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RESEARCH PAPER

Interaction of Two Diclofenac Acid Salts with Copolymers of Ammoniomethacrylate: Effect of Additives and Release Profiles

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ABSTRACT

The copolymer of ammoniomethacrylate Eudragit RL® (ERL) interacted with diclofenac acid salts (sodium and diethylamine salts) in aqueous solutions, forming a complex. Sorption experiments were done in aqueous solutions of either sodium lauryl sulfate (SLS), Tween 20, or Tween 80. The SLS competed strongly with the drug, even at low concentrations, and reduced significantly the amount of drug sorbed by ERL. Tweens at high concentrations exhibited two phase profiles: the sorption phase, which was short and during which drug concentration dropped sharply, and the release phase, during which the drug was released slowly over 24 hr and which was accompanied by dispersion of ERL particles into the colloidal dispersion. The interaction was dependent on temperature, ionic strength, and nature of the additives. The extent of interaction in water and phosphate buffer solutions was in the following order: water > pH 6 > pH 7–8. In-vitro dissolution studies of the dried complex were done over 24 hr. In water, the drug remained bound to the polymer. In aqueous surfactant solutions (SLS, Tween 20, and Tween 80) and phosphate buffer at pH 6.8, a linear relationship between drug concentration and the square root of time was obtained, indicating a matrix diffusion–controlled mechanism. However, 100% release was not reached, and resorption was observed in the phosphate buffer solution.

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INTRODUCTION

Edragit® RL (ERL) and Eudragit® RS (ERS) are copolymers of ammoniomethacrylate with a low content of positively charged quaternary ammonium groups (1). ERL has higher water permeability and swellability than ERS because it contains a higher ratio of these groups (2). The copolymers are currently used for formulations of various controlled-release drug delivery systems (3–5). Recently, interactions of ERL with acidic drugs, primarily via ionic electrostatic interactions, were reported and proposed for use in controlling drug release (6–10). Additives were employed to modify the release of drugs from ERL and ERS; however, their effects on the interaction between drugs and both polymers were not examined (11–14).

Diclofenac acid as a model acidic drug was chosen because it is a potent nonsteroidal anti-inflammatory agent with wide use in the treatment of rheumatoid arthritis and other rheumatic disorders (15). Many studies were performed for preparation of sustained-release dosage forms of diclofenac acid using different excipients, including ERS (4,10,16–18). This study investigates the interaction between ERL and ERS and two salts of diclofenac acid, namely, diclofenac sodium (DS) and diclofenac diethylamine (DDEA). The latter is mainly used for topical applications (16). Moreover, the effect of different excipients currently used in formulation of controlled-release dosage forms on the interaction between both drugs and the polymer was examined. The study also includes in-vitro release investigations to evaluate the performance of the drug-polymer complex as a sustained-release delivery system.

MATERIALS

The DS and DDEA were of pharmaceutical grade and were supplied by Arab Pharmaceutical Manufacturing Company, Sult, Jordan. Eudragit RL powder (free of talc) and granules and Eudragit RS powder (free of talc) were purchased from Rohm, Germany. Polyvinyl pyrrolidone (PVP) K25 (BASF, Germany), gelatin (Croda, UK), sodium carboxymethylcellulose (Skoghal, Kemi, Sweden), sodium alginate (Kelco Co., US), hydroxypropylmethylcellulose (HPMC) E15 (Colorcon, UK), polyethylene glycol (PEG) 4000 (E. Merck, Germany), sodium carbopol (B.F. Goodrich, US), Pluronic F68 and F127 (BASF, Germany), Tween 20 and Tween 80 (Croda, UK), sodium chloride (Nifor, Switzerland), sodium citrate (Janseen, Belgium), and sodium lauryl sulfate (Haenkel, Germany) were pharmaceutical grade. Distilled water for injection was used in all experiments.

METHODS

To monitor the complex formation and possibility of redissociation; short time intervals of sampling and analysis were chosen. For this purpose, a dissolution apparatus (Erweka DT6, Erweka, Germany) was used along with the conventional shaking bottle method. First, 900 ml of distilled water was heated to 37°C in the dissolution apparatus and stirred with a paddle at 100 rpm. The stated amount of either DS (100 mg) or DDEA (75 mg) was dissolved; the drug percentage was determined spectrophotometrically by measuring absorbance at 275 nm (Beckman DU7 spectrophotometer, US) versus a standard solution. A known amount of the additive was then added and stirred until completely dissolved. Blank solution containing the same concentration of the additive in water was prepared, and its absorbance at the same wavelength was measured and considered during the calculation of drug concentration. Most of the additives did not interfere significantly. One gram of polymer powder was added and dispersed evenly in the dissolution medium. Samples of 5 ml each were withdrawn through a 0.45-μm filter (refiltering through a 0.22-μ filter was performed when required) at different time intervals. Drug concentration was then determined after proper dilution if necessary. Dilution of samples minimized the interference of additives to an insignificant level. Runs were done in triplicate.

To study the effect of temperature on the rate of interaction between drug and polymer, the method as described above was conducted at 27°C, 32°C, 37°C, and 42°C in the absence of any additives. Runs were done in triplicate.

The relationship between weight of ERL powder and amount of drug during interactions at 37°C from aqueous solution was studied. The DS solution was prepared at 500 mg per liter, while DDEA solution was prepared at 100 mg per liter because of its poor solubility. Two liters of each solution were placed in a glass bottle and shaken with the stated amount of polymer (1–5 gm polymer for DS and 0.2–1 gm polymer for DDEA) using a water bath adjusted at 37°C and left to run for 24 hr. Drug concentration in solution was then determined. To achieve equilibrium for both drugs, 24 hr were found sufficient. Runs were done in duplicate.

The effect of pH on the interaction between drug and polymer was investigated following the same procedure, but without additives. Phosphate buffer solutions (900 ml) of different pH (5–8) were prepared according to the USP XXIII (19). However, the pH 5 trials for both drugs and the pH 6 trial for DDEA were omitted from this study because both drugs were found too difficult to dissolved. Runs were done in duplicate.

Release patterns of DS or DDEA from the complex were studied for 24 hr under three different conditions at 37°C using the paddle method (USP XXIII) and stirring at 100 rpm. First, the adsorption and release profiles were monitored simultaneously when the surfactant was dissolved before adding the ERL powder. Second, the complex was first prepared, separated by filtration, dried overnight at 40°C, and passed through 250-μm sieves. Dissolution studies were done using water, phosphate buffer of pH 6.8 (USP XXIII), or surfactant solutions of different concentrations. Third, the dried complex powder (fraction passed through 250-μm sieve) was first exposed to 0.1 N HCl (250 ml, 37°C, 100 rpm) for 1 hr, and then the solution was treated to produce 1000 ml phosphate buffer of pH 6. 8. Runs were done in triplicate, except for soaking in 0.1 N HCl, for which runs were done in duplicate.

RESULTS AND DISCUSSION

Eudragit RL powder showed a strong interaction with either DS or DDEA; approximately 100% of the drug interacted from aqueous solution at 37°C in 2–3 hr. In contrast, Eudragit RS powder showed poor interaction power; not more than 10% of the drug interacted in 24 hr under the same conditions. This observation is in agreement with the previous work done by Omari (10). When ERL granules (cylinders, 4 mm length and 2 mm diameter) were used, the same extent of interaction was observed; however, the rate was much slower, with 67%, 94%, and 100% of the drug sorbed after 24, 45, and 120 hr, respectively. The ERL powder showed a faster rate of sorption at 100% within 10 hr. This is attributed to the larger surface area exhibited by ERL polymer powder, definitely larger than the surface area exhibited by polymer granules. An experiment related to ERL granules was conducted in water at 27°C and compared with an experiment for ERL powder run concurrently because granules at 37°C started to disintegrate and disperse after 24 hr. These results indicate that the extent of interaction is not dependent on the particle size of ERL polymer and is not restricted to the surface of ERL polymer granules. However, negatively charged drug molecules diffused into the interior of the hydrated granules and interacted with the active sites on polymer molecules, that is, the positively charged quaternary ammonium groups. Also, results show that the interaction or sorption from phosphate buffer solution of pH 6.8 was equilibrated at 18–24% of the drug concentration remaining in solution, while in aqueous solution, 100% of the drug concentration was sorbed by ERL polymer. The influence of altering pH on interaction between ERL polymer and either DS or DDEA is considered below.

The amount of either DS or DDEA that interacted as a function of ERL polymer weight showed a linear relationship with correlation coefficients of 0.9985 and 0.9962, respectively. For DS, 154–155 mg (0.484 mmol) per g ERL powder was considered as the optimum ratio, while for DDEA it was 170 mg (0.461 mmol) per g ERL polymer powder. Thus, taking into consideration possible experimental error, DS and DDEA interacted with ERL polymer in the same molar ratio, which indicates that the salt has not affected the extent of interaction quantitatively, and the responsible moiety is the diclofenac acid with its negatively charged carboxylic group.

From the study of the effect of temperature, it appears that the rate of interaction was temperature dependent, and it increased according to the following order 27°C $<$ 32°C $<$ 37°C $<$ 42°C for both DS and DDEA. As the temperature increased from 37°C to 42°C, the percentage of drug interacted with ERL polymer increased by 31% after 10 min. Changes in the physicochemical properties are to be considered as the temperature of solution approaches the glass transition temperature T_g of ERL polymer. In a previous study (7), the T_g of ERL polymer film was reported to be 55.1°C. As the temperature of solution (42°C) approaches the T_g of the polymer, the flexibility of its molecules increases, which leads to a higher rate of water permeation, hydration, and swelling (3). Thus, drug molecules will permeate faster into the interior of polymer particles, which results in an increase in the rate of interaction or sorption.

Table 1 shows the influence of pH on the interaction between ERL polymer and either DS or DDEA at 37°C relative to water. Results indicate that the amount of drug interacted with ERL polymer from different solutions decreases in the following order: water $>$ pH6 $>$ pH7 or 8. Interaction or sorption decreased by increasing the pH slightly from 6 to 7 or 8. In previous study (9), the interaction or sorption of salicylic acid (SA) with ERL polymer was found to increase with increasing pH; also, the

Table 1

Influence of pH on the Percentage of Drug Interacted with ERL Polymer After 24 hr at 37°C

	Percentage of Drug Interacted	
Medium	Diclofenac Sodium	Diclofenac Diethylamine
Water	100	99.3
pH 6	89	—
pH 7	83	85
pH 8	83	82

level of SA sorption from each of the phosphate buffer solutions examined was lower than from water for the same initial drug concentration. It was related to the pH and ionic strength dependence of the drug-polymer interaction.

The results of this study are in agreement with the previous study, which used SA with respect to water only. In contrast, this study shows that, by increasing the pH of the phosphate buffer solution above pH 6, the amount of drug interacting with ERL polymer decreases slightly. It is not related to the ionization of the drug because it was reported that by increasing the pH above the pk_a of the drug (DS or DDEA), the ionization, and consequently the solubility, of the drug increased significantly (10). In a basic information report about the ERL polymer (Rohm, Pharma Polymer Company, Germany), it was pointed out that the permeability of the ERL film coatings may be affected by the ion exchange process with buffer salts or medicinal agents. In a study (20) that showed the interaction of croscarmellose sodium (negatively charged sites at pH >2) and chlorpheniramine maleate (positively charged weak base), the minimum interaction occurred in regions of low pH values at which the excipient had uncharged sites and at higher pH (>9), at which the drug molecules were uncharged. Thus, for ERL polymer, decreased drug interaction or sorption by increasing the pH would be due to a decrease in the dissociation of the quaternary ammonium groups of the polymer at a pH higher than 6; consequently, the interaction started to decrease slightly, as shown in Table 1.

As to the effect of ionic strength, it is known that the electrostatic interaction decreases with an increase in ionic strength. This has been observed using sodium chloride and sodium citrate. After 24 hr, the amount of drug remaining in solution was 0%, 18%, 33%, and 38% for DS in the presence of 0, 0.1, 0.5, and 1 M NaCl,

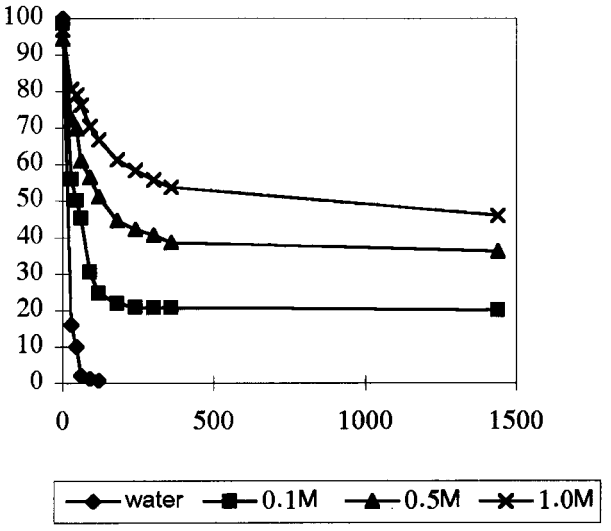

Figure 1. Effect of NaCl on the interaction between DDEA and ERL polymer in aqueous solution at 37°C.

respectively. The same behavior was observed for DDEA, for which 0%, 20%, 36%, and 42% of the drug remained in solution at the same respective concentrations of NaCl. Furthermore, a similar phenomenon was also exhibited by using sodium citrate. The rate of interaction between the drug and ERL polymer was slower at a higher concentration of the salt (Fig. 1). However, a certain level of sorption or interaction was maintained even at very high ionic strengths of sodium chloride (1.0 M), suggesting that nonelectrostatic binding due to hydrogen bonding and van der Waals forces existed. Both drugs exhibited a decrease in interaction with an increase in ionic strength. Jenquin et al. (7–9) previously demonstrated the same behavior between salicylic acid and Eudragit RL polymer.

Results indicate that nonionic polymer (PVP, HPMC, and PEG) and Pluronic additives did not exert any significant effect on the course of interaction between ERL and both drugs. They produced sorption profiles not significantly different from the profile of interaction in water. Also, viscosity did not affect the interaction, perhaps due to the low concentration of the nonionic polymers (0.1% w/v) used in this study. In contrast, anionic polymers showed some effect on the interaction, with the maximum effect produced by Carbopol sodium (CPS). After 3 hr, the amount of DS that remained in solution in the presence of 0.1% w/v CPS was 25.3% compared with 0.9% in the absence of CPS. The corresponding results in the presence of gelatin and amphoteric polymer,

sodium alginate, and sodium carboxymethylcellulose (an anionic polymer) were 10.9%, 8.9%, and 3.0%, respectively. Carbopol is an acidic polymer that is stronger than diclofenac acid because it precipitated the diclofenac acid from the aqueous solution of DS. Thus, CPS competed with the drug at the interacted sites of ERL polymer and reduced the rate and extent of the interaction, an effect that may modify the release pattern of DS or DDEA from the complex with ERL.

For the effect of surfactants, at low concentration (0.011% w/v), the effect of Tween 20 and Tween 80 was not significant, and both DS and DDEA were still bound to ERL polymer particles in a high proportion. By increasing the surfactant concentration to 0.055% w/v, either DS or DDEA was depleted from the interacting sites and released in solution. At a concentration of 0.11% w/v surfactant, the effect of Tween 20 and Tween 80 was prominent; however, Tween 20 was more effective than Tween 80 in removing the drug from the binding sites on ERL polymer particles (Fig. 2). Both DS and DDEA produced similar behavior, thus, only one graph is presented.

The profiles were characterized by two phases, the first one was the sorption phase, in which the drug concentration decreased very rapidly, and the second one was the release phase, in which the drug concentration increased gradually over 24 hr. The profiles of DS and DDEA were similar (i.e., two phases existed). However, Tween 80 showed a sorption phase continuing up to 2 hr, which was then followed by the release phase; Tween 20 showed a sorption phase of a shorter period of 1 hr, and after that, the release phase was dominant. It was observed that, during the sorption phase, the ERL polymer particles were still intact and did not disintegrate or break into smaller particles. In contrast, the release phase coincided with disintegration and dispersion of ERL polymer particles; a larger surface area started to exist. Furthermore, the higher percentage of release was found to coincide with the maximum disintegration and dispersion of ERL polymer particles into a colloidal dispersion with a very large surface area.

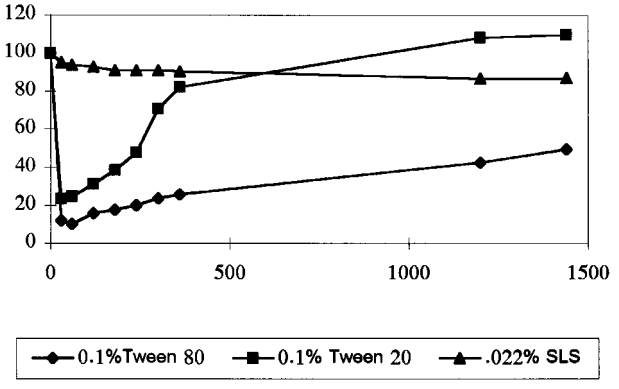

Figure 2. Sorption and release phases of DDEA from wet particles in aqueous surfactant solution at 37°C.

In a separate experiment in which the drug was omitted, Tween 20 (being more hydrophilic than Tween 80) was found to be more efficient in causing disintegration and dispersion of ERL polymer particles into colloidal dispersion. This behavior explains the faster release phase produced by Tween 20 as it reached 100% drug release after 24 hr, while Tween 80 produced 50% drug release only. Tween 20 and Tween 80, at concentrations of 0.11% w/v, were above their critical micelle concentrations (CMCs) (0.006% and 0.0014% w/v for Tween 20 and Tween 80, respectively, as reported in Ref. 21). Thus, the micellization mechanism would contribute to the release of either DS or DDEA into solution after the dispersion of ERL polymer particles into a colloidal form took place. At low concentrations of Tween 20 and Tween 80, ERL polymer particles were not affected and remained intact as small particles suspended in the dissolution medium over 24 hr of the experiment, exhibiting minimum release of drug into solution.

The results of the effect of SLS on the interaction between ERL polymer and either DS or DDEA indicate different mechanisms (10). As the concentration of SLS in solution increased, the percentage of the drug interacted with ERL polymer decreased (e.g., after 1 hr, the percentages of sorbed or interacted DS were 36.7%, 15.0%, and 7.2% for 50, 100, and 200 mg of SLS per 900 ml solution, respectively). The interaction then proceeded slowly until equilibrium was attained after 24 hr, at which point the percentages of interacted DS were 91.4%, 50.5%, and 14%, respectively. As can be seen from Fig. 2, the pattern and extent of drug interaction in the presence of SLS (0.022% w/v) were different from that of either Tween 20 or Tween 80 with concentrations of 0.1% w/v. The CMCs of SLS were reported as 0.23% w/v at 25°C and 0.24% w/v at 37°C (22). Since the concentration of SLS used in this study was lower than the reported CMC, one would expect that the micellization mechanism would not contribute to the effect of the SLS on the interaction between either DS or DDEA and ERL polymer. It appears that the behavior of SLS would be related to the ionic nature of the interaction with ERL polymer, which was dominated by the competition between anionic groups of

SLS and carboxylic groups of either DS or DDEA at the positively charged interacting sites of the polymer (10). Therefore, SLS did not exhibit two-phase profiles; instead, a one-phase profile was observed over the whole period of 24 hr, representing the sorption phase only. Furthermore, the rate of interaction of either DS or DDEA in the presence of SLS was slow due to the strong competition exerted by the anionic groups of the SLS molecules.

Also, it was observed that SLS did not produce a colloidal dispersion of ERL polymer, in contrast to Tween 20 and Tween 80; however, SLS caused flocculation of the polymer particles as a direct effect of electrostatic interaction. A higher concentration of SLS was omitted because, at a concentration of 0.1% w/v, SLS produced a turbid solution that rendered the analytical method inapplicable.

The release of either DS or DDEA from the dried complex powder was studied using different dissolution media: 0.022% w/v SLS, 0.055% w/v SLS, 0.1% w/v Tween 20, 0.1% w/v Tween 80, phosphate buffer solution (pH 6.8), and water. DS and DDEA behaved similarly; results are presented in Fig. 3. Drug release in water was very poor, and the drug was resorbed by the ERL polymer particles. In contrast, other dissolution media exhibited significant drug release; however, after 20 hr, drug concentration in phosphate buffer solution started to decrease due to resorption.

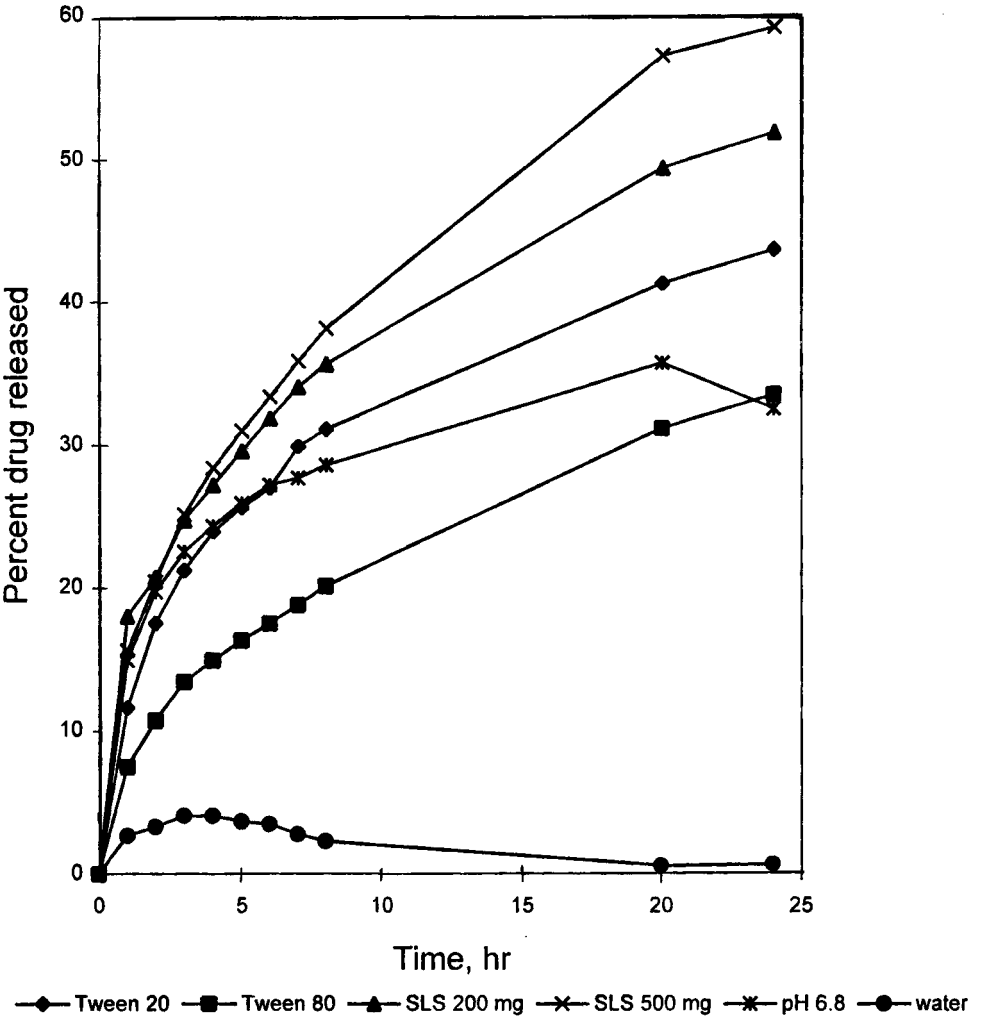

Figure 3. Dissolution of DDEA from the dried complex in the presence of different dissolution media at 37°C.

Table 2

Release Characteristics of Drug-Polymer Dried Complex in Different Dissolution Media

	Diclofenac Sodium			Diclofenac Diethylamine		
		Time$^{1/2}$			Time$^{1/2}$	
Dissolution Media	r_f^2	r^2	K	r_f^2	r^2	K
0.11% Tween 20	0.7031	0.9625	8.134	0.7104	0.9711	7.823
0.11% Tween 80	0.7860	0.9896	6.373	0.8147	0.9988	6.626
0.022% w/v SLS	0.7561	0.9864	9.323	0.7882	0.9926	8.904
0.055% w/v SLS	0.7869	0.9939	10.050	0.7860	0.9957	11.159
phosphate buffer pH 6.8	0.6152	0.8933	4.924	0.6804	0.9445	5.730

r_f^2, correlation coefficient using first-order kinetics; r^2, correlation coefficient using square root of time (time$^{1/2}$) kinetics; K, release rate constant.

Release kinetics were studied using the matrix mechanism and first-order kinetics. In Table 2, the correlation coefficient of drug release in all dissolution media indicated poor linearity when the first-order release pattern was fitted for either DS or DDEA (i.e., it did not fit the first-order release pattern for either DS or DDEA). In the case of the matrix mechanism, the Higuchi equation (23) was applied to the diffusion of a drug from a drug-polymer complex as follows:

$$100 - M = -K \cdot t^{1/2}$$

where M is the drug concentration in solution as a percentage; K is a release rate constant that is a complex function taking into account the initial drug concentration, the solubility, the diffusion coefficient, the porosity, and the tortuousity of the polymers; and t is the time.

The results in Table 2 show that the treatment of release kinetics according to the Higuchi equation exhibited a linear relation between drug amount in solution and square root of time. Correlation coefficients approached a value of 1 (0.8933–0.9988). The lowest correlation coefficient was exhibited by the data for the dissolution in phosphate buffer; this could be attributed to the presence of sorption mechanism that occurred simultaneously. Dissolution in other media suggests that the release process of the drug (DS or DDEA) from the drug-ERL complex was matrix controlled, that is, a Fickian diffusion mechanism. The release rate constant (Table 2) indicated that the rate values were dependent on the type of dissolution medium. The order of rate constants was 0.055% SLS > 0.022% SLS > 0.1% Tween 20 > 0.1% Tween 80 > phosphate buffer solution (pH 6.8). Although SLS was used in a lower concentration than either Tween 20 or Tween 80, it showed the highest K values. This could be explained by the strong and preferential ionic interaction between negatively charged surfactant molecules and positively charged ERL polymer particles, which allowed faster release of drug molecules into solution.

The solubility of diclofenac salts is dependent on pH (24). Thus, their rate of dissolution from a polymer complex will be dependent on the pH of the medium. Consequently, experiments were run using a pH-changing medium comprised of dissolution in 0.1 N HCl (pH 1.2) for 1 hr and then in phosphate buffer of pH 6.8. Figure 4 illustrates the influence of soaking in 0.1 N HCl on the release of either DS or DDEA from the dried complex powder. The results indicate that, at a pH of 1.2 over a 1-hr period, not more than 2.5% of the drug content (DS or DDEA) was released. After neutralization and adjusting the pH to 6.8, the percentage of the drug released was initially high, 17.4% and 21% for DSA and DDEA, respectively. After 27 hr of dissolution, the percentage of the drug released increased slightly and almost reached a plateau at 28% and 33% for DS and DDEA, respectively.

These observations suggest that an equilibrium between sorption and dissolution of the drug was reached in the system under examination. Comparison of the data provided from dissolution in water, in phosphate buffer of pH 6.8, and after soaking in 0.1 N HCl, one can predict that the release may be incomplete in the gastrointestinal tract. Therefore, oral bioavailability is questionable, and in vivo studies are needed to assess the release behavior in the gastrointestinal tract and the effect of biological fluids on the drug-polymer complex. Furthermore, 1 g of ERL polymer exceeds the recommended oral daily dose of this polymer (1). However, the complex of either DS or DDEA with ERL polymer may be useful for the preparation of transdermal drug delivery systems. Further studies are currently under way.

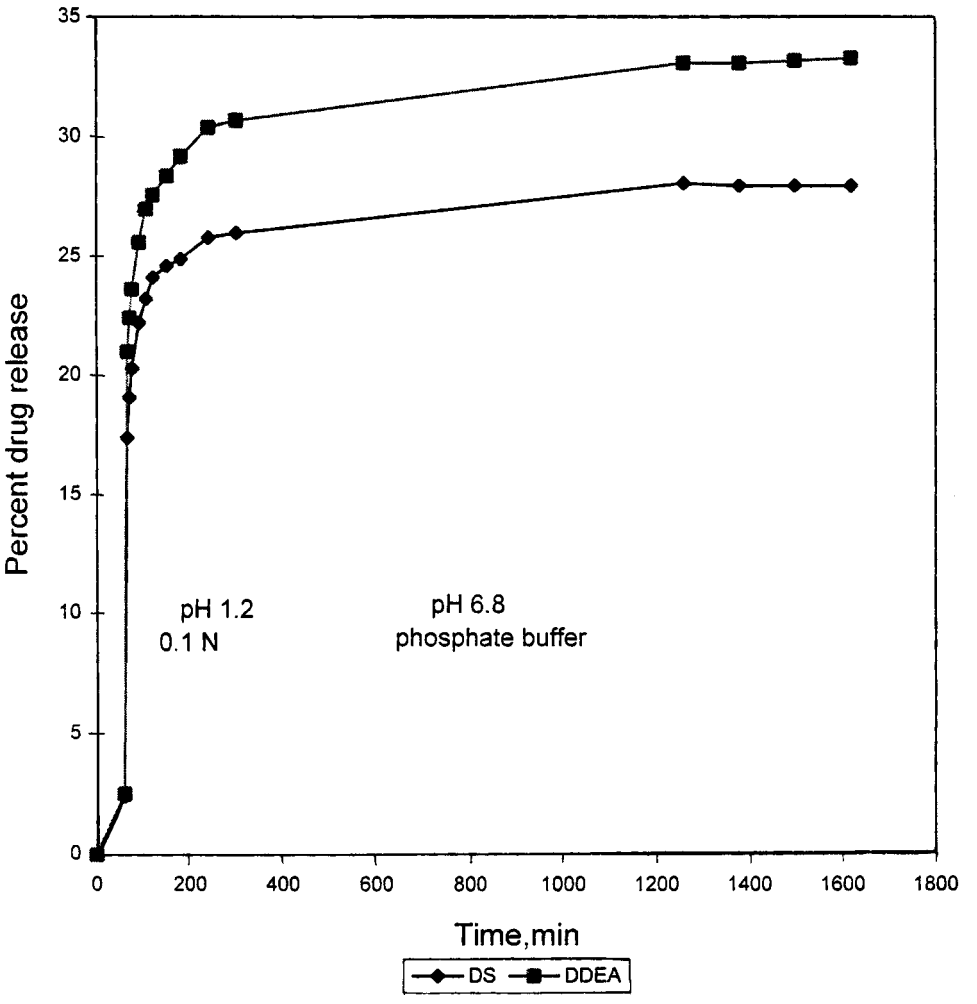

Figure 4. Dissolution of DS and DDEA from dried complex in phosphate buffer solution after soaking in 0.1 N HCl for 60 min.

CONCLUSIONS

The copolymer of ammoniomethacrylate Eudragit ERL interacted strongly with sodium and diethylamine salts of diclofenac acid forming a complex in aqueous solutions. The interaction was dependent on temperature, which affected the rate; the ionic strength, which affected the extent of interaction; and the nature of the additives, which must show stronger acidity than diclofenac acid to compete on the active sites. Interaction was found at maximum in water and decreased in the following order: water > phosphate buffer solution of pH 6 > same buffer of pH 7–8. This could be attributed to a decrease in the dissociation of the quaternary ammonium groups of the polymer. The SLS competed strongly with the drug and reduced the amount of drug sorbed by ERL. Tween 20 and Tween 80 exerted their effect only at high concentrations. Tween 20 and Tween 80 exhibited two-phase profiles: the sorption phase, which was short and during which drug concentration dropped sharply, followed by the release phase, in which the drug was released slowly over 24 hr and was accompanied by dispersion of ERL into a colloidal form. Tween 20 was more efficient than Tween 80 in accelerating the dispersion of ERL; thus, it exhibited a higher rate of drug release in the release phase than Tween 80. The results of dissolution of the dried complex showed that, in water, the drug remained strongly bound to the polymer. In aqueous surfactant solutions and phosphate buffer of pH 6.8, the release exhibited a matrix diffusion-controlled mechanism. Resorption

was observed in phosphate buffer solution. Soaking in 0.1 N HCl prior to dissolution in phosphate buffer solution did not change the release pattern significantly. Accordingly, its usefulness as an oral controlled-release system for diclofenac acid is questionable. However, the complex could be a good candidate for a transdermal delivery system for diclofenac acid salts.

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