Drug Development and Industrial Pharmacy, 28(2), 207–215 (2002)

RESEARCH PAPER

Investigation of Potential Ionic Interactions Between Anionic and Cationic Polymethacrylates of Multiple Coatings of Novel Colonic Delivery System

Vishal K. Gupta,[1,*] Thomas E. Beckert,[2] Norbert J. Deusch,[2] Madhusudan Hariharan,[1] and James C. Price[1]

[1]*University of Georgia, College of Pharmacy, Department of Pharmaceutical and Biomedical Sciences, Athens, Georgia 30602*
[2]*Röhm GmbH, Pharma Polymers, 64293 Darmstadt, Germany*

ABSTRACT

The objective of this work was to investigate potential interactions between anionic (Eudragit FS) and cationic (Eudragit RL) polymethacrylates of multiple coatings of a novel colonic drug delivery system. Aqueous films of pure polymers Eudragit FS (FS) and Eudragit RL (RL) and their superimposed film (FS–RL) were cast on glass slabs. The potential ionic interactions were studied by analyzing the dried films using differential scanning calorimetry (DSC), Fourier transform-infrared spectroscopy (FT-IR), and nuclear magnetic resonance (NMR). The glass transition temperatures (T_g) of pure RL and FS were 60°C and 22°C, respectively; FS–RL showed two distinct glass transitions at 59°C and 24°C in the second heating cycle. In the ^{13}C-MAS spectra of the samples in the solid state, no shifts of the resonance could be detected in the superimposed film compared with the pure polymers. The FT-IR spectra of the superimposed film did not show any significant shift of the bands of the $-NMe_3^+$ group of RL and the $-COO^-$ function of FS compared with the spectra of the pure polymers. No ionic interactions between anionic and cationic polymethacrylates were revealed by DSC, FT-IR, and NMR.

*Corresponding author. Present address: Pharmacia, Pharmaceutical Sciences, Formulation Development, Skokie, Illinois 60077. Fax: +1 (847) 982-4900; E-mail: vishal.k.gupta@pharmacia.com

Key Words: *Colonic delivery; DSC; Eudragits; FT-IR; Ionic interactions; NMR; Pellets*

INTRODUCTION

Delivery of drugs to the colon has gained increasing importance in the last 15 years, both for the treatment of local diseases of the colon like inflammatory bowel disease (IBD) and for its potential for the delivery of large molecules. The colon presents a less hostile environment for drug delivery because of lower enzymatic activity and near-neutral pH (1–4).

In a previous study, the authors developed a novel colonic drug delivery system by selecting polymethacrylates of appropriate dissolution characteristics for the distal end of the small intestine and relying upon relatively constant transit time of the small intestine. The delivery system consisted of drug-layered pellets coated with an inner layer of a combination of two pH-independent polymers, Eudragit RL and Eudragit RS (2:8), and an outer layer of a pH-dependent polymer, Eudragit FS. At pH 6.5, there was no drug release for 12 hr. Release of 5-ASA was sustained for over 12 hr both at pH 7.0 and 7.5. The release rate was faster at pH 7.5 than at pH 7.0. The delivery system demonstrated its potential for colonic delivery by resisting drug release until pH 6.5, and the combination of Eudragit RL and RS in the inner coating proved successful for the sustained delivery of 5-ASA at the expected pH of the colon (5). Multiple response variables of the delivery system were optimized with respect to the release rate of the drug using central composite design. The proportion of the more hydrophilic polymer Eudragit RL had the most significant effect on drug release—higher proportions gave faster release (6,7).

As seen in Fig. 1, the release rate of the drug was slower from pellets having both inner and outer coats than from pellets having only the inner coat. Intuitively, we had expected that after the pH-dependent outer coating of Eudragit FS dissolved, the release rate from the pellets having both inner and outer coats would be the same as from the pellets having only the inner coat, because both types of pellets had the same inner coat (8% Eudragit RL–RS). Since this was not borne out by the dissolution tests, it was hypothesized that there might be ionic interactions between the anionic and cationic polymer coats resulting in a slower than expected release rate (Fig. 2).

The objective of this research was to study potential interactions between cationic (Eudragit RL and RS) and anionic (Eudragit FS) polymethacrylates

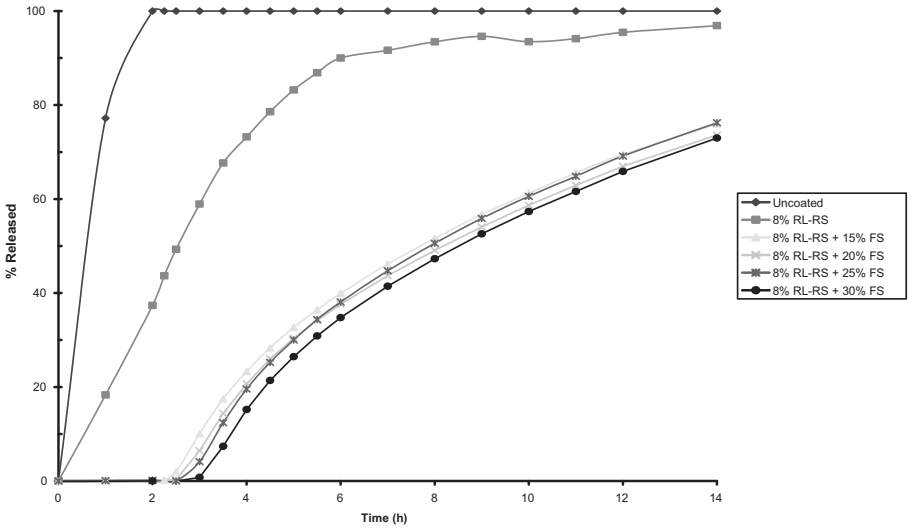

Figure 1. Dissolution of 5-ASA pellets for the first 2 hr at pH 1.2 followed by pH 7.0 USP phosphate buffer.

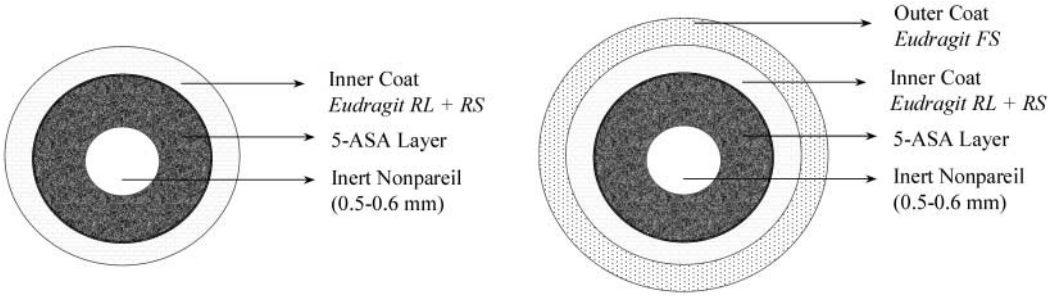

Figure 2. Schematic of a pellet containing only an inner coat and a pellet containing both inner and outer coat.

of multiple coatings using differential scanning calorimetry (DSC), Fourier transform-infrared spectroscopy (FT-IR), and ^{13}C solid state nuclear magnetic resonance (NMR). Of these, DSC has been reported extensively in the literature to determine the glass transition temperature (T_g) of polymers and to study interactions between drugs and polymers. The effect of various factors that influence the release of drugs from acrylic resin films was investigated by Jenquin et al. (8,9). Their DSC studies showed that incorporation of drug in the polymers decreased the T_g, indicating that some drug dissolved in the polymer. Watts et al. (10) utilized FT-IR and ^{13}C NMR for the qualitative and quantitative investigation of drug–polymer interactions. Hsiue et al. (11) used FT-IR to discover direct evidence of an interaction involving hydrogen bonding between theophylline and Eudragit L in the microspheres. The fraction of hydrogen-bonded theophylline increased with an increase in the amount of Eudragit L present in the microspheres. Solid state ^{13}C NMR was used by Vachon and Nairn (12) to elucidate physico-chemical associations of various homologs of salicylic acid with Eudragit RS in matrix microcapsules. The authors noted that electrostatic association of the drug with charged quaternary residues of the polymer may have been responsible for the observed stability of acetylsalicylic acid in aqueous swollen microspheres.

EXPERIMENTAL

Materials

Mesalazine (5-aminosalicylic acid) was purchased from CHEMIE S.p.A., Cinisello Balsamo, Italy. Eudragit RL30D, RS30D, FS30D were obtained in-house from Röhm GmbH, Chemische Fabrik, Darmstadt, Germany. Nonpareil beads were purchased from Hans G. Werner GmbH, Reutlingen, Germany. All other excipients used to prepare pellets and for coating were of standard pharmaceutical grade, and all chemical reagents used were of analytical grade.

5-Aminosalicylic acid (5-ASA) was used as a model drug for the preparation of pellets. It is slightly soluble in water (1 mg/mL, 20°C). Three dissociation constants (**–COO**: $pK_{a1} = 3.0$, **–NH2**: $pK_{a2} = 6.0$, and **–OH**: $pK_{a3} = 13.9$) have been reported for 5-ASA (13).

Eudragits are copolymers of methacryclic acid. The rigid molecular structure of polymethyl methacrylate (PMMA) is due to the backbone of a continuous chain of carbon atoms, which is additionally stabilized by methyl groups. Eudragit FS30D is a relatively new polymer—it is an anionic copolymer of methyl acrylate, methyl methacrylate (MMA), and methacrylic acid (MA) in a proportion of 7:3:1 (Fig. 3). It has a T_g of 22°C and forms films which are insoluble in pure water and diluted acids. The polymer is pH-sensitive; the carboxylic groups are ionized above pH 6.5 and the polymer dissolves (14). In the present study, Eudragit FS30D was used to provide an outer coating for the pellets. Eudragit RL and RS30D are cationic copolymers of ethyl acrylate (EA), MMA, and trimethylammonioethyl methacrylate chloride (TAMCl) in proportions of 1:2:0.1 and 1:2:0.1, respectively (Fig. 4). Eudragit RL and RS have the same chemical structure, except, that Eudragit RL has double the number of hydrophilic quaternary ammonium groups (cation density 1:20 repeating units) than Eudragit RS (cation density 1:40 repeating units). Both the polymers have a T_g of 60°C and are pH-independent; they swell and become permeable after coming in contact with digestive juices. The

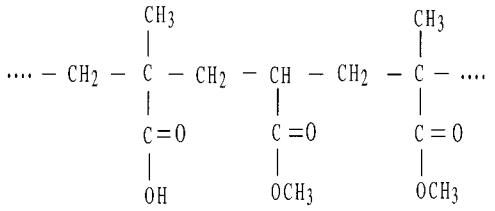

Figure 3. Chemical structure of Eudragit FS polymer unit.

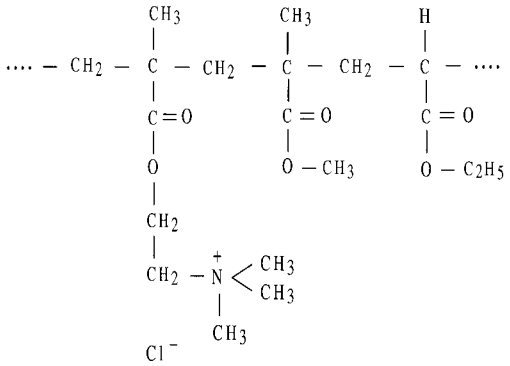

Figure 4. Chemical structure of Eudragit RL polymer unit.

release of most drugs is faster from Eudragit RL than from Eudragit RS, hence the pellets can be coated with different combinations of Eudragit RL and RS to provide various degrees of sustained release of the drug. Eudragit FS30D is produced by an emulsion polymerization process, whereas Eudragit RL and RS30D are produced by a direct emulsification process (15–17).

Preparation and Coating of Pellets

The method for the preparation and coating of pellets was described in a previous publication (18). Briefly, the pellets were prepared by powder layering of 5-ASA on nonpareil beads (nuclei) in a conventional coating pan (Erweka, Dusseldorf, Germany). Binder solution was continuously sprayed on the moving nonpareil beads and the powder composition was layered onto the particles. The drug-loaded pellets were dried in an oven, after which sieve analysis was done and the pellets were coated.

For the inner coat, the pellets were coated with a combination of Eudragit RL and RS in a fluidized-bed coating apparatus (GPCG 1.1, Glatt, Binzen, Germany). After the coating, the pellets were cured in an oven. The cured pellets containing an inner coat of Eudragit RL–RS were further coated with Eudragit FS30D in the fluidized-bed processor and cured again.

Scanning Electron Microscopy Studies

The surface characteristics of the pellets were observed by scanning electron microscopy (SEM) using a scanning electron microscope (Jeol, Tokyo, Japan). The pellets were sputter-coated with Au/Pd alloy for 6–7 min in a Hammer sputter-coating machine. Micrographs were taken at an excitation voltage of 5.0 kV using a TMAX 100-speed film.

Software

Automatic calculations of the drug concentration from ultraviolet (UV) absorption values were done using UV WinLab® software.

Dissolution Studies

Dissolution studies ($n = 6$) were done using modified USP XXIII, Method B for enteric-coated products (paddle method, 100 rpm, 37°C). For the *acid stage*, 200 mg of pellets was added to 700 mL 0.1 N hydrochloric acid and dissolution was done for 2 hr. At the end of 2 hr, 200 mL 0.20 M tribasic sodium phosphate was added to all the dissolution vessels, the pH was adjusted to 7.0, and the dissolution was continued for another 12 hr for the *buffer stage*. The dissolution apparatus (DT 80, Erweka, Dusseldorf, Germany) was attached to a spectrophotometer for automated sampling and online analysis.

Preparation of Films

Because of the difficulty of separating the coating from the pellets, potential interactions between the polymers were investigated by casting films. For the films of pure polymers, aqueous dispersions of Eudragit FS30D and RL30D were diluted with water from 30% to 10% polymer content. Diluted polymeric dispersions were poured on glass slabs and allowed to dry at ambient room temperature for two to five days until the films appeared dry. For the superimposed film of two polymers, first a film of Eudragit RL was cast and allowed to

dry as described earlier, and then a film of Eudragit FS was cast on top of the Eudragit RL film and again allowed to dry. Small pieces of the dried films were cut and used for DSC, NMR, and FT-IR studies.

Since Eudragit RL and RS have the same chemical structure and differ only in the content of quaternary ammonium groups, it was not considered necessary to include Eudragit RS in the superimposed film to study potential interactions.

DSC, FT-IR, and NMR Studies

Differential scanning calorimetry thermograms were recorded with a power-compensation calorimeter (Pyris 1, Perkin-Elmer, Shelton, CT, USA) at a heating rate of 10 K/min. The values of T_g were measured as the temperature corresponding to the half-height of the thermal capacity increment during the second heating scan. The samples were scanned from −40 to 100°C in aluminum pans with a hole in the cover.

The FT-IR spectra of the films were taken with an infrared microscope (NicPlan) coupled to a spectrometer (Nicolet Magna 550) in ATR mode using an objective (Spectra-Tech) with an aperture of 2.5 mm.

Nuclear magnetic resonance studies were performed on a Varian instrument (VXR 300 S) equipped with a MAS-Probe (Jacobsen) at a frequency of 75.5 MHz. The films were wound into a zirconium oxide rotor. The measurements were carried out at ambient temperature by cross-polarization with different contact times and by direct excitation (Bloch decay) of the ^{13}C nucleus at a spinning rate of approximately 6 kHz.

RESULTS AND DISCUSSION

The micrographs of the pellets showed uniformity and homogeneity of both inner and outer coats.

DSC

The T_g values of pure Eudragit RL and Eudragit FS were 60°C and 22°C, respectively. The superimposed film of the two polymers Eudragit FS and Eudragit RL showed two distinct glass transition temperature values in the first heating cycle at the expected temperatures of 60°C and 22°C. In the second heating cycle, the T_g values were 59°C and 24°C, respectively (Fig. 5). In case there was an interaction between the two polymers, the superimposed film would not have shown two distinct glass transition values corresponding to the values of the pure polymers. A small shift in T_g during the second heating cycle is probably because of the

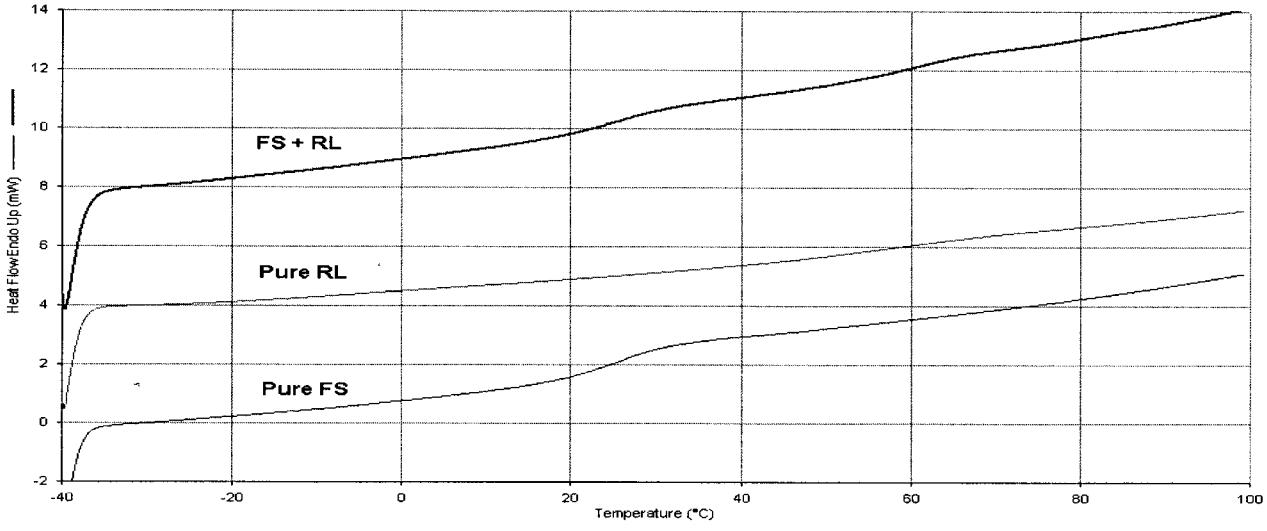

Figure 5. DSC thermogram of pure Eudragit FS (FS), pure Eudragit RL (RL), and superimposed-film of Eudragit FS and Eudragit RL (FS + RL).

residual moisture present in the films that acts as a temporary plasticizer.

FT-IR

If there is indeed an interaction between the quaternary ammonium group ($-NMe_3^+$) of Eudragit RL and the carboxylic acid group ($-COO^-$) of Eudragit FS, evidence of the interaction should be observed at the corresponding vibrations of 1700 (C=O) and 960 ($-NMe_3^+$) cm^{-1}, respectively. However, the spectrum of the superimposed film did not show any significant shift of the bands when compared with the spectra of the pure polymers (Fig. 6). In the ATR spectra, the HO vibration of the acid was too weak to detect an interaction by H-bridge to the halogen.

NMR

In order to study potential interactions between the $-NMe_3^+$ and $-COO^-$ groups, ^{13}C-MAS spectra of the samples in solid state were measured. The chemical shift is sensitive to changes in the environment of the functional group. However, no shifts in resonance could be detected in the superimposed-film when compared with the pure polymers (Fig. 7). The resonance of the quaternary ammonium group was absolutely stable concerning the linewidth of solid spectra (1–3 ppm). The resonance of the carboxylic acid group was hidden by the more intense ester-carbonyl group at 177 ppm (Table 1).

None of the results indicated any ionic interaction between the multiple coatings of the delivery system. However, physical interactions resulting from steric hindrance of $-NMe_3^+$ groups of Eudragit RL by $-COO^-$ groups of Eudragit FS cannot be ruled out. These physical interactions could lead to lower hydration of Eudragit RL, thus slowing the release of drug from the pellets having both inner and outer coat.

Another possible explanation for the slower release could be different degrees of hydration of the Eudragit RL–RS layer in both cases. The release from Eudragit RL–RS is primarily diffusion-controlled and depends on the hydration caused by the hydrophilic $-NMe_3^+$ groups present in the polymer. When only the RL–RS polymer coating is applied, it is instantaneously available for hydration in the dissolution medium from the pellets. However, when the second coating (outer coating) of Eudragit FS is applied, the RL–RS coating becomes only gradually accessible to the dissolution medium as the –COO groups of Eudragit FS

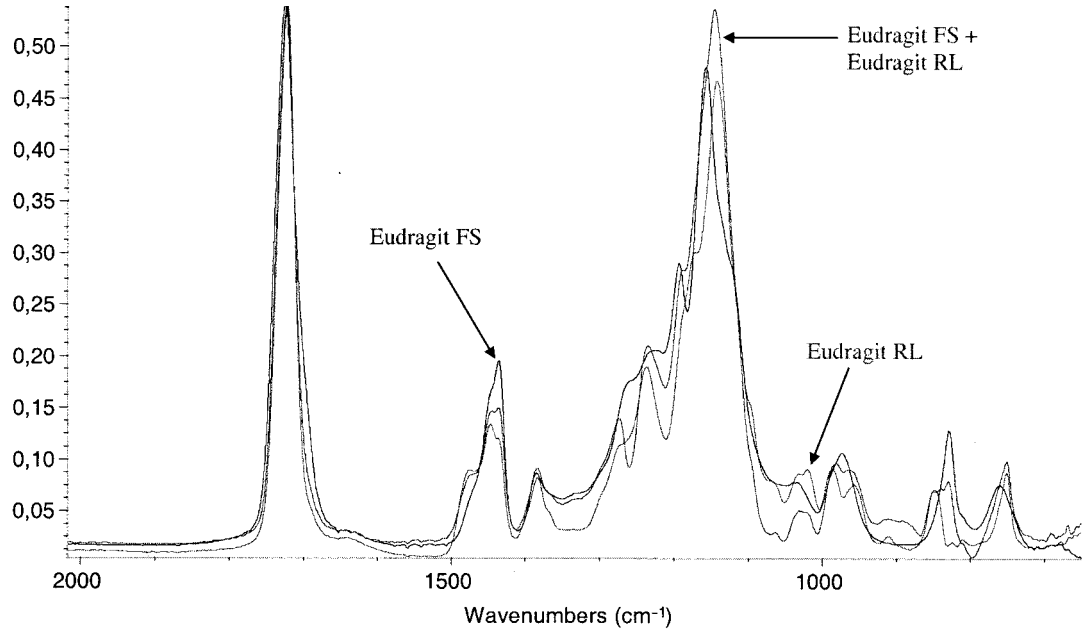

Figure 6. FT-IR spectra of Eudragit RL, Eudragit FS, and superimposed-film of Eudragit RL and FS.

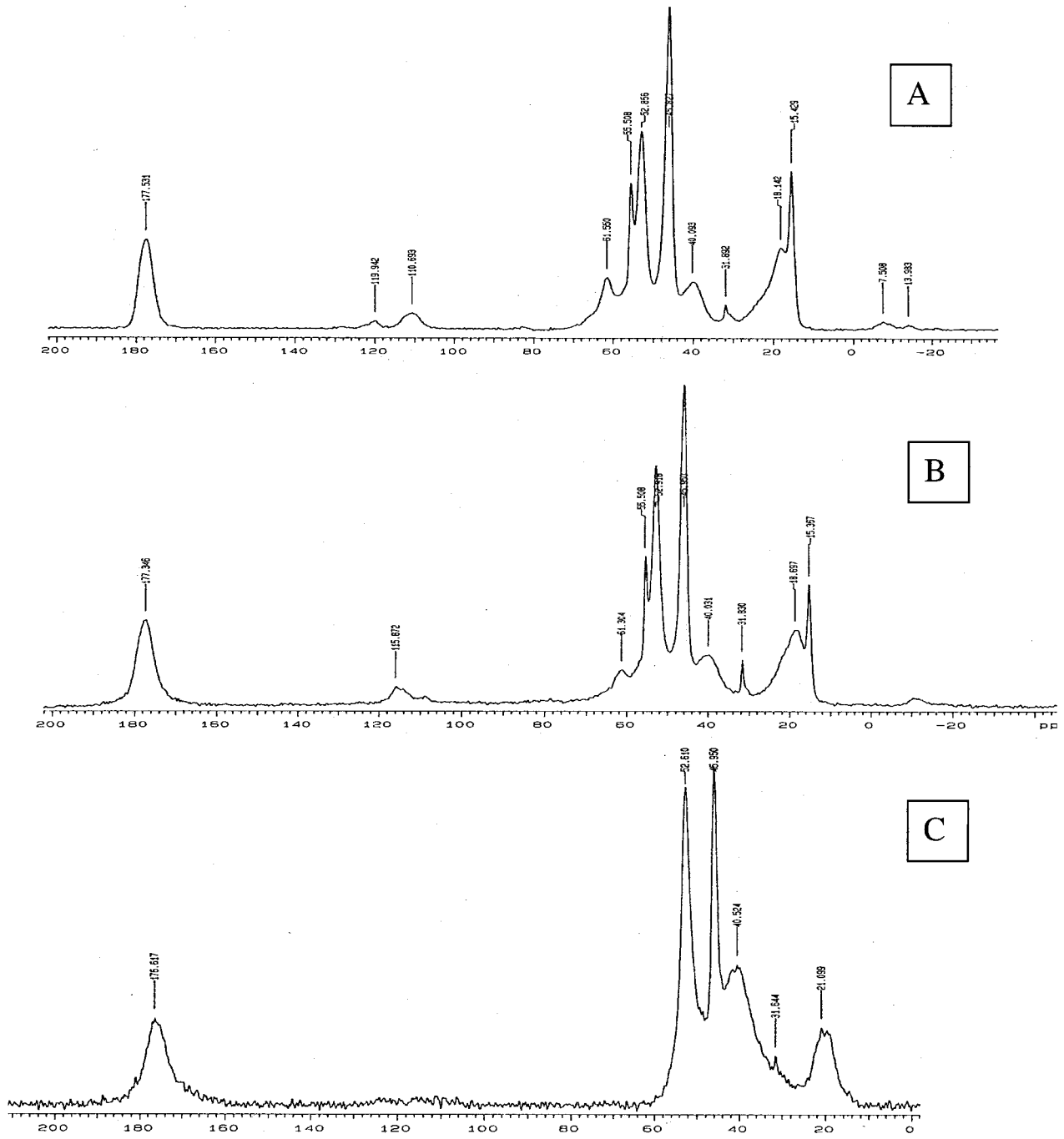

Figure 7. NMR spectra of superimposed-film of Eudragit RL and FS (A), pure Eudragit RL (B), and pure Eudragit FS (C).

ionize on the pellets. As the Eudragit FS coating gradually dissolves at slightly alkaline pH, the dissolution medium seeps into the inner layer of the Eudragit RL–RS layer, causing it to swell and become permeable. Thus the overall slower hydration of Eudragit RL–RS results in a slower than expected release rate of the drug from pellets coated with both an inner layer of Eudragit RL–RS and

Table 1

Values of Chemical Shift and Relaxation Time for Various Polymer Films

Polymer Film		Carbonyl	NMe_3^+	O-Methyl	C (q) (Backbone)	Me (Backbone)	O-Ethyl-C_2
Eudragit RL	δ	177.2	55.5	52.9	45.8	18.3	15.4
	TlρH	2765	—	—	1902	—	2437
Eudragit FS	δ	176.6	—	52.6	45.9	21.1	—
	TlρH	—	—	1180	1158	—	1103
Eudragit RL + FS	δ	177.2	55.4	52.9	46.1	19.6	15.4
	TlρH	1594	—	1769	1242	1696	2139

δ = Chemical shift (ppm), TlρH = relaxation time.

an outer layer of Eudragit FS compared with pellets coated with the same level of Eudragit RL–RS alone.

CONCLUSION

None of our results revealed any chemical interaction between Eudragit RL and FS films. However, physical interactions resulting from steric hindrance of $-NMe_3^+$ groups of Eudragit RL by $-COO^-$ groups of Eudragit FS cannot be ruled out. These physical interactions may possibly lead to lower hydration of Eudragit RL, thus slowing the release of drug from the pellets having both inner and outer coat. It is possible that some weak ionic interactions between the two polymers exist that might not have been uncovered by the techniques used in this study. Further studies using more sensitive techniques would be necessary to ascertain the nature of the interactions, if any.

REFERENCES

1. Mrsny, R.J. The Colon as a Site for Drug Delivery. J. Contr. Rel. **1992**, *22*, 15–34.
2. Ashford, M.; Fell, J.T. Targeting Drugs to the Colon: Delivery Systems for Oral Administration. J. Drug Target. **1994**, *2*, 241–258.
3. Haeberlin, B.; Friend, D.R. Anatomy and Physiology of the Gastrointestinal Tract: Implications for Colonic Drug Delivery. In *Oral Colon-Specific Drug Delivery*; Friend, D.R., Ed.; CRC Press: Boca Raton, FL, 1992; 1–44.
4. Rubinstein, A. Approaches and Opportunities in Colon-Specific Drug Delivery. Crit. Rev. Ther. Drug Carr. Syst. **1995**, *12* (2&3), 101–149.
5. Gupta, V.K.; Beckert, T.E.; Price, J.C. Development of a Novel Multi-particulate Colonic Delivery System Using Multi-functional Coatings of Aqueous Polymethacrylates. In Third World Meeting (APV/APGI) on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology. Berlin, Germany, Apr 4–6, 2000.
6. Gupta, V.K.; Assmus, M.W.; Beckert, T.E.; Price, J.C. Statistical Optimization of a Novel Colonic Delivery System Containing Multiple Coatings of Aqueous Polymethacrylates. In 27th International Symposium on Controlled Release of Bioactive Materials (CRS), Paris, France, Jul 9–13, 2000.
7. Gupta, V.K.; Assmus, M.W.; Beckert, T.E.; Price, J.C. A Novel pH- and Time-Based Multi-unit Potential Colonic Drug Delivery System. II. Optimization of Multiple Response Variables. Int. J. Pharm. **2001**, *213* (1&2), 93–102.
8. Jenquin, M.R.; Liebowitz, S.M.; Sarabia, R.E.; McGinity, J.W. Physical and Chemical Factors Influencing the Release of Drugs from Acrylic Resin Films. J. Pharm. Sci. **1990**, *79* (9), 811–816.
9. Jenquin, M.R.; Sarabia, R.E.; Liebowitz, S.M.; McGinity, J.W. Relationship of Film Properties to Drug Release from Monolithic Films Containing Adjuvants. J. Pharm. Sci. **1992,** *81* (10), 983–989.
10. Watts, P.J.; Tudor, A.; Church, S.J.; Hendra, P.J.; Turner, P.; Melia, C.D.; Davies, M.C. Fourier Transform-Raman Spectroscopy for the Qualitative and Quantitative Characterization of Sulfasalazine-Containing Polymeric Microspheres. Pharm. Res. **1991**, *8* (10), 1323–1328.
11. Hsiue, G.H.; Liao, C.M.; Lin, S.Y. Effect of Drug-Polymer Interaction on the Release Characteristics of Methacrylic Acid Copolymer Microcapsules Containing Theophylline. Artif. Org. **1998**, *22* (8), 651–656.

12. Vachon, M.G.; Nairn, J.G. The Use of 13C Solid State NMR to Elucidate Physico-chemical Association in Eudragit RS100 Microencapsulated Acyl Esters of Salicylic Acid. Eur. J. Pharm. Biopharm. **1998**, *45* (1), 9–21.
13. Dash, A.K.; Brittain, H.G. Mesalamine. In *Analytical Profiles of Drug Substances and Excipients*, Vol. 25; Brittain, H.G., Ed.; Academic Press: New York, 1998; 209–242.
14. Lehmann, K.O.R. Chemistry and Application Properties of Polymethacrylate Coating Systems. In *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*; McGinity, J.W., Ed.; Marcel Dekker: New York, 1997; 1–76.
15. Röhm GmbH and Rohm America, Eudragit literature, 1999.
16. Lehmann, K.O.R.; Petereit, H.-U. Film Coatings Based on Aqueous Polymethacrylate Dispersions for Sustained Release in the Intestinal Tract. Drugs Made in Germany **1994**, *37* (1), 19–21.
17. Lehmann, K.O.R.; Dreher, D. Coating of Tablets and Small Particles with Acrylic Resins by Fluid Bed Technology. Int. J. Pharm. Technol. Prod. Manuf. **1981**, *2* (4), 31–43.
18. Gupta, V.K.; Beckert, T.E.; Price, J.C. A Novel pH- and Time-Based Multi-unit Potential Colonic Drug Delivery System. I. Development Int. J. Pharm. **2001**, *213* (1&2), 83–91.