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RESEARCH PAPER

The Influence of Polymeric Subcoats and Pellet Formulation on the Release of Chlorpheniramine Maleate from Enteric Coated Pellets

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ABSTRACT

The influences of aqueous polymeric subcoats and pellet composition on the release properties of a highly water-soluble drug, chlorpheniramine maleate (CPM), from enteric coated pellets were investigated. Three different aqueous polymeric subcoats, Eudragit® RD 100, Eudragit® RS 30D, and Opadry® AMB, were applied to 10% w/w CPM-loaded pellets that were then enteric coated with Eudragit® L 30D-55. Observed drug release from the coated pellets in acidic media correlated with water vapor transmission rates derived for the subcoat films. The influence of pellet composition on retarding the release of CPM from enteric coated pellets in 0.1 N HCl was investigated. The rate of drug release was greatest for pellets prepared with lactose, microcrystalline cellulose, or dibasic calcium phosphate compared with pellets formulated with citric acid and microcrystalline cellulose. Citric acid reduced the pellet micro-environmental pH, decreasing the amount of drug leakage in 0.1 N HCL during the first 2 hr of dissolution. Polymer flocculation was observed when CPM was added to the Eudragit L 30D-55 dispersion. An adsorption isotherm was generated for mixtures of CPM and the polymer and the data were found to fit the Freundlich model for adsorption. Adsorption of CPM to the polymer decreased with the addition of citric acid to the drug-polymer mixtures.

Key Words: Eudragit® L 30D-55; Enteric polymer; Subcoat; Water vapor transmission; Micro-environmental pH; Freundlich isotherm.

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INTRODUCTION

Enteric polymeric coatings are applied to solid oral dosage forms to target drug release to the upper gastrointestinal tract, protect the stomach from irritating active compounds, or to prevent degradation of acid labile drugs. After oral ingestion, release of the active ingredient from enteric coated dosage forms is delayed until reaching the duodenum, where ionization and solubilization of the enteric polymer occurs.

The enteric polymer, Eudragit® L 30D-55, is an anionic copolymer based on methacrylic acid and ethyl acrylate, with free carboxyl groups in a ratio of 1:1 with the ester groups. The carboxylic groups begin to ionize in aqueous media at pH 5.5 and above, rendering the polymer resistant to the acidic environment of the stomach, but soluble in intestinal fluid. Acrylic-based enteric coatings have lower permeabilities and are more resistant to hydrolysis compared with cellulose-based enteric coatings. Due to the lower permeabilities of the acrylic polymers, gastric resistance can be achieved with less applied polymer; however, this may vary due to processing conditions, formulation, and substrate solubility, resulting in high polymer weight gain required for acid resistance, even for acrylic based polymers.[1–4]

Four mechanisms control the rate of drug release from coated dosage forms: transport of drug through flaws or cracks in the matrix or uncoated system; transport of drug through media-filled pores in the coating; transport through a hydrated or swollen film; and transport through the nonporous coating due to drug permeability of the film.[5] Several authors have reported that highly water-soluble drugs require higher polymer coating levels than poorly soluble compounds for sustained or delayed drug release.[6–8] This was attributed to migration of the water-soluble drug into the aqueous film coating during film application, where presence of the drug may lead to pore formation during dissolution. For these compounds, higher coating levels are therefore required to prevent premature drug release from the polymeric film.

Subcoating has been proposed by several researchers[9–12] as a method to improve acid resistance for enteric coated dosage forms. Polymeric subcoats function by sealing the substrate from the aqueous enteric film coating, thus preventing the migration of water-soluble drugs into the polymeric film, as well as preventing drug–polymer interactions. Subcoating or seal coating has been described in the patent literature,[13] where an aqueous film subcoat was used as a barrier between an enteric film coating and the acid labile drug, omeprazole, to prevent degradation of the compound. Although subcoats have been utilized in the literature to act as barriers to help either stabilize or retard drug release, few studies have addressed the criteria for selecting polymeric subcoat materials.

In addition to subcoating, drug release rates from film-coated dosage forms are also influenced by composition of the tablet or pellet core. Incorporation of pH adjusters such as acids, buffers, or salts into pellets or tablets has been utilized to maintain the micro-environmental pH in a range that will either increase or decrease drug solubility. Bianchini et al. found that the presence of fumaric acid in uncoated pellets containing d-Indobufen slowed the drug-release rate in the initial hours of dissolution due to lowering of pellet micro-environmental pH and resultant change in drug solubility.[14] Sustained release of noscapine hydrochloride was achieved with the incorporation of organic acids into tablet formulations coated with Eudragit® RS 100 and Eudragit® RL 100 in order to prevent precipitation of the drug when the pH of intestinal fluid exceeded the pKa of the drug.[15]

The objectives of the current research were to investigate the effectiveness of polymeric subcoating in retarding release of the highly water-soluble drug, CPM, from pellets enteric coated with Eudragit L 30D-55. Properties of the polymeric subcoats, Eudragit RD 100, Eudragit RS 30D, and Opadry® AMB, were studied in order to select the optimum subcoat material. The influence of pellet composition on retarding drug release from enteric coated CPM pellets in acidic media was also investigated.

MATERIALS AND METHODS

Chlorpheniramine maleate (CPM) and theophylline were purchased from Spectrum Chemical, Gardena, CA. Eudragit L 30D-55 [Poly(methacrylic acid, ethyl acrylate)]; Eudragit® RS 30D [Poly(ethyl acrylate, methyl methacrylate) trimethylammonioethyl methacrylate chloride]; Eudragit RD 100 (consisting of 91 parts Eudragit RL 100 and nine parts sodium carboxymethyl cellulose) were donated by Röhm America, LLC Piscataway, NJ; Opadry AMB (Polyvinyl alcohol) was donated by Colorcon, Westpoint PA. Polyvinyl pyrrolidone, Kollidon® 90, was donated by BASF Corporation, Mount Olive, NJ. Citric acid monohydrate, sodium phosphate tribasic, and polysorbate 80 were purchased from Spectrum Chemical, Gardena, CA. Microcrystalline cellulose, Avicel® PH 101, was donated by FMC

Corporation, Newark, DE. Lactose monohydrate was donated by Sheffield Products, Norwich, (NY), and dibasic calcium phosphate, Emcompress® was received from Penwest Pharmaceutical Co., Patterson, (NY). Sugar spheres were donated by CHR Hansen, Mahwah, NJ; Talc, Altalc 500, was donated by Luzenac America, Alpine, AL; Triethyl citrate (TEC) and dibutyl sebacate (DBS) were kindly donated by Morflex Inc., Greensboro, NC.

Pellet Preparation

The core pellets contained 10% w/w CPM, 47% w/w Avicel PH 101, 40% w/w lactose monohydrate, and 3% w/w Kollidon K-90. Pellets containing 25% w/w CPM were prepared by combining 36% w/w Avicel PH 101 with 36% w/w lactose monohydrate, and 3% w/w Kollidon K-90. For comparison, theophylline pellets of 30% w/w active ingredient, 40% w/w Avicel PH 101, 27% w/w lactose monohydrate, and 3% w/w Kollidon K-90 were also prepared. The dry ingredients were combined and mixed in a twin-shell blender for 15 min and then transferred to a planetary mixer where the aqueous binder solution was slowly added. The wet mass was extruded with a LCI Benchtop Granulator through a 1.2 mm screen. The extrudate was spheronized for 4 min in a Caleva model 120 spheronizer. The beads were dried at 40°C for 24 hr and then sized through 14–20 mesh screens. The drug-containing pellets were combined in a ratio of 1:2 with placebo pellets of the same size range prior to coating. Pellets loaded with 10% w/w CPM containing different fillers and pH adjusting agents were prepared, and the composition of these pellets appears in Table 1.

Pellet Porosity Determination

The true and apparent densities of pellets were determined using a helium pycnometer (Micrometrics Corporation, Norcross, GA, Model 1330). The apparent density of the bulk spherical pellets was determined by placing a 1 g sample in the pycnometer. The same pellets were pulverized and the true density of the crushed material was measured. Three density determinations were performed in each case and the average value reported. The intraparticular porosity was calculated from:

$$\text{Intraparticular porosity} = (1 - \rho_a/\rho_t) \times 100 \quad (1)$$

Table 1. Composition of pellets prepared by wet-mass extrusion and spheronization.

Additive % composition	Formulations				
	A	B	C	D	E
CPM	10	10	10	10	10
Avicel	47	87	35	70	50
Lactose monohydrate	40	—	—	—	—
Emcompress	—	—	55	—	—
Citric acid monohydrate	—	—	—	20	40
Kollidon K 90	3	3	—	—	—

where ρ_a is the apparent density of the pellets and ρ_t is the true density of the pellets.

Pellet Friability

The friability of the uncoated pellets was determined by inserting a 100 g sample of pellets inside a Strea I fluidized bed unit fitted with a Wurster insert. The pellets were fluidized for 15 min at 30°C. Pellets were then transferred from the Strea I and the residual powder was removed prior to recording the final weight. The percent friability was calculated from the ratio of pellet weight before and after fluidization.

Pellet pH

The pH of uncoated pellets was measured by grinding a 2 g sample of pellets and combining the resultant powder with 20 mL of deionized water to form a slurry. The slurry was then mixed for 5 min and the pH measured using a Corning® model 220 pH meter.

Preparation of Polymeric Film Coatings

Eudragit RD 100 was diluted to a 10% w/w solids content. Polysorbate 80 was added to the coating dispersion, 20% w/w based on polymer dry weight. An appropriate amount of water was heated to disperse the polysorbate, and after cooling, the Eudragit RD 100 was dispersed using a Lightnin®

mixer. The mixture was equilibrated for 30 min prior to coating.

Eudragit RS 30D was diluted to a solids content of 15% w/w. Triethyl citrate (TEC) was incorporated into the dispersion at 15% w/w, based on the dry polymer weight, and 50% w/w talc, based on dry polymer weight, was also added. The suspension was equilibrated for at least 30 min prior to coating.

Opadry AMB was dispersed into water and diluted to a solids content of 10% w/w using a Lightnin mixer. The polymer mixture was equilibrated for 45 min prior to coating.

A 30% w/w dispersion of Eudragit L 30D-55 was diluted to a final solids content of 15% w/w. The TEC was added at a concentration of 15% w/w, based on dry polymer content. Talc, 50% w/w, based on dry polymer weight, was also dispersed in water and combined with the polymeric dispersion. The mixture was equilibrated for 30 min prior to coating. After coating, pellets were cured for 24 hr at 40°C. An additional dispersion of Eudragit L 30D-55 was prepared with 15% w/w, based on dry polymer weight, dibutyl sebacate (DBS) as the plasticizing agent. The polymer dispersion containing DBS was equilibrated for 24 hr prior to coating. Film coatings were applied to a 300-g charge of pellets in a Niro Aeromatic Strea I fluidized bed coating unit with a Wurster column insert. The nozzle diameter was 1 mm and the atomization pressure was maintained at 2 Bar. The coating conditions for each polymeric dispersion are summarized in Table 2.

Pellet Morphology

The surface morphology of the enteric pellet film coatings was examined using a Philips Model 515 scanning electron microscopy (SEM) at 15 kV. Pellets were sputter coated with 60/40 Au/Pd for 60 s using a Ladd Bench Top sputter coater. To examine film structure after exposure to the acidic medium, hydrated pellets were removed after 2 hr dissolution testing in 0.1 N HCl and dried for 48 hr at 25°C and 0% relative humidity (RH) before sputter coating.

Table 2. Polymer film coating processing conditions.

Conditions	Eudragit® RS30D	Eudragit® RD100	Opadry AMB	Eudragit® L30D-55
Inlet temp (°C)	36	36	60	40
Outlet temp (°C)	30–32	30–32	50	34–36
Spray rate (g/min)	2	3	2	4

X-ray Photoelectron Spectroscopy Surface Analysis of Enteric Coated CPM Pellets

X-ray photoelectron spectroscopy (XPS) surface analysis was used to identify CPM on the surface and in the enteric coating of 10% w/w CPM pellets coated with 10% weight gain Eudragit L 30D-55. The XPS data were obtained using a Physical Electronics PHI5700 ESCA system equipped with an Al monochromatic source (Al Kα radiation at 1486.6 eV). The base pressure in the XPS UHV chamber was 1×10^{-10} Torr. Wide range (survey) scans were obtained with a step size of 1 eV and pass energy of 11.75 eV. The Ag3d5/2 XPS peak at 368.3 eV from a sputtered-clean Ag foil was used to calibrate the system. Sputtering was performed on the pellet samples up to 50 nm into the film coating surface using as Ar^+ ion gun from Physical Electronics (PHI 04-303A) operated at 3dV. The ion current at the sample during sputtering was 1 μA. The analysis area of the sample was approximately 0.5 mm^2. The elemental concentration was calculated based on determination of elemental peak area and sensitivity factor from a plot of counts vs. binding energy for each atom identified. The percent concentration is the percent atomic concentration of atoms identified at the site of analysis.

Drug Release Studies

The drug-release properties of the enteric coated pellets were studied according to the United States Pharmacopeia (USP) 24, delayed-release articles, as per method A, apparatus 2 at 100 RPM and 37°C, using a Van Kel 600 dissolution apparatus. Samples were removed at 30 min or 1 h intervals during the first 2 hr in 750 mL 0.1 N HCl. After 2 hr, the media pH was increased to 6.8 with the addition of 250 mL of 0.20 M sodium triphosphate buffer.

Dissolution samples were analyzed using a Beckman Instruments model DU 65 spectrophotometer at a wavelength of 261 nm and 271 nm for

CPM and theophylline, respectively. All dissolution samples were filtered using a 0.45 μm Whatman polypropylene syringe filter prior to analysis. Ultraviolet (UV) scans were performed on dissolved polymeric coating materials to assure no interference at 261 or 271 nm. The polymers did not contribute to the absorbance at these wavelengths.

Triethyl Citrate (TEC) Release Studies

The release of TEC from the enteric film coated pellets was measured during 2 hr dissolution in 0.1 N HCl, 100 rpm, 37°C using apparatus 2. The amount of TEC leaching into the dissolution media was determined using a reversed-phase high-performance liquid chromatography (HPLC) method on a Waters model 501 pump and a 996 PDA detector equipped with a 717 autosampler. A sample volume of 50 μL was injected onto a Phenomenex Luna C18(2) column 150 × 4.6 mm, 3 μ at 1 mL/min. Triethyl Citrate (TEC) was detected at 210 nm with a retention time of 7.5 min. The mobile phase consisted of 63% w/v 25 mM sodium phosphate monobasic (pH adjusted to 2.3 using phosphoric acid) and 37% w/v acetonitrile. A stock standard of TEC was prepared in methanol and working standards were diluted in mobile phase.

Water Vapor Transmission Studies

A modified American Society for Testing and Materials (ASTM) method (E96-95) was used to measure water vapor transmission rates of free films.[17] Cast films were prepared using the same formulation as the polymeric dispersions prepared for film coating, but the talc was excluded from the formulations. Dispersions of Eudragit RS 30D (15% w/w solids), Eudragit RD 100 (10% w/w solids), and Opadry AMB (10% w/w solids) were prepared and allowed to equilibrate before casting onto 6 × 6 in Teflon plates, which were then placed in a 35°C oven for 72 hr. After drying, the films were stored for 72 hr in a desiccator at 0% relative humidity. The films were cut into circles having a 4 cm diameter. The thickness of the films was measured in five places using a Starret® micrometer. Films were sealed over aluminum cups containing 10 g of indicating anhydrous calcium sulfate desiccant. The apparatus was then placed inside a chamber maintained at 75% relative humidity. The cumulative change in weight over 6 days was measured for each sample and the data normalized to remove variance due to film thickness ($n = 3$ per polymer film cast). The cumulative weight gain was plotted vs. time for each film and the water vapor transmission rate determined by using least squares regression to calculate the slope of the line. The water vapor transmission (WVT) was calculated based on the following relationship:

$$\mathrm{WVT} = G/tA \tag{2}$$

where G = the weight change (mg), t = time (hr), and A = area of exposed film (mm^2).

Contact Angle Measurement of Polymeric Films

Contact angle measurements were performed using a goniometer (Ramé-hart, Inc., Montain Lakes, NJ, Model 100-00-115). Films composed of Eudragit RS 30D, Eudragit RD 100, or Opadry AMB were cast onto glass slides. The contact angle was measured 5 s and 5 min after dropping 10 μL of either deionized water or 0.1 N HCl onto the surface of the dry film. Three measurements were performed and the average contact angle value was calculated.

X-ray Diffraction Studies

Crystallinity of the polymeric films was determined using a Philips PW 170 x-ray generator equipped with a PW 1710 x-ray diffractometer. The operating current and voltage were 40 kV and 40 mA, respectively. Measurement was conducted at 2θ scanning from 5° to 50° at a scanning rate of 2°/min.

Thermal Analysis of Polymeric Films

The glass transition temperature of the polymeric films was measured using a modulated differential scanning calorimeter (MDSC, TA Instruments, Newcastle, DE). A 10–20 mg sample was sealed in an aluminum pan. The film samples were heated at a rate of 5°C per minute with 1 min modulation ramping from −20°C to 120°C. Three measurements were performed on each film sample. The MDSC was calibrated using an indium standard.

Adsorption Studies

An adsorption isotherm was generated for mixtures of CPM and the Eudragit L 30D-55 polymer. A stock solution of CPM was prepared to contain 50 mg/mL CPM in water. A 10 g amount of the CPM solution was combined with increasing amounts of the Eudragit L30D-55 polymer in Falcon tubes and diluted with deionized water. A control was prepared containing only the fixed amount of drug solution and water. The tubes were sealed and placed on a shaker for 24 hr at 25°C. After 24 hr, the mixtures were centrifuged in a Beckman model TJ-6 centrifuge at 2000 rpm for 10 min. The supernatant was analyzed for CPM content using a Beckman spectrophotometer (Model DU 65) at 261 nm. Additional samples were prepared as described above except that a fixed amount of citric acid solution (resulting in a 1:2 or 1:4 w/w ratio of drug to citric acid content) was added to each vessel along with the CPM and polymer. The supernatant of the samples was analyzed by spectrophotometry for CPM content. Ultraviolet scans of the citric acid solution indicated that there was no citric acid absorption interference at 261 nm. There was no observable interaction between the citric acid and Eudragit L 30D-55. Additionally, there was no interference at 261 nm from the enteric polymer.

Fourier Transform Infrared Analysis

Fourier Transform Infrared (FTIR) analysis was conducted for samples consisting of 1:1 w/w ratio of a physical mixture of CPM and dried Eudragit L30D-55 film, or a 1:1 w/w ratio of CPM and Eudragit L30D-55 precipitate that was ground into fine granules. The dried samples were blended with KBr to prepare a pellet, and the samples were also dissolved with acetone and a drop of solution placed onto a NaCl disc for analysis. Samples were analyzed using a Nicolet Model 360 FTIR (Thermo Nicolet, Madison, WI) with Omnic E. S. P. software.

RESULTS AND DISCUSSION

Properties of CPM Pellets

The influence of drug loading and polymer weight gain on the release of CPM from pellets enteric coated with Eudragit L 30D-55 is demonstrated in Fig. 1. To pass the official USP enteric test, enteric coated dosage forms must be able to withstand 2 hr dissolution in acidic media with less than 10% drug release, and release greater than 75% of the active pharmaceutical ingredient after 45 min in pH 6.8 phosphate buffer. Pellets containing 10% and 25% w/w CPM drug loading failed the enteric test in acidic media with the application of 10% weight gain of Eudragit L 30D-55, but were able to meet the test requirement with higher polymer weight gain. Film failure may be due to the migration of the highly water-soluble CPM into the film coating.[6] Additionally, water-soluble drugs can migrate and deposit on the outer surface of the pellet after preparation and during drying as the granulating fluid evaporates,[18] leading to more surface area contact of the drug with the film coating during deposition.

X-ray photoelectron spectroscopy (XPS) surface analysis on pellets containing 10% w/w CPM and a 10% weight gain of Eudragit L 30D-55 was used to determine CPM migration into the coating. The pellet surface was bombarded with monochromatic x-ray beams. X-ray photons were absorbed by the coating and the transferred energy was used to

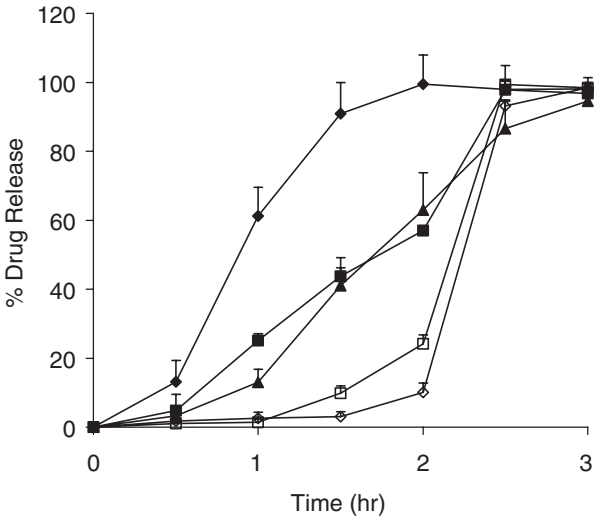

Figure 1. Influence of drug loading on the release of CPM from pellets enteric coated with Eudragit® L 30D-55.
Key: ◆ 25% w/w CPM and 7% weight gain Eudragit® L 30D-55; ■, 10% w/w CPM and 7% weight gain Eudragit® L 30D-55; ▲, 25% w/w CPM and 10% weight gain Eudragit® L 30D-55; □, 10% w/w CPM and 10% weight gain Eudragit® L 30D-55; ◇, 10% w/w CPM and 12% weight gain Eudragit® L 30D-55. Dissolution media consisting of 0.1 N HCl, pH 1.2 from 0–2 hr and 0.05 M phosphate buffer from 2–3 hr, 37°C, 100 rpm ($n = 3$).

Table 3. X-ray photoelectron spectroscopy surface analysis of 10% w/w CPM pellets film-coated with 10% weight gain Eudragit® L 30D-55.

Element	Sensitivity factor	Coated pellet surface		50 nm depth into coating	
		Area (Cts-eV/s)	Concentration (%)	Area (Cts-eV/s)	Concentration%
Cl_2p	5.16	0	0	72	0.46
C1s	2.01	2078	57	4901	81
O1s	5.14	3990	43	2919	19
N1s	3.33	0	0	0	0

excite core level electrons. Electrons associated with chlorine atoms (attached to the CPM molecule) were detected at a depth of 50 nm into the film coating. The total concentration of chlorine detected was 0.46% at this depth and the data are shown in Table 3. The presence of chlorine in the film coating confirms migration of the water-soluble drug into the film, contributing to film failure. Formulation additives and processing conditions also contribute to film failure. In order to further investigate the cause of enteric coating failure, the influence of plasticizers and processing conditions on pellet drug release and the surface morphology of the coated pellets were examined.

Plasticizers have been reported to influence drug-release properties from enteric coated pellets.[1,19] These researchers demonstrated improved enteric protection using the water-insoluble compound, dibutyl phthalate, as a plasticizer rather than triethyl citrate in film coatings prepared with Eudragit L 30D-55. In the current studies, addition of a similar hydrophobic, water-insoluble plasticizer, dibutyl sebacate, to the Eudragit L 30D-55 coating dispersion failed to result in a significant difference in the amount of drug released from the film coated CPM pellets after 2 hr in acidic media, compared with enteric film coated pellets containing the plasticizer TEC, as shown in Fig. 2. As a result of these findings, triethyl citrate was considered to be a suitable plasticizer for the dispersion.

To verify that the polymeric colloidal coating dispersion formulation and the coating process parameters did not influence the functionality of the enteric coating, pellets containing 30% w/w theophylline were coated with Eudragit L 30D-55 using the same formulation and processing conditions that were used to coat the CPM pellets. A 7% weight gain of Eudragit L 30D-55 resulted in 1.2% theophylline release following 2 hr in acidic media, as shown in Fig. 3. No theophylline was released after 2 hr in acid when a 10% weight gain of polymer was applied to the pellets. The results from these studies demonstrated that the coating formulation and processing conditions for Eudragit L 30D-55 were suitable to achieve enteric protection.

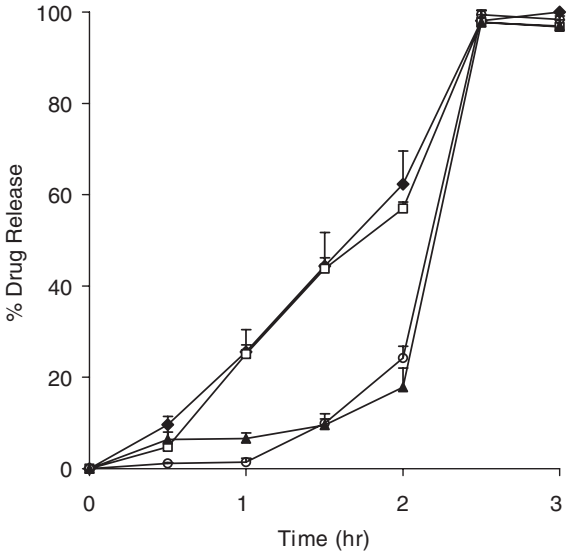

Figure 2. Influence of dibutyl sebacate or triethyl citrate on the release of 10% w/w CPM pellets enteric coated with Eudragit® L 30D-55.
Key: ◆, 7% weight gain Eudragit® L 30D-55 (15% DBS); □, 7% weight gain Eudragit® L 30D-55 (15% TEC); ▲, 10% weight gain Eudragit® L 30D-55 (15% DBS); ○, 10% weight gain Eudragit® L 30D-55 (15% TEC). Dissolution media consisting of 0.1 N HCl, pH 1.2 from 0–2 hr and 0.05 M phosphate buffer from 2–3 hr, 37°C, 100 rpm ($n = 3$).

The amount of TEC released from the CPM and theophylline-containing pellets coated with a 7% weight gain of Eudragit L 30D-55 was measured and compared following 2 hr dissolution in 0.1 N HCl. For both pellet types, 100% TEC was released during exposure to the dissolution media. Figure 4 shows the film surface of both 30% w/w theophylline and 10% w/w CPM-containing pellets coated with a

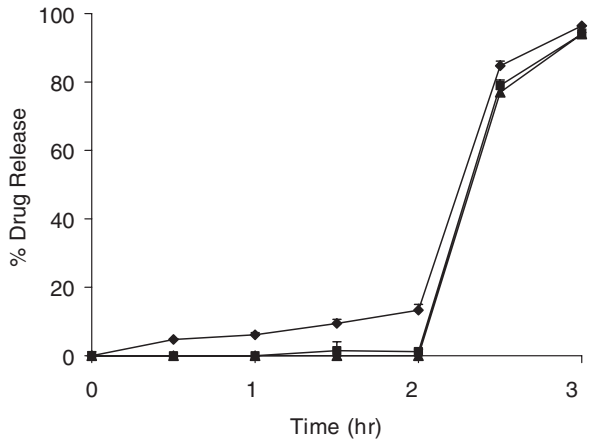

Figure 3. Drug release from enteric coated pellets containing 30% w/w theophylline.
Key: ◆, 4% weight gain Eudragit® L 30D-55; ■, 7% weight gain Eudragit® L 30D-55; ▲, 10% weight gain Eudragit® L 30D-55. Dissolution media consisting of 0.1 N HCl, pH 1.2 from 0–2 hr and 0.05 M phosphate buffer from 2–3 hr, 37°C, 100 rpm ($n = 3$).

7% weight gain of Eudragit L 30D-55 before and after hydration in 0.1 N HCl for 2 hr. The pellet surfaces appeared smooth prior to dissolution testing, indicating that the polymeric nanoparticles had coalesced to form a continuous film. Scanning electronic microscopy (SEM) photomicrographs of the pellet film surfaces after 2 hr in the dissolution media, however, showed pore formation in the film as a result of leaching of the water-soluble plasticizer into the aqueous media. Although TEC formed channels or pores in the film due to leaching, the release of theophylline was substantially lower compared with the release of CPM after 2 hr. These data indicate that pore formation due to plasticizer leaching may not have been the most significant factor contributing to premature release of CPM in 0.1 N HCl. Additional factors contributing to the accelerated release of CPM in acidic media include drug solubility, drug migration into the film, and possible interactions between the drug and the polymer.

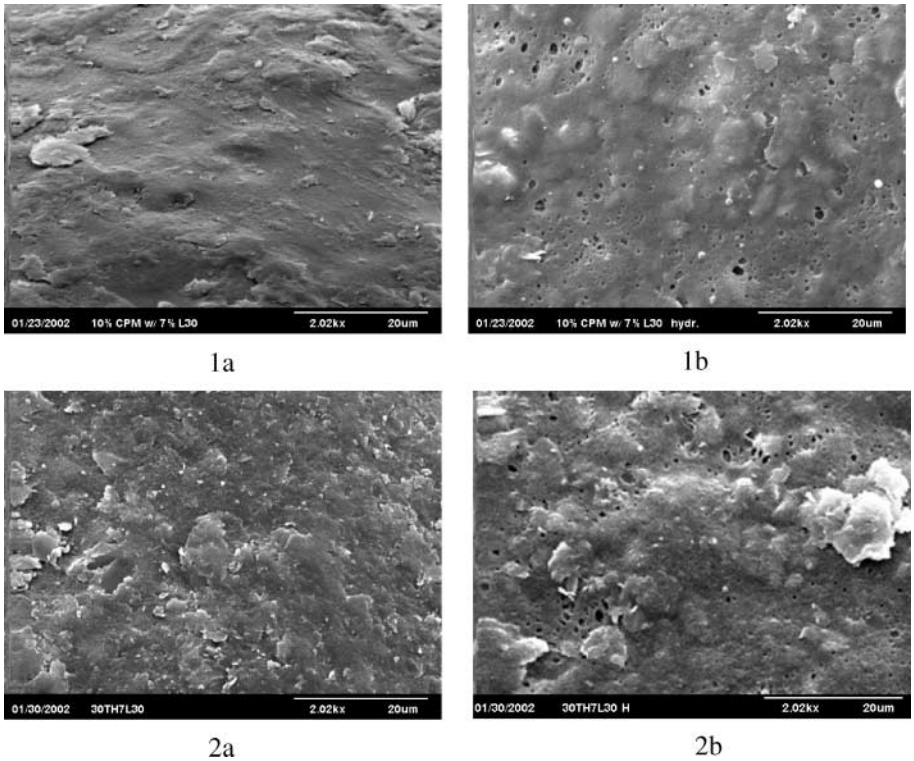

Figure 4. SEM micrographs of 10% w/w CPM and 30% w/w theophylline pellets coated with 7% weight gain of Eudragit® L 30D-55.
Key: 1a, 10% w/w CPM pellet coated with 7% weight gain Eudragit® L 30D-55 prehydration; 1b, 10% w/w CPM pellet coated with 7% weight gain Eudragit® L 30D-55 hydrated 2 hr in 0.1 N HCl; 2a, 30% w/w theophylline pellet coated with 7% weight gain Eudragit® L 30D-55 prehydration; 2b, 30% w/w theophylline pellet coated with 7% weight gain Eudragit® L 30D-55 hydrated 2 hr in 0.1 N HCl.

Influence of Subcoating on Drug-Release Properties of CPM Pellets

A physical barrier in the form of a polymeric subcoat was applied to the CPM pellets to prevent the potential migration of the water-soluble CPM into the enteric film coating during the coating process. The applied subcoating should immediately release the drug from the pellet core after the enteric polymer dissolves. Three polymers, including Eudragit RD 100, Eudragit RS 30D, and Opadry AMB, were selected as subcoating agents and were applied to 10% w/w CPM pellets to a 3% polymer weight gain. Eudragit RD 100 is a powder composed of 91 parts of dry Eudragit RL 100 and nine parts of sodium carboxymethylcellulose (NaCMC). When dispersed into water, the Eudragit RD 100 forms a rapidly disintegrating film coating. In contrast, Eudragit RS 30D is a 30% w/w aqueous latex dispersion of RS 100, a copolymer of acrylic and methacrylic acid esters containing quaternary ammonium groups. This polymer has a low permeability and is generally used as a sustained-release film coating either alone or in combination with Eudragit RL 30D. Opadry AMB consists of polyvinyl alcohol and is an immediate release water-soluble polymer that is used to reduce moisture sorption to substrate cores.[20]

After applying the polymeric subcoats, the pellets were overcoated with 7% and 10% weight gain of Eudragit L 30D-55. All pellet formulations were found to fail the USP enteric test even with the application of the subcoat polymer. The pellets subcoated with Eudragit RD 100 had the fastest rate of drug released in 2 hr in 0.1 N HCl due to the rapidly disintegrating NaCMC contained in the material. The release rates of the subcoated pellets with a 7% weight gain of Eudragit L 30D-55 are shown in Fig. 5. The drug-release rates were dependent upon the type of subcoat polymer used. A slower drug-release rate resulted when Eudragit RS 30D or Opadry AMB were used as subcoats. The drug release rates correlated with the contact angle values of the polymeric films as shown in Table 4. A low contact angle value is an indication that the polymer is hydrophilic or wettable, and will readily imbibe dissolution media and dissolve. In contrast, high contact-angle values are an indication that the polymeric material is hydrophobic, and thus will act as a suitable barrier between the pellet core and dissolution media. Contact angle was measured after 5 s and after 5 min to determine wettability of the film surface after exposure to media over time. The results indicated that the Eudragit RD 100 was readily wetted compared with Eudragit RS 30D and Opadry AMB. Pellets subcoated with Eudragit RS 30D and Opadry AMB had lower drug release rates as a result of the initial hydrophobic properties of the polymeric materials. The contact angle of each polymeric film continued to decrease after 5 min exposure to media, indicating that wettability increases over time. Pellets subcoated with Opadry AMB released the least amount of CPM after 2 hr in acidic media followed by immediate

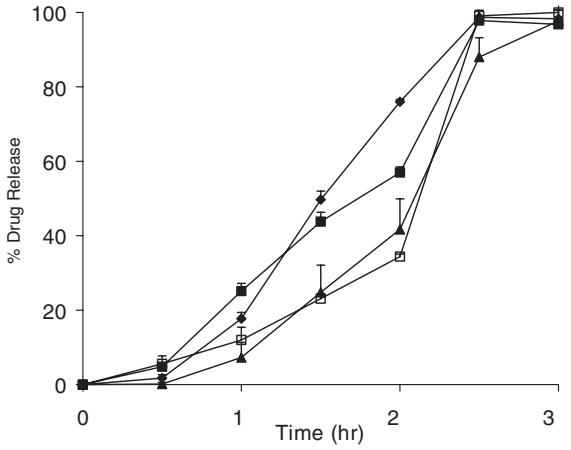

Figure 5. Comparison of drug release from subcoated pellets containing 10% w/w CPM enteric coated with 7% weight gain Eudragit® L 30D-55.
Key: ◆, 3% weight gain Eudragit® RD 100 Subcoat; ■, no subcoat; ▲, 3% weight gain Eudragit® RS 30D subcoat; □, 3% weight gain Opadry® AMB subcoat. Dissolution medium consisting of 0.1 N HCl, pH1.2 from 0–2 hr and 0.05 M phosphate buffer from 2–3 hr, 37°C, 100 rpm ($n = 3$).

Table 4. Contact angle measurement of polymeric films.

	Eudragit® RD 100		Eudragit® RS 30D		Opadry® AMB	
	5 sec	5 min	5 sec	5 min	5 sec	5 min
DI water	18.5 (3.3)	12.3 (2.5)	65.5 (3.5)	52.4 (3.8)	61.5 (3.2)	44.8 (3.8)
0.1 N HCl	15.4 (1.9)	13.4 (2.1)	65.1 (2.4)	51.3 (4.5)	59.9 (3.3)	43.7 (3.5)

Parentheses denote standard deviation for $n = 3$.

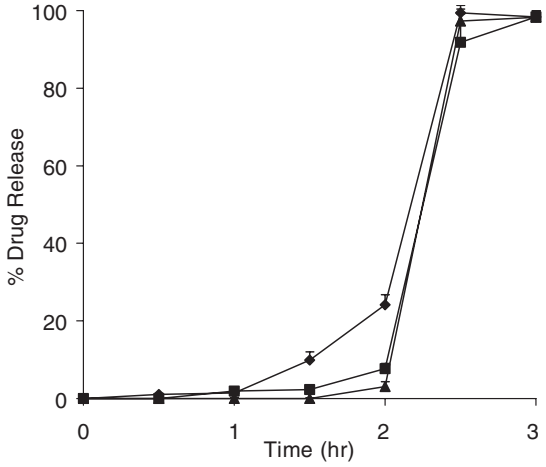

Figure 6. Influence of Opadry® AMB subcoats on drug release from 10% w/w CPM pellets coated with 10% weight gain Eudragit® L 30D-55.
Key: ♦, no subcoat; ■, 3% weight gain Opadry® AMB subcoat; ▲, 5% weight gain Opadry® AMB subcoat. Dissolution medium consisting of 0.1 N HCl, pH 1.2 from 0–2 hr and 0.05 M phospate buffer from 2–3 hr, 37°C, 100 rpm ($n = 3$.)

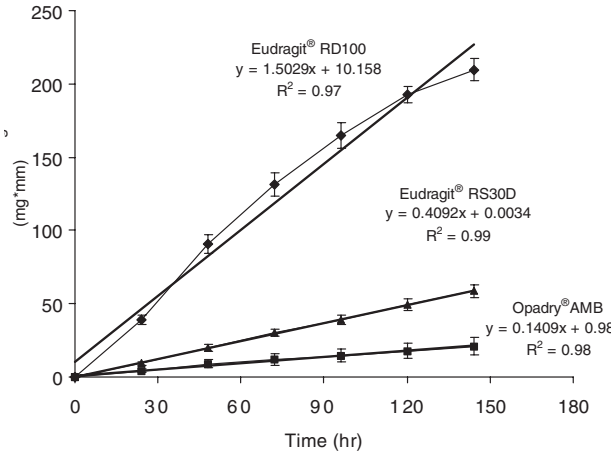

Figure 7. Water vapor transmission rates for polymeric subcoat films: Eudragit® RD 100, Eudragit® RS 30D, and Opadry AMB.
Key: ◆, Eudragit® RD 100; ▲, Eudragit® RS 30D; ■, Opadry® AMB. Storage conditions: 25°C and 75% RH for 6 days, ($n = 3$); Exposed film area: 1257 mm^2.

release of drug when the media pH was increased to 6.8 (Fig. 5). Opadry AMB was therefore selected for further evaluation.

The influence of the thickness of the Opadry AMB subcoat on the release of CPM from pellets coated with 10% weight gain of Eudragit L 30D-55 is shown in Fig. 6. The pellets did not pass the enteric test prior to the application of a subcoat. Drug release was decreased from 24% to 3% in acid after 2 hr using a 5% weight gain of Opadry AMB subcoat and a 10% weight gain of enteric polymer. The additional amount of Opadry AMB applied to the pellets resulted in a more homogenous and continuous film on the pellet surface, increased the thickness of the diffusional barrier between the drug and the dissolution media, and prevented contact between the drug and the Eudragit L 30D-55 dispersion.

Water Vapor Transmission of Polymeric Films

The water vapor transmission (WVT) rates shown in Fig. 7 demonstrate that the rate of transmission through the Eudragit RD 100 film was greater than that of Eudragit RS 30D, with Opadry AMB exhibiting the lowest rate. These rates correlate with the results obtained from the drug-release profiles of subcoated pellets that are shown in Fig. 5. The water vapor transmission rate of a material is proportional to its permeability.[17] Subcoat polymers with lower WVT rates and lower permeabilities were more effective in retarding drug release from the pellets. Opadry AMB had the lowest water vapor transmission rate and provided the greatest protection as a seal or subcoat to the CPM pellets. Opadry AMB, consisting of polyvinyl alcohol, is a semicrystalline polymer. Peaks were observed in the x-ray diffraction patterns of Opadry AMB at 2 θ values of 9.5, 20, 24.5, 29, 37, 45, and 47. No peaks were observed in films consisting of the amorphous polymers Eudragit RS 30D and Eudragit RD 100. Crystallinity and cross-linking in a film hinders polymer chain mobility and leads to a decrease in the size and number of diffusion pathways and diffusivity.[21] Polymer membrane permeability increases as glass transition temperatures decrease.[22] Opadry AMB had a higher glass transition temperature when measured using modulated differential scanning calorimetry (Tg = 68°C) compared with the amorphous, plasticized polymers Eudragit RD 100 and Eudragit RS 30D (Tg = 34°C and 30°C), respectively. The temperature of the dissolution media (37°C) exceeds the glass transition temperature for Eudragit RD 100 and Eudragit RS 30D. These films will therefore exist in a rubbery rather than glassy state during dissolution, and rubbery polymers are reported to be more permeable than glassy polymers.[23]

Pellet Compositions

The influence of the pH of the pellet core on the release of CPM from the enteric coated pellets was investigated. Pellets were prepared containing varying levels of Avicel, lactose monohydrate, Emcompress, and citric acid monohydrate. Avicel (microcrystalline cellulose) is a widely used diluent that is insoluble in water, with a 1.2% w/v dispersion yielding a pH value ranging from 6–8.[24] Emcompress (dibasic calcium phosphate) is a diluent that is practically insoluble in water, but is slowly soluble in acid. This material is slightly basic (pH = 7.4 for a 20% w/v slurry).[24] Both agents were incorporated together into pellets to maintain the micro-environmental pH in a neutral or slightly alkaline region and to influence the wettability of the pellet core. Citric acid monohydrate was incorporated into pellets to lower the solid-state pH of the uncoated pellets. The influence of micro-environmental pH on the drug release properties of the pellets was determined by measuring the pH of a 10% w/v slurry of crushed, uncoated samples from each pellet formulation.

The amount of CPM released in 0.1 N HCl after 2 hr from each of the enteric coated pellet formulations was determined and the results are shown in Fig. 8, for formulations A–E (Table 1). Formulation C, containing 55% w/w dibasic calcium phosphate, demonstrated a 17% increase in drug release (28% released after 2 hr) in acidic media when compared with control pellet formulation A (24% released after 2 hr). Statistical analysis of the mean drug release amounts at 2 hr using a two-tailed t-test ($p = 0.05$) demonstrated that the differences in drug release between formulations B and C compared with the control formulation A were not significantly different. The dibasic calcium phosphate increased the pH of the uncoated pellet from 4.8 to 6.0 due to its basic properties. Eliminating lactose and increasing the amount of microcrystalline cellulose in the pellet to 87% w/w (formulation B) resulted in a 25% reduction in the amount of drug released (from 24% to 18% after 2 hr) compared with the control. The pH of the uncoated pellet remained unchanged compared with the control formulation (pH of uncoated pellet formulation B was 4.8), and the reduction in drug release was attributed to a decrease in the wettability of the pellet core.

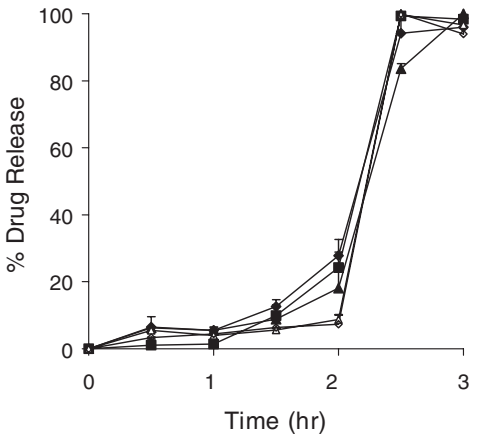

Figure 8. Influence of pellet composition on drug-release properties of pellets comprised of 10% w/w CPM and varying levels of Avicel®, Emcompress® or citric acid and coated with 10% weight gain Eudragit® L 30D-55.
Key: ◆, Formulation C, 55% Emcompress®; ■, formulation A, 47% Avicel® & 40% lactose; ▲, formulation B, 87% Avicel®; △, formulation D, 20% citric acid; ◇, formulation E, 40% citric acid. Dissolution media consisting of 0.1 N HCl, pH 1.2 from 0–2 hr and 0.05 M phosphate buffer from 2–3 hr, 37°C, 100 rpm ($n = 3$).

Inclusion of citric acid in the pellet formulation at 20% w/w and 40% w/w (formulations D and E, respectively) lowered the amount of drug released from 24% to 8.7% and 7.3%, respectively, with a 10% weight-gain application of Eudragit L 30D-55 (Fig. 8). The differences in drug release between formulations D and E, containing citric acid, compared with the control were found to be significantly different. The observed decrease in drug release was attributed to a reduction in pH of the pellet core. The pH of the uncoated pellets was 2.9 and 2.6 for pellets containing 20% and 40% w/w citric acid monohydrate, respectively. The percent drug release from the coated pellets was plotted as a function of the pH of the uncoated pellets. The results are shown in Fig. 9 and illustrate that as drug release from the enteric coated pellets increased, the pH of the uncoated pellet also increased.

Researchers have demonstrated that the pH of the diffusion layer at the surface of a dosage form resembles that of a saturated solution of drug and excipients in the dissolution media and represents the micro-environmental pH of the system.[25,26] During dissolution, the enteric polymer can imbibe dissolution medium that may eventually penetrate into the pellet core, resulting in a saturated solution of drug and excipients. The pH of the saturated diffusion layer at the surface of the pellet becomes high enough to begin to ionize the carboxylic groups of the enteric polymer. Lowering the pellet micro-environmental pH with the inclusion of citric acid in the pellet core acts to suppress the ionization of the methacrylic acid groups in the enteric polymer. The lowered micro-environmental pH does not affect CPM

Table 5. Friability and porosity results of uncoated pellet compositions A–E ($n = 3$).

	Formulation				
	A	B	C	D	E
Friability %	0.480 ± 0.01	0.033 ± 0.02	0.297 ± 0.04	0.100 ± 0.02	0.133 ± 0.02
Porosity %	2.16 ± 0.26	7.42 ± 0.15	7.33 ± 0.11	9.50 ± 1.1	7.52 ± 0.98

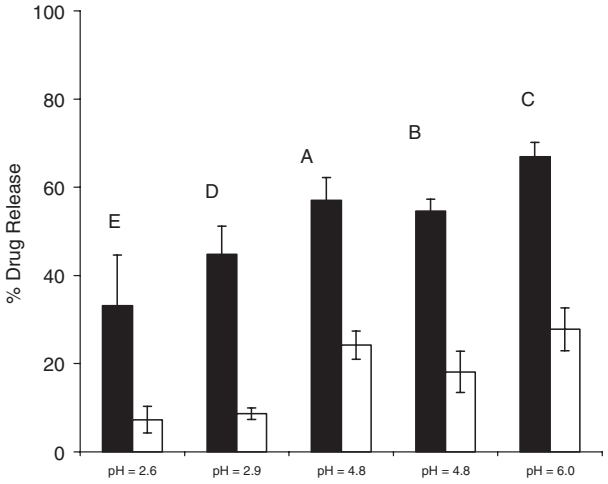

Figure 9. Comparison of drug release properties of enteric coated pellet formulations A–E after 2 hr in 0.1 N HCl, pH 1.2, as a function of uncoated pellet core pH.
Key: ■ Pellets coated with 7% weight gain Eudragit® L 30D-55; □, pellets coated with 10% weight gain Eudragit® L 30D-55. Dissolution conditions: 2 hr, 750 mL 0.1 N HCl, 37°C, 100 rpm ($n = 3$).

solubility since it remains soluble over the pH range of 1–8.[27] Dangel et al. 2000 [28,29] also observed that alkaline and acidic properties of tablet cores influenced the enteric properties of methacrylic acid copolymer film coatings. Tablets containing the alkaline drug diclofenac sodium had a lower resistance to gastric media compared with tablets containing the acidic drug indomethacin. The authors theorized that the acidic properties of indomethacin prevented deprotonation of the enteric film, whereas diclofenac sodium encouraged the ionization of the film coating. These findings demonstrated that ionization of the enteric polymer will result in an increase in film permeability and film failure.

Pellet Characterization

The results from the friability and porosity studies are shown in Table 5. All pellet compositions had friability values of less than 1%, demonstrating their ability to withstand the fluidization process during coating. The porosity data did not provide a clear trend to aid in explaining pellet drug release behavior in acidic media.

Drug–Polymer Interaction Studies

A visible interaction was observed between CPM and Eudragit L30D-55 when the drug and polymer were combined and flocculation of the colloidal dispersion resulted. This flocculation phenomenon was not observed with theophylline and may explain the difference in the drug-release behavior between the enteric coated theophylline and CPM-containing pellets. To study the nature of the interaction between CPM and Eudragit L30D-55, adsorption isotherms were generated. Data from this study correlated best with the Freundlich model, indicating that adsorption of CPM to Eudragit L 30D-55 takes place in multiple layers rather than by localized adsorption due to a specific chemical interaction.[30] The Freundlich relationship[31] is given by:

$$Y = X/m = kC^{1/n}$$

where Y is equal to the amount of drug adsorbed (X) per unit mass (m) of adsorbent; C is the equilibrium drug concentration, and k and n are constants that are empirically derived. A linear relation was given by the equation:

$$\log X/m = 1/n \log C + \log k$$

where k represents the amount of drug adsorbed per unit weight of adsorbent, and the slope of the line $1/n$ represents the amount of drug adsorbed for a given change in drug concentration. The application of the Freundlich model for the adsorption of CPM from aqueous solution by Eudragit L 30D-55 is shown in Fig. 10 where the log of the amount of drug adsorbed per unit mass adsorbent is plotted as a function of log CPM concentration remaining in solution. Incorporating 1:2 or 1:4 w/w ratios of drug to citric acid in the mixtures reduced the amount of CPM adsorbed by the polymer. The

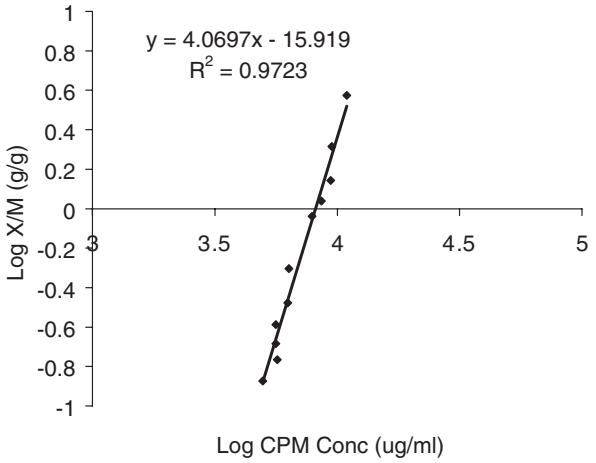

Figure 10. Freundlich plot for the adsorption of CPM to Eudragit® L 30D-55.

Key: Samples consisted of 10 g CPM solution (50 mg/mL) combined with increasing amounts of Eudragit® L 30D-55 and agitated for 24 hr at 25°C.

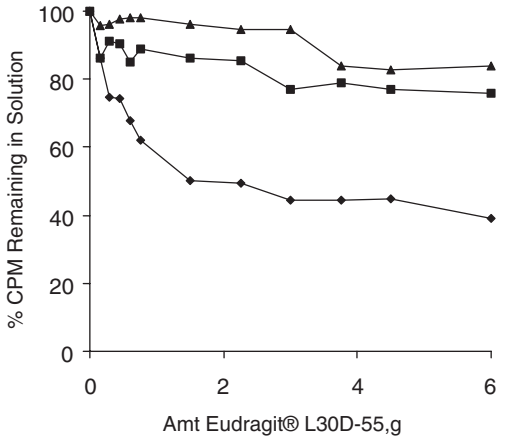

Figure 11. Effect of citric acid on the adsorption of CPM to Eudragit® L 30D-55.

Key: ◆, no citric acid; ■, 1:2 w/w ratio of drug to citric acid; ▲, 1:4 w/w ratio of drug to citric acid. Samples consisted of 10 g mixtures of CPM and citric acid in a 1:2 or 1:4 w/w ratio combined with increasing amounts of Eudragit® L 30D-55 and agitated for 24 hr at 25°C.

data in Fig. 11 represent the amount of CPM remaining in the supernatant as a function of polymer concentration. With the addition of citric acid, the percent CPM remaining in solution was increased, indicating that citric acid inhibited the interaction between the CPM and the polymer. The FTIR spectra (Fig. 12) of a 1:1 w/w physical mixture of the drug and the polymer and a 1:1 w/w precipitate between the drug and polymer were identical and indicated that no specific chemical bonding between the CPM and Eudragit L 30D-55 occurred, thus implying that no chemical interaction occurred between the drug and the polymer. The interaction between CPM and the Eudragit L 30D-55 dispersion can be explained by a reduction in thickness of the diffuse ionic layer among polymer particles caused by addition of the charged CPM molecules, resulting in entrapment of the drug within the flocculent. Such a drug–polymer interaction would interfere with film formation when Eudragit L 30D-55 was applied to the CPM-containing pellets, necessitating an increased weight gain of the polymeric film coating to prevent leakage of drug from the pellets during dissolution. This is in concurrence with findings by Goodman and Banker,[32] who also reported a flocculation phenomenon between an anionically charged, acrylic copolymer composed of acrylic and methacrylic acid and ester groups and cationic drugs.[32]

CONCLUSIONS

Enteric coated pellets containing the highly water-soluble drug CPM required increasing weight gain of polymeric coating to pass the USP enteric test as drug loading was increased. Polymeric subcoats were used to seal the water-soluble pellet core to prevent migration of the drug into the enteric polymer during processing. The effectiveness of the polymeric subcoat was a function of the water vapor transmission rate, as well as the wettability, crystallinity, and glass transition temperature of the polymer. Opadry AMB was shown to be the best subcoat material tested and had the lowest rate of water vapor transmission compared with Eudragit RD 100 and Eudragit RS 30D. Opadry AMB was also more hydrophobic as indicated by its relatively high contact-angle value and was found to have both crystalline and amorphous properties that influenced its permeability. The CPM pellets subcoated with a 5% weight gain of Opadry AMB and a 10% weight gain of Eudragit L 30D-55 passed the official USP enteric test.

The pellet composition was also found to influence release of CPM from the pellets coated with Eudragit L 30D-55. Incorporation of 20% w/w or 40% w/w amount of the water-soluble acidic component, citric acid, into the pellet core was effective in retarding the release of CPM in 0.1 N HCl from pellets coated with a 10% weight gain of Eudragit L 30D-55. Drug release from the enteric coated pellets was observed to increase in acidic media as the core pellet pH increased. This finding indicated that the micro-environmental pH was influenced by the pellet

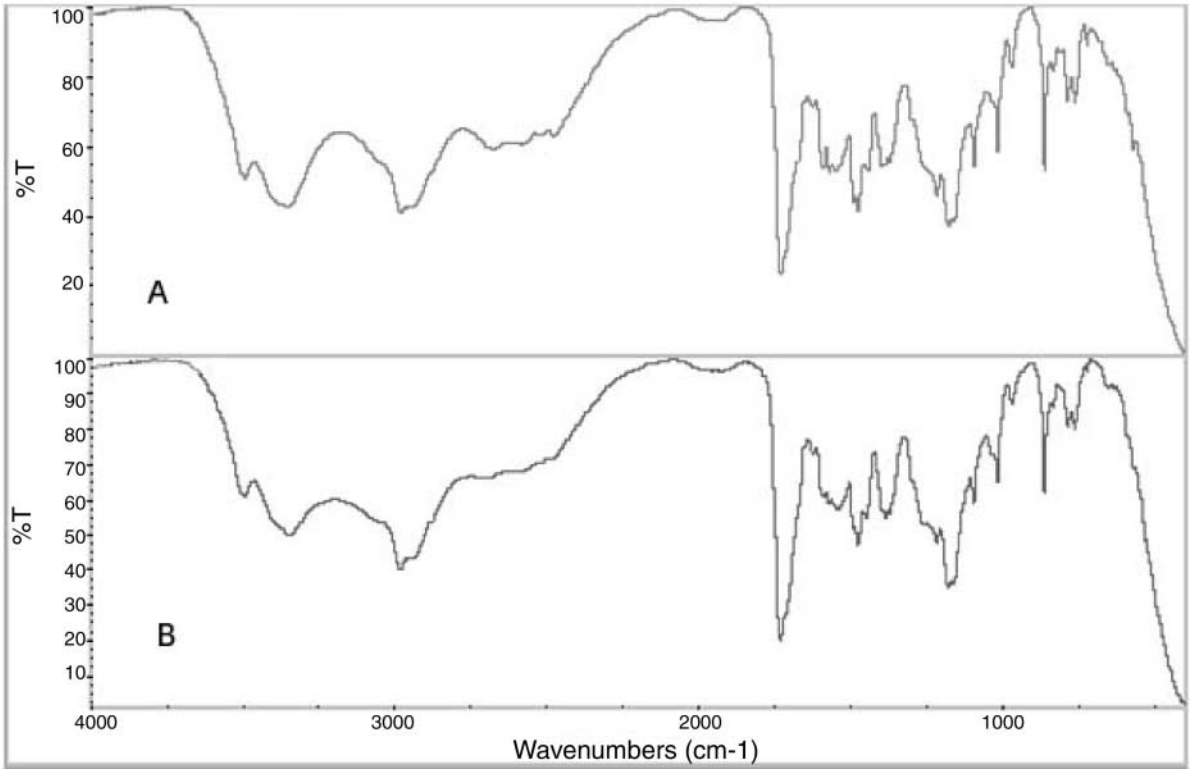

Figure 12. FTIR spectra of CPM and Eudragit® L 30D-55 precipitates and physical mixture. *Key:* A, CPM and Eudragit® L 30D-55 precipitate 1:1 w/w ratio; B, CPM and Eudragit® L 30D-55 physical mixture 1:1 w/w ratio.

formulation. Lowering of pellet micro-environmental pH by including citric acid into the pellet core reduced the permeability of the enteric polymer by preventing its ionization. A flocculation phenomenon observed between CPM and Eudragit L 30D-55 was due to adsorption of CPM to the Eudragit L 30D-55 as indicated by generation of a Freundlich isotherm at 25°C. The FTIR analysis however, demonstrated that chemical bonding did not occur between the drug and the polymer. In addition to influencing pellet micro-environmental pH, citric acid was also shown to inhibit the physical interaction between CPM and Eudragit L 30D-55 by reducing the amount of drug adsorbed to the polymer. By inhibiting adsorption, citric acid promoted improved polymer coalescence and film formation, resulting in enteric drug release properties utilizing less enteric polymer.

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