate the difficulties arising from the high molar extinction coefficient of TER-HCl and for detecting released drug without dilution, 100 ml of phosphate buffer solution were used in all release studies. TER-HCl release was determined spectrophotometrically at 222 nm. The calibration tests achieved with UV absorption measurements of pure TER-HCl at different pH values showed no changes in the spectra of drug. The controlled release of non-specifically adsorbed TER-HCl followed at pH 8.0. pH values of 7.0, 6.1 and 5.2 were used for the controlled release of specifically adsorbed terbinafine hydrochloride from hydrogels. After the completion of release at pH 5.2, the hydrogels were immersed in pH 4.0 buffer solution and subsequently in pH 3.0 buffer solution for 2 days to remove any remaining terbinafine in the gel system. Released TER-HCl was completely soluble at these pH values, and no precipitation was observed even when the drug release reached equilibrium. Every data point shown on the release figures is the average of triple measurements.

3. Results and discussion

3.1. Composition of hydrogels

When pure *N*-vinyl 2-pyrrolidone (VP) monomer has been irradiated with gamma-rays, polymerization and cross-linking reactions take place simultaneously (Şen, 1988). Because of its high tendency towards polymerization, IA can easily copolymerize with the monomer, VP when otherwise, it is very difficult to homopolymerize, IA, being such a typical monomer. The considerations or selection of the particular feed compositions were determined as the solubility of IA in aqueous VP solution and the shape stability of obtained hydrogels in their fully swollen state. The maximum solubility of IA was found to be 240 mg in 2 ml of VP per 1 ml of water mixture. Thus, only hydrogels with four compositions were investigated in this study. For the preparation of mechanically stable hydrogels, the ternary monomer mixtures of VP/IA/EGDMA in water were irradiated to 25 kGy with gamma-rays. The mole percentages of IA in the P(VP/IA)-1, P(PV/IA)-2, P(VP/IA)-3 and P(VP/IA)-4 hydrogels are 2.6, 5.2, 8.7, 12.2, respectively.

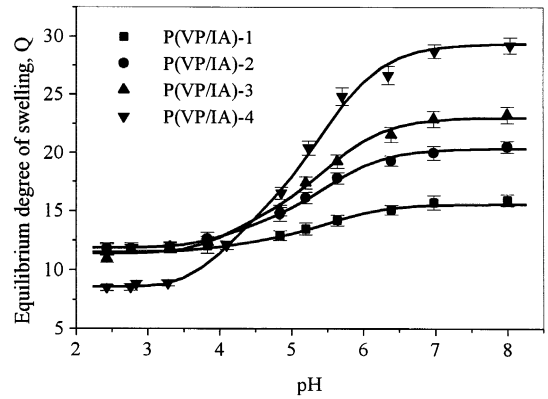

Fig. 2. Effect of pH on the equilibrium degree of swelling of P(VP/IA) hydrogels (solid curves are theoretical predictions). The mole percentages of IA in the P(VP/IA)-1, P(VP/IA)-2, P(VP/IA)-3 and P(VP/IA)-4 hydrogels are 2.6, 5.2, 8.7 and 12.2, respectively.

3.2. Swelling properties

One of the most important properties for the characterization of pH-sensitive drug-delivery systems can be proposed as the equilibrium degree of swelling (EDS), Q, (Eq. (1)) and it is variation with solution pH. Fig. 2 represents the EDS of P(VP/IA) hydrogels at 25 °C in phosphate buffer solutions from pH 2 to 9 at a fixed ionic strength

of $I = 0.1$ M. Consistent with poly-electrolytic behavior, the swelling of the hydrogels was found to increase with pH. The solid curves in these figures represent the theoretical swelling curves of the hydrogels. The construction of theoretical swelling curves has been explained in detail in our previous work (Şen and Güven, 1998). In all compositions, maximum extents of swelling were reached at pH 7, this being due to the complete dissociation of acidic groups of IA at this pH value. The first and second dissociation constants of IA are $pK_{a1} = 3.85$, $pK_{a2} = 5.44$, respectively (Weast, 1972). Since the two dissociation constants for IA are rather close, the consecutive swelling around these pH values overlaps, and only single-step but broadened S-shaped (compared to the swelling curves of monoprotic acid containing systems) swelling versus pH curves are observed in Fig. 2.

For the investigation of the effect of drugs on EDS, hydrogels were also swollen in the TER-HCl solution. The percentage mass swelling values of hydrogels in distilled water and in 1.25 and 3.75 mg/ml TER-HCl solutions at pH 4 are given in Fig. 3. It can be seen that there is an increase in ionic strength of the solution and adsorption of terbinafine in the gel system, with the exclusion of water molecules, the EDS values show a sharp decrease, and this effect becomes more pronounced at higher IA contents. When the concentration of drug was decreased from 3.75 to 1.25

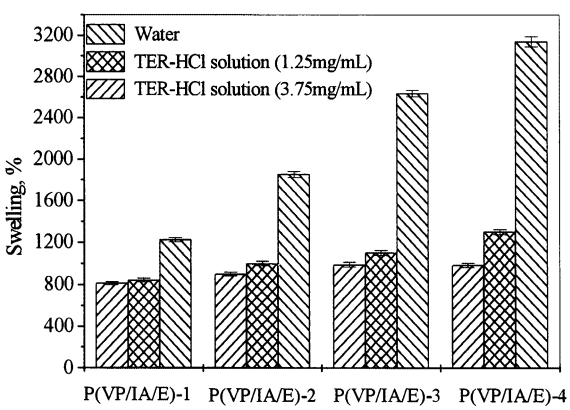

Fig. 3. Effect of TER-HCl on the equilibrium mass swelling of and P(VP/IA) hydrogels when the adsorption is achieved from 3.75 mg/ml of TER-HCl solution.

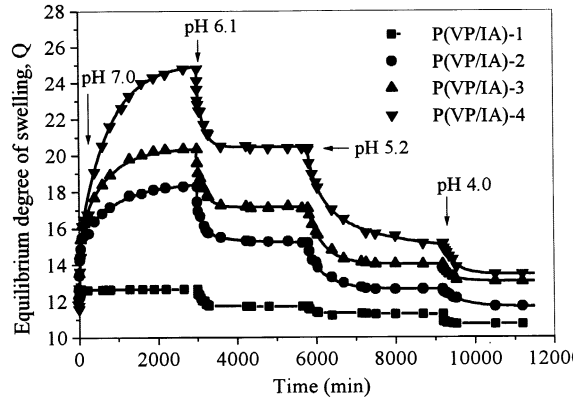

Fig. 4. Effect of pH on the equilibrium degree of swelling of drug absorbed P(VP/IA) hydrogels and swelling and deswelling kinetics. The mole percentages of IA in the P(VP/IA)-1, P(VP/IA)-2, P(VP/IA)-3 and P(VP/IA)-4 hydrogels are 2.6, 5.2, 8.7 and 12.2, respectively.

mg/ml, a slight increase in the swelling values was observed. An increase in ionic strength generally decreased swelling because the difference in concentration of mobile ions between the gel and solution is reduced causing a decrease in osmotic swelling pressure of these mobile ions inside the gel.

The effect of external stimuli such as pH, ionic strength, metal ions and the presence of drug molecules on the swelling properties of diprotic acid hydrogels systems has been evaluated extensively in our previous studies (Kantoğlu et al., 1999; Şen et al., 1999b, 2000).

The EDS of hydrogels after drug loading and release at pH 7.0, 6.1, 5.2 and 4.0 are given in Fig. 4 with swelling and deswelling kinetics. The sharp increase of swelling at pH 7.0 and a decrease again at low pH values were attributed to pH-sensitive swelling and deswelling of hydrogels, as observed in buffer solutions in Fig. 2.

3.3. Adsorption of TER-HCl

For the investigation of cationic drug adsorption behavior of P(VP/IA) hydrogels prepared in this study, hydrogels were initially swollen in TER-HCl solution at pH 4.0 in a concentration range of 0.20–3.75 mg/ml. The consideration for selecting the particular drug concentration and

pH is referred as the solubility of TER-HCl in aqueous solution. The maximum solubility of TER-HCl was found to be 3.75 mg/ml in 1×10^{-4} M HCl solution, and then, 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. 5. As can be seen from the figure, the amount of total TER-HCl taken increased with increasing IA content and initial drug concentration. The reason for 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 the initial concentration of TER-HCl solution on the adsorption capacities of hydrogels is also shown in Fig. 5. As can be seen from the figure, an increase in 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). TER-HCl adsorption capacities of P(VP/IA) hydrogels prepared in this study were compared with poly(acrylamide/maleic acid) hydrogels in our previous study (Şen et al., 2000), where we observed an approximately twofold increase in the drug adsorption. The reason for this increase was attributed to the higher diprotic acid content of the gel system and specific bonding of positively

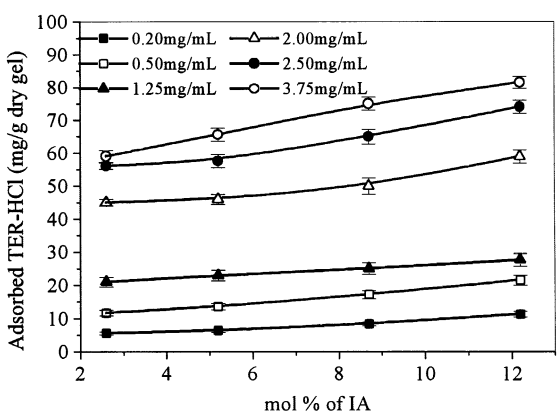

Fig. 5. Effect of IA content and drug concentration on the adsorption capacities of P(VP/IA) hydrogels.

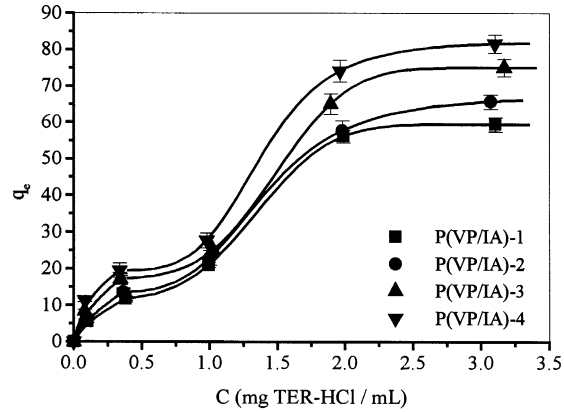

Fig. 6. TER-HCl adsorption isotherms of P(VP/IA) hydrogels. The mole percentages of IA in the P(VP/IA)-1, P(VP/IA)-2, P(VP/IA)-3 and P(VP/IA)-4 hydrogels are 2.6, 5.2, 8.7 and 12.2, respectively.

charged drug to partially ionized hydrogel and to the higher free volume available for diffusion.

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

$$q_e = \left(\frac{(C_i - C)}{m}\right) \times V_t \quad (2)$$

where q_e is in mg adsorbate per gram of dry adsorbent, C_i and C are the initial and equilibrium concentrations of adsorbate solution in mg/ml, V_t is the volume of solution treated in ml, and m is the mass of dry adsorbent, in g. As can be seen from Fig. 6, an increase in the content of ionic comonomer IA 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 an increased in swelling. The L_4 type curves in P(VP/IA) hydrogels indicate that the type of isotherm for all hydrogel systems is multimolecular (Giles et al., 1960).

3.4. Release behavior of hydrogels

For the investigation of drug-release behavior of P(VP/IA) hydrogels, first, drug loading experi-

ments were conducted in 0.2–3.75 mg/ml of TER-HCl solutions. In order to determine the amount of non-specific adsorbed TER-HCl, hydrogels were first placed in pH 8.0 phosphate buffer solution. Fig. 7 shows the percentage release non-specific adsorbed TER-HCl from P(VP/IA) hydrogels. The non-specifically adsorbed TER-HCl was assessed by measuring its concentration upon reaching equilibrium release conditions. While 11.3% of drug was released from P(VP/IA)-4 hydrogels, this value decreased to 5.6 with decreasing IA content in the gel when the initial drug concentration was 0.2 mg/ml. As can be seen from this figure, increasing the drug concentration also decreased the extent of non-specific release from gel systems.

The percentage release of TER-HCl at pH 8 was calculated from the following equation:

$$\text{Percentage release} = \frac{w}{w_{\text{total}}} \times 100 \quad (3)$$

where w is the weight of released TER-HCl at pH 8.0, 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 8 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

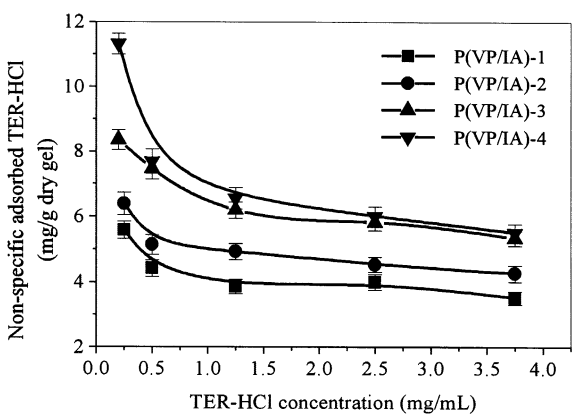

Fig. 7. Effect of drug concentration and IA content on the percent release of non-specific adsorbed TER-HCl. The mole percentages of IA in the P(VP/IA)-1, P(VP/IA)-2, P(VP/IA)-3 and P(VP/IA)-4 hydrogels are 2.6, 5.2, 8.7 and 12.2, respectively.

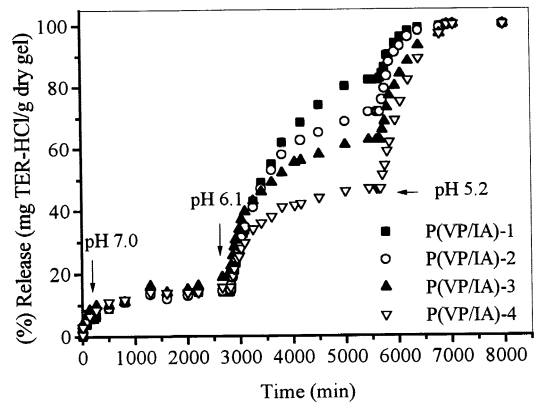

Fig. 8. Release of specific adsorbed TER-HCl from P(VP/IA) hydrogels. Adsorption is achieved from 3.75 mg/ml TER-HCl solution, and the mole percentages of IA in the P(VP/IA)-1, P(VP/IA)-2, P(VP/IA)-3 and P(VP/IA)-4 hydrogels are 2.6, 5.2, 8.7 and 12.2, respectively.

the amount of specific adsorbed TER-HCl in the hydrogel.

The controlled release of specific adsorbed TER-HCl from P(VP/IA) hydrogels was investigated primarily at pH 7.0. The drug release was followed until equilibrium, and then hydrogel was transferred into TER-HCl-free buffer at pH 6.1 After reaching a new equilibrium at 6.1, it was again transferred into another buffer solution at pH 5.2. The percentage release values of TER-HCl with time for P(VP/IA) hydrogels are given in Fig. 8. The percentage release values of specific adsorbed TER-HCl at pH 7.0, 6.1 and 5.2 were calculated from the following equation:

$$\%\ \text{release of specific adsorbed TER-HCl} = \frac{w_{\text{pH}}}{w_{\text{sp}}} \times 100 \quad (4)$$

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 the figure, percentage releases of specific adsorbed TER-HCl for each hydrogel at pH 7 were approximately of the same magnitude. This could be explained by the same extent of ionization or protonization of hydrogel at this pH value. Fig. 8 also indicates that the release rate and percentage release decreased at pH 6.1 with increasing IA content in the gel

system due to the increase of specific adsorption of drug to hydrogel structure. Approximately 82, 72, 61 and 47% drug releases are observed in the equilibrium release of P(VP/IA)-1, P(VP/IA)-2, P(VP/IA)-3 and P(VP/IA)-4 hydrogels at pH 6.1, respectively. The percentage release of TER-HCl from hydrogels was opposite in trend at pH 5.2 due to the higher drug content of hydrogel. A more favored controlled release of higher TER-HCl containing systems near the skin pH, 5.5, imparts additional advantages to higher IA-containing hydrogel P(VP/IA)-4 by causing retardation of release of drug compared with lower IA-containing P(VP/IA)-1 hydrogel. In this study, the release of TER-HCl was followed in batch systems, and burst release profiles were observed at each pH value. The drug release kinetics of TER-HCl adsorbed hydrogels on human skin could not be achieved yet due to the uncertainty of the prepared hydrogel systems, but it is anticipated that TER-HCl-loaded hydrogels would provide a more prolonged release on skin due to diffusion phenomena.

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. 9 and 10. As can be seen from those figures, while all the adsorbed drug was released at pH 6.1 for P(VP/IA) hydrogels in 0.50 mg/ml of initial

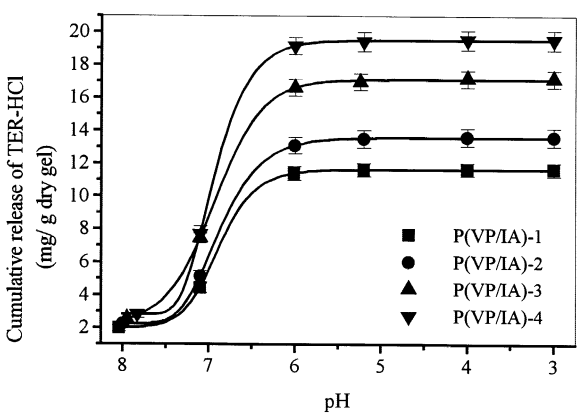

Fig. 9. Effect of pH on the cumulative release of TER-HCl from P(VP/IA) hydrogels when the adsorption is achieved from 0.50 mg/ml of TER-HCl solution. The mole percentages of IA in the P(VP/IA)-1, P(VP/IA)-2, P(VP/IA)-3 and P(VP/IA)-4 hydrogels are 2.6, 5.2, 8.7 and 12.2, respectively.

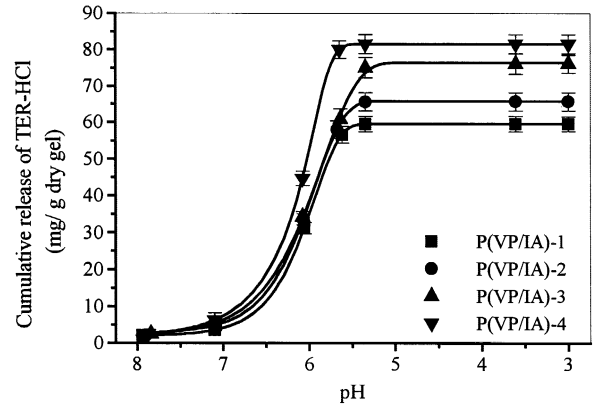

Fig. 10. Effect of pH on the cumulative release of TER-HCl from P(VP/IA) hydrogels when the adsorption is achieved from 3.75 mg/ml of TER-HCl solution. The mole percentages of IA in the P(VP/IA)-1, P(VP/IA)-2, P(VP/IA)-3 and P(VP/IA)-4 hydrogels are 2.6, 5.2, 8.7 and 12.2, respectively.

drug concentration, this pH shifted to 5.2 with increasing drug concentration in the gel system. This can be explained again by the increase of specific interactions between drug and hydrogel with increasing drug adsorption and may be due to changes in the dissociation constant of IA in the gel–drug–phosphate buffer system.

4. Conclusion

In this study, the preparation of P(VP/IA) 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 IA content in the gel system. This has been explained as being due to the incorporation of more specific acidic groups into the network and an almost higher swelling capacity of the gels. The release studies show that one of the basic parameters affecting the drug-release behavior of P(VP/IA) hydrogels is the pH of the solution. To conclude, 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 transdermal delivery applications of cationic drugs.

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