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Characterization of acrylic resin matrix films and mechanisms of drug-polymer interactions

Michelle R. Jenquin [1] and James W. McGinity

The University of Texas at Austin, Division of Pharmaceutics, College of Pharmacy, Austin, TX 78712–1074 (USA)

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Summary

A polymeric matrix system for controlled drug release was developed employing the model drugs, salicylic acid and chlorpheniramine maleate, along with two acrylic resin polymers of varying permeability (Eudragits RL and RS). During drug release studies and sorption experiments with salicylic acid and the Eudragit RL polymer, the presence of an interaction between the drug and polymer was found. The physical and chemical properties of this drug-polymer complex were investigated to elucidate the mechanisms of interaction. The solubility of the salicylic acid and chlorpheniramine maleate in the polymeric films was determined to be greater than 10% w/w using DSC, SEM and powder x-ray diffraction. At a 10% drug loading, the drug molecules were dissolved in the polymer and the matrix existed as a solid solution. X-ray diffraction studies revealed that sorbed salicylic acid was in solution with the polymer rather than present as dispersed crystalline material. These Eudragit polymers interacted with acidic compounds in a manner similar to ion exchange resins which contain quaternary ammonium groups, as found in these polymers. Both reversible and irreversible binding of salicylic acid were observed during desorption studies, suggesting the presence of more than one type of binding interaction. The reversibility of salicylic acid binding with a change in ionic conditions supported the theory that the drug interacted with these polymers primarily via ionic electrostatic interactions. The absence of observed changes in the location or breadth of specific infrared absorption bands, suggested that hydrogen bonding between the salicylic acid and the polymer was minimal in the drug-polymer interaction. No evidence of new covalent chemical bond formation between the drug and the polymer was found. The dissolution release profiles for salicylic acid and chlorpheniramine maleate were directly correlated to the drug-polymer interactions. Decreases in pH or increases in ionic strength which minimized ionization of the anionic drug resulted in decreased drug sorption and increased drug release from the matrix films.

Introduction

Pharmaceutically, Eudragit acrylic resins have been used to formulate oral controlled-release delivery systems by coating small particles and tablets (Jambhekar et al., 1987; Lehmann, 1989), by addition to direct compression tablet formulations (Cameron and McGinity, 1987), and in the preparation of microcapsules (Fouli et al., 1983; Kawata et al., 1986). The properties of monolithic slab devices have been reported by various investigators (Bodmeier et al., 1990; Jenquin et al., 1990).

Correspondence to ([1] present address): M.R. Jenquin, Rhône-Poulenc Rorer, 500 Arcola Road-Bldg. SW11, Collegeville, PA 19426-0107, U.S.S.

During drug release studies involving salicylic acid and the Eudragit RL polymer the presence of an interaction between the drug and polymer which significantly influenced drug release was recently reported (Jenquin et al., 1990). The Eudragits RL and RS are copolymers synthesized from acrylic and methacrylic acid esters which contain a low level of quaternary ammonium groups. The RL polymer contains a greater molar ratio of these ionizable groups, which causes it to be more readily permeable than the Eudragit RS (Lehmann, 1989). The sorption of salicylic acid to the Eudragit polymers was found to agree with the Freundlich relationship; however, the mechanism of this interaction has yet to be characterized.

Recent investigators have examined the adsorption of drugs to polymeric materials such as microcrystalline cellulose (Okada et al., 1987) and polycarbophil (See et al., 1987). Freundlich adsorption constants were calculated for those drugs that were found to interact with the microcrystalline cellulose. The pH dependence of drug adsorption mainly resulted from the dissociation of carboxyl groups on the cellulose surface with increasing pH. The influence of ionic strength on drug adsorption was believed to be due to the restriction of the electric double layer around the cationic drug and/or anionic microcrystalline cellulose. The adsorption and release of drugs and inorganic ions onto and off a hydrophilic polymer with repeating carboxylate groups, polycarbophil, also seemed to follow the characteristics of an ion exchange resin (See et al., 1987).

The release of salicylic acid and *p*-aminosalicylic acid from a polymeric matrix was found to be influenced by interactions with the cationic Eudragit E and anionic Eudragit L methacrylate copolymers investigated (Badawi et al., 1980). The cationic polymer bound both drugs and affected drug release, especially at drug low concentrations. The anionic type copolymer interacted only slightly with salicylic acid, while the *p*-aminosalicylic acid interaction was more pronounced, indicating a possible reaction between the amino group of the drug and the anionic group of the polymer.

Adsorptive binding interactions are generally characterised as physical adsorption or chemical adsorption. Physical adsorption is due to electrostatic interactions, hydrogen bonding or van der Waals forces and is usually reversible; while in chemical adsorption, the adsorbate is attached to the adsorbent by primary chemical bonds, including ion exchange, protonation and complexation, and is irreversible. In complicated systems, several adsorption mechanisms can operate simultaneously, depending on the concentration, pH and temperature.

The primary objective of this study was to elucidate the mechanisms of drug-polymer interaction between acidic drugs and the Eudragit RL and RS polymers. This was investigated by characterization of the matrix films and of drug adsorption. The solubility of the drugs in the polymers and the crystalline state of the polymers and drugs were examined by scanning electron microscopy (SEM), differential scanning calorimetry (DSC) and powder X-ray diffraction. These three evaluations characterized the physical state of the matrix films. The mechanism of drug interaction with the polymer was investigated by employing qualitative adsorption studies, X-ray diffraction and infrared spectroscopy (IR). A desorption study was conducted to determine if the drug-polymer binding was predominately reversible or irreversible. Finally, the influence of pH upon drug sorption and dissolution drug release from the matrix was evaluated for the model drugs and correlated to the mechanisms of drug interaction.

Materials and Methods

Materials

Salicylic acid and chlorpheniramine maleate were purchased from Sigma Chemical Co., St Louis, MO. Methylene chloride (A.C.S. grade), 85% phosphoric acid, 0.1 N sodium hydroxide solution, sodium phosphates (monobasic, dibasic and tribasic), sodium chloride, citric acid, sodium citrate, sulfathiazole and theophylline were obtained from Fisher Scientific Co., Fair Lawn, NJ. The glycine was bought from J.T. Baker, Inc., Phillipsburg, NJ. The sodium salicylate and propranolol-HCl were purchased from Mallinckrodt,

Inc., Paris, KY. The Eudragit™ polymers (RL PM, RS PM, RL100 and RS100) were donated by Röhm Pharma, Darmstadt, Germany.

Film preparation

Polymer matrix films containing drug, salicylic acid or chlorpheniramine maleate, were prepared by solvent casting with methylene chloride at room temperature, dried over a desiccant for 24 h and cured for 7 days, as previously described (Jenquin et al., 1990).

Differential scanning calorimetry (DSC)

The solubility of the drugs in the polymeric matrix was analyzed using a Perkin-Elmer differential scanning calorimeter model DSC 2-C with a thermal analysis data station TADS system, computer and plotter interface. The instrument was calibrated with an indium standard. Film samples of 3–5 mg were accurately weighed into aluminum pans and then sealed. The endothermic heat of melting for drug dispersed in the polymer was evaluated over a concentration range of 10–90% drug using a scan rate of 20°C/min conducted over a temperature range of 2–227°C.

Powder X-ray diffraction

Powder X-ray diffraction patterns were obtained with a Phillips X-ray diffractometer with CuK_α radiation (0.154 nm) at 35 kV and 20 mA over a 2θ range of 4–45°. Diffraction patterns for the drug, polymer and drug-polymer mixtures were obtained. The drug samples were used as obtained from the suppliers. The Eudragit RL100 and RS100 polymers were used to avoid any complications or diffraction due to the talc added to the Eudragit RL PM and RS PM samples. The polymer pellets and cast films were ground before analysis. Physical mixtures of drugs (10%) and Eudragits (90%) were made by grinding polymer with drug. Salicylic acid was adsorbed to the Eudragit RL100 polymer at an initial concentration of 1.5 mg/ml. After equilibrium was reached, the excess drug solution was removed and the polymer was dried and ground.

Infrared spectroscopy

A KBr pellet was formed by mixing 2% sample with dried KBr. From this mixture, 100 mg were pressed under 4000 kg force to form a transparent pellet sample. This pellet was scanned from 4000 to 600 cm^{-1} in a Perkin-Elmer model 1320 Infrared spectrophotometer.

Drug release studies

The USP XXII Method IV (paddle-over-disk) was used to evaluate dissolution drug release from the matrix films at 30°C over a 24 h period. Samples were taken at specified time intervals and analyzed spectrophotometrically (salicylic acid at 298 nm and chlorpheniramine maleate at 263 nm) for drug content. Drug release profiles were determined using the following media: distilled-deionized water, 50 mM citric acid-sodium citrate buffer at pH 5.0, 50 mM sodium phosphate buffer USP at pH 7.0 and 50 mM glycine-NaOH buffer at pH 9.0.

Drug release study with media change

The release of salicylic acid from the Eudragit RL PM matix film into 500 ml distilled-deionized water was followed for 24 h. After the 24 h dissolution sample was taken, the matrix films were transfered into new media; 500 ml of fresh deionized-distilled water or 500 ml of 0.5 M NaCl solution. All other conditions of the dissolution experiment were unchanged. An additional sample was taken 12 h after the films were transferred.

Drug-polymer sorption

Sorption of drug to the Eudragit RL100 polymer was achieved by mixing drug solutions (20 ml) of varying concentrations with 0.2 g polymer 420–600 μm in size, on a Vanderkamp® Sustained Release Apparatus at 30 rpm in a 30°C water bath. The equilibrium solution concentration was spectrophotometrically assayed for drug content and the amount of drug sorbed was calculated. The sorption of several drugs (sodium salicylate, sulfamerazine, theophylline, propranolol-HCl, diphenhydramine-HCl, and sulfathiazole) according to acid-base chemical classifications, was evaluated. The influence of pH on drug sorption to the polymers was determined using 1 mg/ml salicylic acid in 50 mM phosphate buffers ranging in pH from 2 to 11.5 (phosphoric

acid, sodium phosphate: monobasic, dibasic and tribasic; were combined in different ratios to achieve the desired pH).

Adsorption / desorption

Salicylic acid was allowed to sorb to the polymer as outlined above; initial drug concentrations of 300, 600, 900, 1200 and 1500 μg/ml. After equilibrium was reached, all of the drug solution was collected and the amount of drug remaining was determined. Fresh distilled-deionized water (without drug) was added to the drug-polymer complex. This new mixture was rotated for 24 h, the liquid again collected and the amount of drug desorbed into solution assayed. This extraction procedure was repeated twice more. The amount of drug initially adsorbed and the amount desorbed during each extraction was determined.

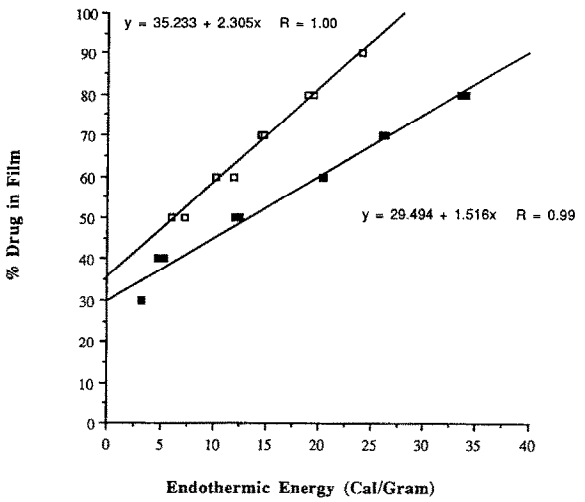

Fig. 1. Mass fraction of drug vs endothermic energy of melting for salicylic acid (■) and chlorpheniramine maleate (□) in cast Eudragit RL100 films.

Results and Discussion

Characterization of the physical state of drugs within the polymer matrix

In order to evaluate dissolution and adsorption mechanisms, it was necessary to determine whether the drugs were dissolved (solid solution) or dispersed (solid dispersion) within the polymers.

Morphological properties of the films

At a 20% (200 mg/g) drug loading in Eudragit RS100, salicylic acid crystals were visible under 60 × magnification with a scanning electron microscope. In these films the salicylic acid clearly existed as solid crystalline material dispersed within the polymer film. There were no visible signs of drug crystallization in Eudragit RL100 films containing up to 15% salicylic acid nor in Eudragit RS 100 or Eudragit RL100 films containing 20% chlorpheniramine maleate. These Eudragit films were clear, colorless slabs.

Thermal analysis of matrix films

The approximate solubility of each drug in the polymeric films was determined by plotting the percentage of drug in the film against the endothermic energy for films containing from 90 to 20% drug. These plots are given in Figs 1 and 2 for chlorpheniramine maleate and salicylic acid in Eudragit RL 100 and RS 100 films, respectively. The endothermic energy decreased with decreasing drug concentration until there was no longer a measurable heat of melting generated from films containing 20% or less drug. In addition,

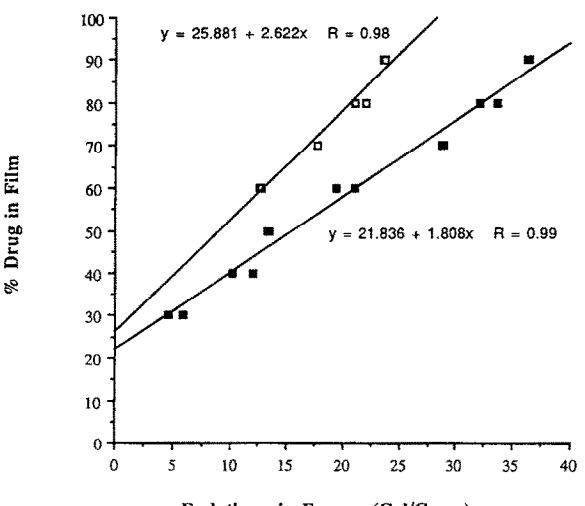

Fig. 2. Mass fraction of drug vs endothermic energy of melting for salicylic acid (■) and chlorpheniramine maleate (□) in cast Eudragit RS100 films.

the location of the melting peak experienced slight shifts towards lower temperatures with higher levels of polymer. These shifts in the melting transition temperature coupled with the absence of a drug melting peak for drug concentrations below 20% provide evidence of some interaction, in terms of solubilization, between the polymers and the model drugs (Theeuwes et al., 1974; El-Shattawaty et al., 1981).

From the *y*-intercepts for each drug shown in Fig. 1, the solubility of chlorpheniramine maleate in Eudragit RL 100 was found to be 35% (350 mg/g) and that of salicylic acid was 30% (300 mg/g). Similar calculations were performed with the data in Fig. 2 to obtain the solubilities of 26% (260 mg/g) for the chlorpheniramine maleate and 22% (220 mg/g) for the salicylic acid in Eudragit RS 100. Since the measured solubilities of the drugs in the polymers as determined by thermal techniques are at the melting temperature of the drugs, these values may be slightly higher than the true solubility at room temperature.

For the drug-polymer systems under investigation, it was clear from the *y*-intercepts of Figs 1 and 2 and from examination under scanning electron microscopy, that a 10% drug loading was well below the solubility limit for both drugs and polymers and at this concentration, all of the drug molecules were dissolved in the polymer and the matrix existed as a solid solution.

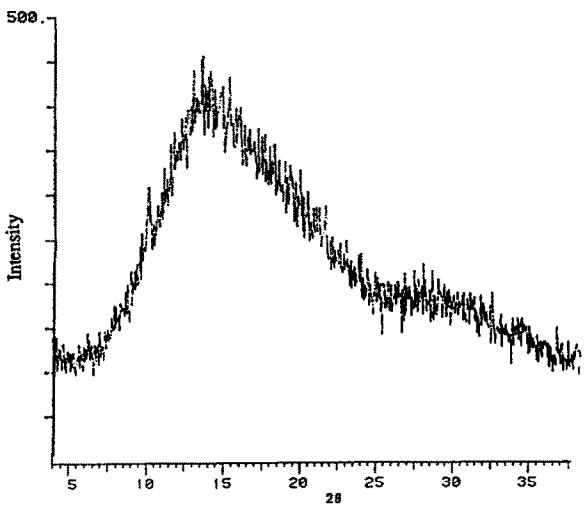

Fig. 3. Powder X-ray diffraction patterns of pure Eudragit RL100 polymer.

The chlorpheniramine maleate was found to be more soluble than salicylic acid in both polymers. This higher solubility of the antihistamine suggested that it was more compatible with these polymers and participated in intermolecular interactions with the polymeric chains more actively than the salicylic acid. Both drugs showed higher solubilities in the Eudragit RL 100 polymer than the Eudragit RS 100 polymer. The higher content of quaternary ammonium groups in the Eudragit RL polymer provided more sites for hydrophilic interactions between the drugs and the polymer to occur. This greater hydrophilicity of the Eudragit RL100 polymer accounted for the greater compatibility and solubility of the drugs in the Eudragit RL polymer.

Powder X-ray diffraction properties

Additional support for the characterization of these drug-polymer matrices as solid solutions at room temperature was gained from powder X-ray diffraction analysis. The Eudragit RL and RS polymers are amorphous in nature due to the absence of complete steroregularity and the presence of bulky side groups. A representative X-ray diffraction pattern for these polymers, as shown in Fig. 3 for Eudragit RL100, is devoid of sharp peaks. The crystallinity of salicylic acid and chlorpheniramine maleate was clearly demonstrated by their unique X-ray diffraction patterns shown in Fig. 4a and c, respectively. The diffraction pattern from a physical mixture of 10% drug, salicylic acid or chlorpheniramine maleate, with pure polymer contained sharp diffraction peaks corresponding to the crystalline drug molecules present in the mixture, as displayed in Fig. 4b and d. The presence of diffraction peaks in a physical mixture of 10% drug with the Eudragit polymer demonstrated that the presence of undissolved, crystalline drug dispersed in the matrix would exhibit diffraction peaks when exposed to X-rays.

The diffraction patterns from cast films of Eudragit RL100 containing 10% of salicylic acid and chlorpheniramine maleate are displayed in Fig. 5a and b, respectively, and do not contain

any peaks associated with crystalline drug molecules. These diffraction patterns were identical to those of the pure polymer, shown in Fig. 3, suggesting that at a 10% loading, the drug was either dissolved in the polymer or present in an amorphous state within the polymer matrix. Films containing drug loadings above the solubility of the drug in the polymer (i.e., a matrix film containing 50% drug) exhibited diffraction peaks associated with crystalline drug material. If the drug present in the solid dispersion was amorphous in nature, little or no diffraction peaks would have been observed. This reappearance of sharp diffraction peaks at high drug concentrations further supported the contention that at a 10% loading dose, the both drugs were dissolved in the polymer and the matix existed as a solid solution.

Drug release from the polymer matrices

During drug release studies involving salicylic acid and the Eudragit RL polymer the presence

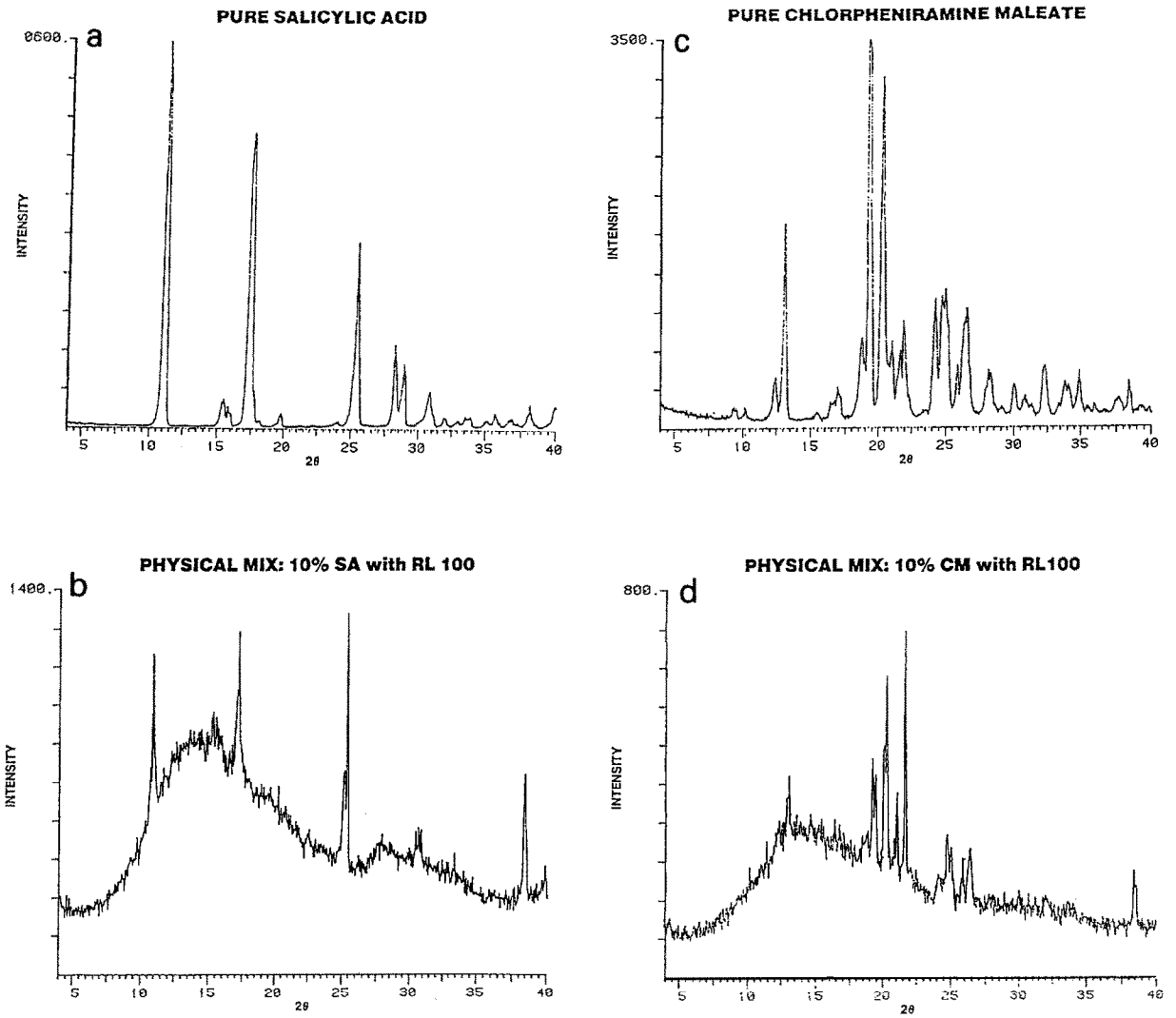

Fig. 4. Powder X-ray diffraction patterns of: (a) pure salicylic acid, (b) 10% salicylic acid physically mixed with Eudragit RL100, (c) pure chlorpheniramine maleate and (d) 10% chlorpheniramine maleate physically mixed with Eudragit RL100.

of an interaction between the drug and polymer which significantly influenced drug release was discovered (Jenquin et al., 1990). At a 10% drug loading, between 50 and 60% of salicylic acid remained in the matrix film. This concentration corresponded to approx. 55 mg drug bound per g Eudragit RL PM polymer. In an attempt to release additional drug and elucidate the mechanism of interaction, Eudragit RL PM films exhibiting this drug-polymer complex with salicylic acid were placed in two different dissolution media and the results are shown in Fig. 6. Placement of the drug-polymer complexed matrix film from the dissolution studies into fresh distilled-deionized water did not liberate additional drug. However, exposing the films to a high ionic strength solution (0.5 M NaCl) resulted in release of more than 95% drug from the matrix.

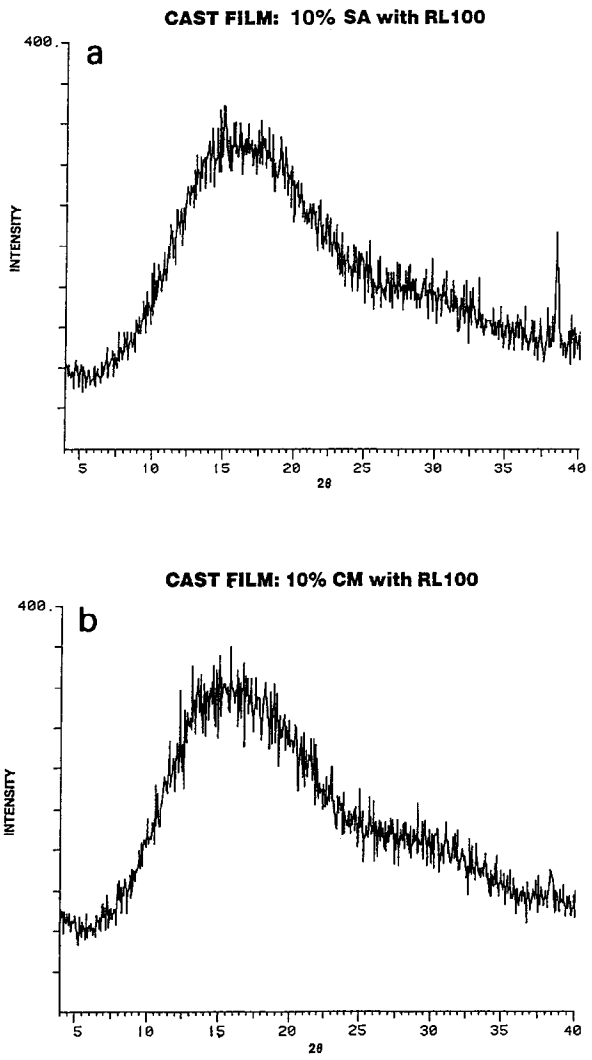

Fig. 5. Powder X-ray diffraction of (a) Eudragit RL100 matrix film with 10% salicylic acid, and (b) Eudragit RL100 matrix film with 10% chlorpheniramine maleate.

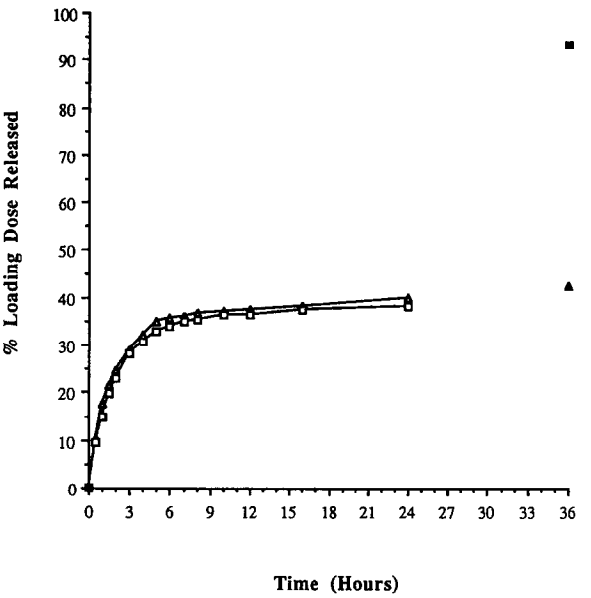

Fig. 6. Dissolution release profiles of salicylic acid from Eudragit RL PM films with transfer of films to 500 ml new media after 24 h. (△, □) Dissolution in water, (▲) transfer to water, and (■) transfer to 0.5 M NaCl.

The displacement of salicylic ions by the chloride ions resulted from competition between ions for binding sites on the polymer where the bound salicylic acid was exchanged for the smaller chloride (Cl^-) ions. This reversibility of salicylic acid binding with a change in ionic conditions supported the hypothesis that the salicylic acid complexed with these polymers primarily via ionic electrostatic interactions.

Interaction of Eudragit RL with acidic drugs

The sorption of several other drugs to Eudragit RL100 according to an acid-base chemical classification was evaluated quantitatively. The theoretical mechanism of interaction being an ionic electrostatic binding between an anionic drug molecule and the cationic quaternary am-

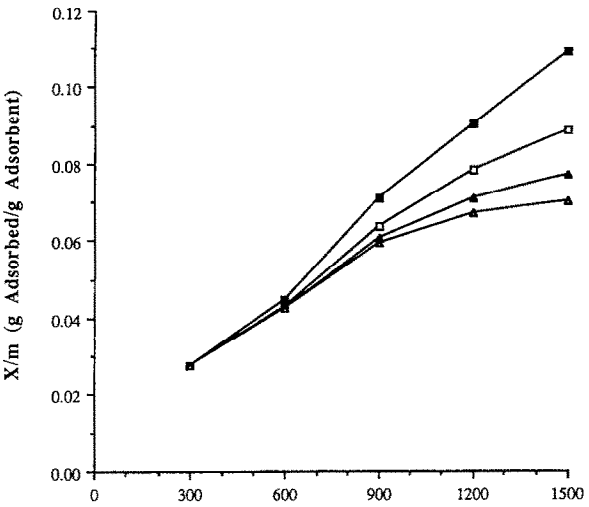

Fig. 7. Adsorption of salicylic acid to Eudragit RL100 followed by desorption by extraction with fresh medium. (■) Adsorption, (□) 1st extraction, (▲) 2nd extraction, and (△) 3rd extraction.

monium group, was further supported by the selective adsorption of acidic compounds. In all cases, the acidic drugs were sorbed from solution by the Eudragit RL100 polymer and the basic drugs were not. Between 35 and 95% of the sulfonamides and salicylates (acids and salts) tested were adsorbed from solution, while 96–99% of the basic drug substances, including theophyline, propranolol-HCl and diphenhydramine-HCl, remained in solution. These observed sorption characteristics of these Eudragit RL and RS polymers was very similar in nature to those of an anion exchange resins containing quaternary ammonium groups (Vincent, 1966; Schacht, 1983).

The sorption of salicylic acid to Eudragit RL100 polymer and three desorption extractions were performed to show the extent to which salilcylic acid interacts with the polymer and to evaluate for reversible binding. The results are shown in Fig. 7. The Eudragit RL100 was suspended in a concentrated solution of salicylic acid and the drug was allowed to sorb to the polymer. The drug solution was analyzed for loss of salicylic acid from solution and at the greatest concentration, the amount sorbed corresponded to about 100 mg salicylic acid per gram of Eudragit RL 100. By a simple extraction process, some drug sorbed at higher concentrations could be removed from the polymer. However, much of the drug (100–65%) remained irreversibly bound to the polymer under the aqueous conditions of study. The desorption process appeared to plateau at a sorptive capacity between 60 and 70 mg salicylic acid per g of polymer, for irreversible binding under aqueous conditions. This sorptive capacity corresponds well with the 55 mg of salicylic acid which remained bound per g of polymer during dissolution studies in water (Fig. 6). These findings of both reversible and irreversible binding under aqueous conditions suggest the presence of more than one type of binding interaction. In addition to the primary ionic electrostatic interactions, hydrogen bonding and van der Waals forces may be influencing drug interaction with the polymer.

Mechanisms of drug-polymer interaction

In such associations, new chemical bonds and strong complexations (hydrogen bonding) can alter the crystalline and spacial structure of the adsorbate, resulting in a changed X-ray diffraction pattern as demonstrated by Porubcan and co-workers (1978). The powder X-ray diffraction pattern of the above drug/polymer complex did not contain any diffraction peaks associated with crystalline salicylic acid. In fact, the diffraction pattern did not exhibit any evidence of drug bound to the polymer, but was identical to that of the pure polymer shown in Fig. 3. The absence of diffraction peaks from crystalline material showed that the bound salicylic acid interacted with the polymer at the molecular level. The sorbed drug was either dissolved in the polymer or present as an amorphous material. Because undissolved drug in films cast with high drug content (drug loadings greater then the drug solubility in the polymer) exhibited X-ray diffraction peaks, the sorbed salicylic acid was most likely in solution with the polymer. The mechanism of salicylic acid sorption involved more than simple partitioning of crystalline drug into the polymer.

Infrared spectroscopy was employed to study the drug-resin complex for changes in the molec-

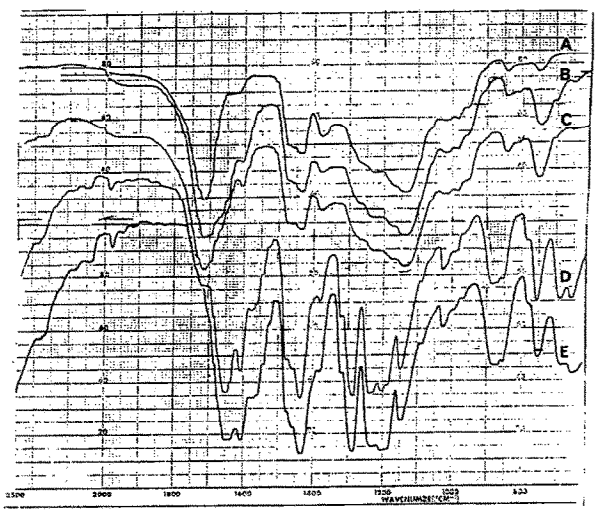

Fig. 8. Transmission infrared spectra, over the 700–2500 cm^{-1} region, of: (a) Eudragit RL100, (b) salicylic acid adsorbed to Eudragit RL100, (c) 10% salicylic acid in Eudragit RL100 polymer film, (d) 50% salicylic acid in Eudragit RL100 polymer film, (e) salicylic acid.

ular structure. Porubcan and co-workers (1978) reported that no change in the infrared spectrum was usually indicative of reversible binding and physical adsorption. The transmission infrared spectra of various scans over the 700–2500 cm^{-1} region are displayed in Fig. 8. Intermolecular interactions between salicylic acid and the Eudragit RL100 polymer could be reflected in the emergence of additional bands or alterations in wavenumber position or shape of the proton-donating and accepting bands in the spectra.

Salicylic acid with an aromatic carboxylic acid group, is capable of hydrogen bonding. The carboxylate anion stretching band of this group occurred in the 1400–1500 cm^{-1} region. At low drug concentrations, this band was completely covered by bond stretches from the polymer. The carbonyl stretching vibrations were present in the 1600–1700 cm^{-1} region. Some of this band remained visible when polymer was present in the sample. Several bands appeared in the 750–900 cm^{-1} region due to C-H bending from the substituted aromatic ring of the salicylic acid and from the polymer chains. The OH stretching vibrations of salicylic acid absorbed energy in the 3300–3200 cm^{-1} range. This band was also completely overshadowed by the polymer.

Those salicylic acid bands which remained visible upon combination with the polymer showed no discernable shifts or broadening. No changes in peak resonance were observed with any of the stretching bands from the drug or the polymer. Shifts toward lower wavenumber would indicate an increase in hydrogen bonding energy resulting from the orientation of the proton-donating and receiving groups, or differences in the electronegativities of the groups. The absence of observed changes in band location or breadth, suggested that hydrogen bonding between the salicylic acid and the Eudragit RL100 polymer was of minor importance in the drug-polymer interaction.

The infrared absorption spectrum of salicylic acid adsorbed to the Eudragit RL100 polymer or cast with the polymer did not contain any stretching bands that were not associated with either the drug or polymer. New chemical bonds formed between the drug and polymer would be expected to result in the emergence of additional bands or alterations in wavenumber position (Dyer, 1965; Coutts, 1969). No evidence of intermolecular chemical bonding between the drug and polymer existed. This provided further mechanistic support that the adsorption interaction of acidic drugs with the Eudragit RL and RS polymers was primarily electrostatic in nature and did not involve the formation of covalent chemical bonds.

Influence of pH: support for electrostatic mechanism of drug-polymer interaction

The influence of pH upon drug adsorption and dissolution drug release further support an electrostatic binding interaction and show that the dissolution profiles directly correlate with the drug-polymer interactions. The sorption of salicylic acid to Eudragit RL100 was found to increase with pH, as demonstrated in Fig. 9. The pH dependence of drug sorption resulted mainly from the dissociation of the salicylic acid. Since the pK_a of salicylic acid is 2.97 (Steele, 1966), as the pH of the media was increased above this value, a greater percentage of the salicylic acid would become ionized. An ionized acid molecule would be capable of electrostatic interactions with

the quaternary ammonium groups of the Eudragit polymers and account for the higher levels of sorbed drug to the polymer. The fluctuations in adsorption at pH 4.5 and 10 could be artifacts of the low buffer capacity experienced by the sodium phosphate buffer around pH 4.7 and 9.9. The variations in the sorption at very high pH values are believed correlated to ionization of the phenol group of the salicylic acid ($pK_{a_2} = 13.4$). With an increase in pH from 5 to 9, drug sorption increased approx. 40%. Also, the level of salicylic acid sorption from each of the phosphate buffer solutions was lower than from water (comparison made at the same initial drug concentration of 1 mg/ml).

Corresponding results were observed for the release of salicylic acid from Eudragit RL PM films exposed to dissolution media at different pH values as shown by the dissolutions profiles in Fig. 10. As the sorption of salicylic acid increased with the more basic conditions, the extent of drug release diminished. At a pH of 5, salicylic acid reached 90% release, while at pH 9, only 60% drug release was achieved. Increasing the pH of the dissolution media favored ionization of the anionic drug and caused increased association and decreased drug release from the matrix films. Salicylic acid release into water (Fig. 6) approached only about 40% of that loaded, while release in all buffers studied were higher. This corresponds to the reduced levels of drug sorption observed from the phosphate buffers and further supports the pH and ionic strength dependence of drug-polymer interaction. These evaluations show dissolution profiles for salicylic acid to directly correlate with the drug-polymer interactions capable of occurring in this system.

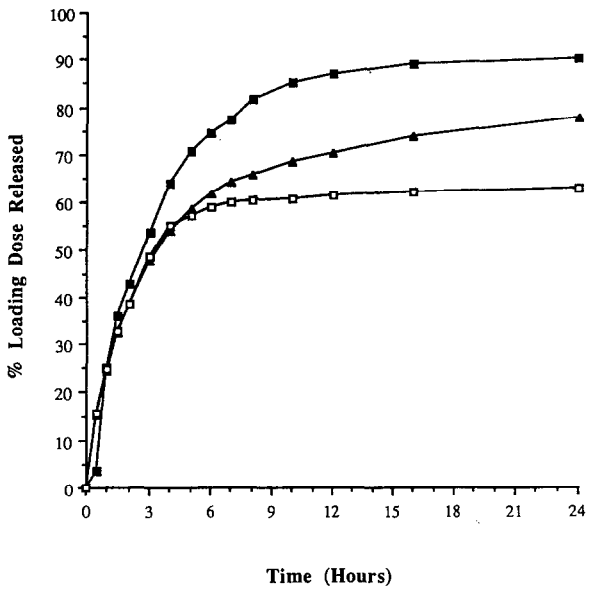

Fig. 10. The effect of pH on the release of salicylic acid from Eudragit RL PM films conducted in (■) citric acid-sodium citrate buffer at pH 5.0, (▲) sodium phosphate buffer USP at pH 7.0, and (□) glycine-sodium hydroxide at pH 9.0.

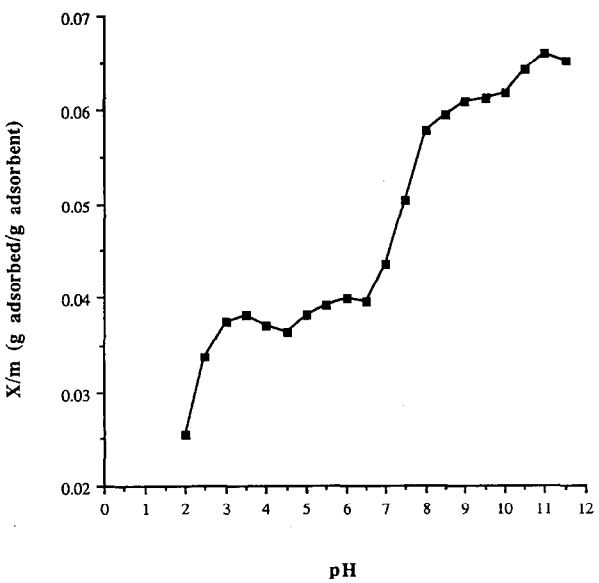

Fig. 9. The influence of pH on the sorption of salicylic acid from a 1 mg/ml solution to Eudragit RL100 in 50 mM sodium phosphate buffers.

The same three buffers systems were used to examine the influence of pH on the dissolution of chlorpheniramine maleate from Eudragit RL PM films, and these results are presented in Fig. 11. The extent of drug release from the Eudragit RL PM matrix films was not influenced by pH. The observed variances in the rate of chlorpheniramine maleate diffusion at the three pH values evaluated were most likely influenced by differences in drug solubility with pH. The antihistamine was steadily liberated at all pH values studied, until 90% of the loading dose was re-

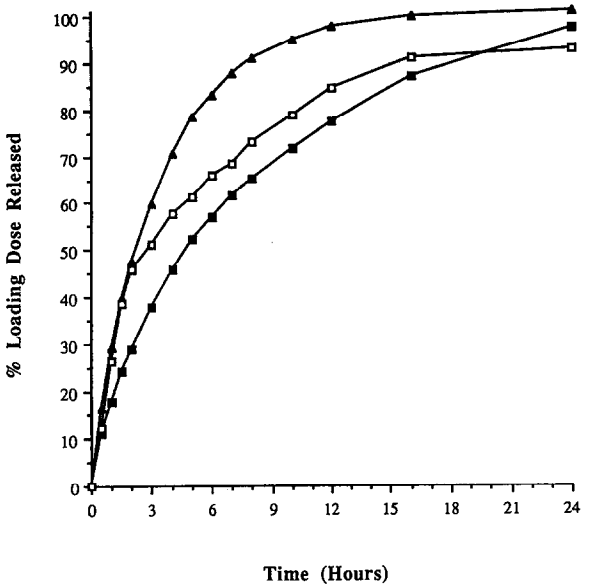

Fig. 11. The effect of pH on the release of chlorpheniramine maleate from Eudragit RL PM films conducted in (■) citric acid-sodium citrate buffer at pH 5.0, (▲) sodium phosphate buffer USP at pH 7.0, and (□) glycine-sodium hydroxide at pH 9.0.

leased and the depletion zone was reached. These results further support the sorption findings that basic compounds, such as chlorpheniramine maleate, do not interact with these polymers and diffuse from the matrix system without retardation due to binding.

Summary

From this investigation, the following conclusions regarding the mechanisms of drug-polymer interaction of this matrix system were made: (1) The sorption of acidic drugs, such as salicylic acid, by the Eudragit RL and RS polymers was primarily due to ionic electrostatic interactions. The exclusive adsorption of anionic drug molecules showed the Eudragit RL polymer to be functioning similarly to an anion exchange resin containing quaternary ammonium groups. (2) Powder X-ray diffraction patterns typical of amorphous materials were obtained for pure polymer, adsorbed drug and cast films with 10% drug loading suggesting van de Waals forces and solubilization of drug by the polymer were possible secondary mechanisms of interaction. (3) From the IR studies, the absence of observed changes in the location or breadth of specific infrared adsorption bands indicated that hydrogen bonding was of minor importance in the drug-polymer interaction. In addition, the IR scans showed no evidence of new covalent chemical bonds formed between the drug and the polymer. (4) Bound drug could be liberated by decreasing the pH or increasing the ionic stength of the media to decrease the electrostatic binding interactions between the drug and polymer. (5) The dissolution profiles for salicylic acid and chlorpheniramine maleate were found to directly correlate with the drug-polymer interactions.

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