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Research paper

Influence of processing parameters and formulation factors on the drug release from tablets powder-coated with Eudragit® L 100-55

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Abstract

The aim of this study was to develop a dry powder coating process for chlorpheniramine maleate (CPM) tablets using Eudragit® L 100-55 as the delayed release polymer. Powder coating, a water and organic solvent-free process, was investigated as a method to prevent the migration of an ionizable, highly water soluble model drug into the polymeric film during the coating process. Eudragit® L 100-55 was pre-plasticized with triethyl citrate (TEC) using hot-melt extrusion at levels of 20%, 30%, and 40%, based on the polymer weight. The extrudate was subsequently cut into pellets and cryogenically ground into a fine powder. Talc was incorporated into the coating powder as an anti-tack agent. PEG 3350 was used as a primer for the powder coating of tablets with pre-plasticized Eudragit® L 100-55. The addition of polyethylene glycol 3350 (PEG 3350) to the pre-plasticized Eudragit® L 100-55 was necessary to enhance the adhesion of the coating powder to the tablet cores. PEG 3350 also improved film formation and coalescence of the polymeric particles due to its plasticization effects on the acrylic polymer. For comparison, theophylline tablets were also coated with pre-plasticized Eudragit® L 100-55. Theophylline was selected as a less water soluble model drug. The powder coating process was performed in a modified laboratory scale spheronizer. The drug release rate was dependent both on TEC content and the coating level. The stability of the powder-coated CPM tablets was confirmed at 25 °C/60% RH over a storage time of 12 weeks.

Keywords: Powder coating; Eudragit® L 100-55; Chlorpheniramine maleate; Theophylline; Enteric polymers; Film formation

1. Introduction

Although widely employed in other industrial applications since the 1950s, dry powder coating was not described in the pharmaceutical literature until the late 1990s. The primary advantage of this process is that it circumvents many limitations of established organic and aqueous coating systems for pharmaceutical products. The traditional use of organic solvents in coating processes creates environmental, toxicological, and safety-related concerns. Problems of aqueous coating are primarily due to the limited applicability for water-sensitive active ingredients [1], the migration of drugs into the polymer coatings during processing [2], and the physical aging of the polymeric films that leads to changes in the drug release rate during product storage [3–5].

The first approach to powder-coat pharmaceutical dosage forms was reported by Obara and coworkers in 1999 [6]. The process involved the direct application of polymeric particles and the simultaneous spraying of a mixture of a plasticizer and acetylated monoglyceride onto drug containing cores. An aqueous hydroxypropyl methylcellulose (HPMC) solution was applied during the curing step to improve film formation [6]. Pearnchob et al. modified the technique using an aqueous HPMC solution in combination with a plasticizer, while still separately feeding the polymer powder onto the solid substrates during the coating process [7–9]. Investigations from these researchers

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encompassed cellulose derivatives, the acrylic polymer Eudragit® RS, and shellac [7–9]. Both methods [6–9] required a minimal amount of water, and it was demonstrated that dry-powder coating compared to aqueous coating procedures generally required higher coating levels, higher plasticizer concentrations, and higher processing temperatures. Nevertheless, the processing time in dry-powder coating operations was significantly shorter due to the high solid content of the coating mixture.

Recently the dry coating method developed by Obara was modified by Kablitz et al. by replacing the anti-tacking agent talc with colloidal silicon dioxide and eliminating the use of water in the curing step [10].

A novel water and solvent-free powder coating technique was developed by Cerea et al. and Zheng et al. in 2004 [11,12]. This dry coating technique did not utilize water or any other liquid during the entire coating process. The process was successfully applied for the acrylic polymers Eudragit® RS PO, Eudragit® RL PO, and Eudragit® E PO for the coating of tablets to modify the drug release rate. Dry powder coating was shown to prevent the aging of the polymeric film, a phenomenon which has been reported for aqueous coated dosage forms during storage. The powder coating process itself consists of three steps, namely, priming, powder layering, and curing. To facilitate the direct application of the acrylic polymers onto the solid substrates, the solid Eudragit® RS PO and Eudragit® RL PO powders were pre-plasticized using a hot-melt extrusion process. The extrudates were subsequently cryogenically ground into a micronized coating powder [12]. The pre-plasticization step was not needed for Eudragit® E PO due to the low glass transition temperature of this polymer [11].

Eudragit® L 100-55, an anionic copolymer, is based on methacrylic acid and ethyl acrylate in a 1:1 ratio and has not been studied in dry powder coating applications. Its glass transition temperature was reported to be within the range of 124–129 °C [13,14].

The objective of the present study was to investigate the properties of chlorpheniramine maleate (CPM) and theophylline tablets that were powder-coated with pre-plasticized Eudragit® L 100-55. CPM is a freely water soluble drug. It was reported that CPM pellets required higher coating levels of the enteric polymer than pellets containing theophylline, a less soluble drug, in order to pass the dissolution specification in acidic media due to the migration of the drug into the Eudragit® L 30 D-55 coating [2].

Powder coating, a water and organic solvent-free process, was employed as a method to prevent the migration of the highly water soluble drug CPM into the film coating. The drug release properties of the powder-coated tablets as well as storage stability under accelerated storage conditions were studied. Film formation and surface morphology of powder-coated tablets were characterized, and the function and influence of the primer on powder adhesion and film formation were studied.

2. Materials

Eudragit® L 100-55 was donated by Degussa Corp. (Piscataway, NJ). Chlorpheniramine maleate USP/NF, anhydrous theophylline USP, magnesium stearate NF, and lactose monohydrate NF were purchased from Spectrum Chemical Mfg. Corp. (Gardena, CA). Triethyl citrate NF (TEC) was donated by Morflex Inc. (Greensboro, NC). Talc USP (Imperial 500) was supplied by Luzenac America, Inc. (Centennial, CO). Polyethylene glycol (PEG) 3350 NF was donated by The Dow Chemical Company (Midland, MI). Microcrystalline cellulose (MCC, Avicel® PH-101) was donated by FMC BioPolymer (Newark, DE). Polyvinylpyrrolidone K-30 (PVP, Kollidon® 30) was supplied by BASF Corp. (Mt. Olive, NJ). Colloidal silicon dioxide (CAB-O-SIL® M-5P) was donated by Cabot Corporation (Billerica, MA).

3. Methods

3.1. Coating powder preparation and characterization

The pre-plasticization process for Eudragit® L 100-55 was based on the method reported by Zheng et al. [12] for Eudragit® RS and Eudragit® RL PO. After combining Eudragit® L 100-55 with TEC (20%, 30%, or 40% based on the polymer weight) in a high shear mixer, the powder blend was extruded using a single screw extruder (Randcastle Model RC 0750, Cedar Grove, NJ). The extruder temperature zones were set to: zone 1 = 80 °C, zone 2 = 110 °C, zone 3 = 115 °C, and die = 120 °C. A cylindrical die with an inner diameter of 6 mm was used. The extrudate was subsequently cut into pellets with a Randcastle RCP-2.0 pelletizer and then cryogenically ground into a fine powder using a CF Mikro-Bantam Cryogenic Grinder (Micron Powder Systems, Summit, NJ). To obtain a more uniform particle size distribution and exclude fines and large particles, the ground pre-plasticized polymer was sieved by mechanical shaking for 15 min. The particle size fraction between 100 and 200 mesh (75–150 μm) was used for the dry powder coating experiments.

Laser light diffraction was employed to analyze the particle size distribution of the coating powder using a Malvern Mastersizer S (Malvern Instrument Limited, Malvern, Worcestershire, UK). D_v 10, D_v 50, and D_v 90, the cumulative percent undersize, were determined using the diffractive index of Eudragit® L 100-55 ($n_D^{20} = 1.3899$). The measurements were performed in triplicate in purified water ($n_D^{20} = 1.3300$).

The TEC content in the extrudates was determined at a wavelength of 210 nm using a Waters high performance liquid chromatography (HPLC) system (Waters, Milford, MA) equipped with a photodiode array detector (Model 996). Depending on the TEC concentration, 500 mg (20% and 30% TEC) or 300 mg (40% TEC) of processed polymer was initially dissolved in 50 mM, pH 7.4, buffer and then 1:2 diluted with 50 mM, pH 2.5, phosphate buffer to

remove the polymer from the solution ($n = 3$). The samples were filtered using 0.2 μm nylon filters prior to analysis. Fifty microliter samples were injected by an autosampler (Model 717plus), and Empower® Version 5.0 software was used to collect and analyze the data. An ODS-3 3 μm, 150 mm × 4.6 mm column (Alltech Inertsil™, Deerfield, IL, USA) was employed at a column temperature of 30 ± 2 °C. The mobile phase contained a mixture of acetonitrile: pH 2.5, 10 mM phosphate buffer in volume ratios of 55:45. The flow rate of 1 mL/min resulted in a retention time of 4.0 min for TEC. Linearity was demonstrated in the concentration range of 100–500 μg/mL ($R^2 = 0.99995$).

A MF-50 Moisture Analyzer (A&D Engineering, Inc., Milpitas, CA) was used to determine the loss on drying of the coating powder. A sample of 2 g was dried to a constant weight, as defined by a weight change of less than 0.05% per minute at 110 °C.

3.2. Differential scanning calorimetry

To characterize the thermal properties of the melt extrudates, modulated differential scanning calorimetry (MDSC) was conducted using a Thermal Advantage Model 2920 (TA Instruments, New Castle, DE) equipped with Universal Analysis 2000 software. Ultrahigh pure nitrogen was used as the purge gas at a flow rate of 150 mL/min. The polymeric film or polymer powder samples were sealed in aluminum pans (Kit 0219-0041, Perkin-Elmer Instruments, Norwalk, CT). The temperature ramp rate was 3 °C/min at a modulation rate of ±1.00 °C every 60 s. The initial temperature was at least 30 °C below the expected glass transition temperature. The final temperature exceeded the glass transition temperature by a minimum of 10 °C. The reverse heat flow of the second heating cycle was used to determine the inflection glass transition temperature.

To study any potential interactions between PEG 3350 and the model active pharmaceutical ingredients (API), conventional differential scanning calorimetry (DSC) was used employing the same instrument as described above. The samples were heated from 50 to 300 °C using a temperature ramp rate of 10 °C/min. The raw materials were analyzed as well as physical mixtures of API and PEG 3350 in ratios of either 1:1, 1:2 or 1:10. The heat flow of the first heating cycle was used to determine the melting points and heat of fusion values.

3.3. Tablet preparation

The compositions of CPM and theophylline tablets appear in Table 1. The API, Avicel® PH 101, lactose monohydrate, and the binder were mixed in a V-shape blender (Model Yoke, Patterson–Kelley Co., East Stroudsburg, PA) for 15 min. Following the addition of the magnesium stearate and colloidal silicon dioxide, the mixture was blended for an additional 5 min. The tablets were compressed on a rotary press (Model FJS-B2 Stokes, Bristol, PA) using deep concave 5 mm punches and characterized by their dimensions and weight (Table 1). The tablet hardness was measured on a hardness tester (WTP-3, Heberlein & Co. AG, Wattwil, Switzerland). The disintegration time was determined according to USP 29 using a USP Disintegration Tester (VanKel Industries Inc., Chatham, NJ). The tablet friability was tested according to USP 29 with a Tablet Friability Apparatus (VanKel Industries Inc., Chatham, NJ).

Table 1
Chlorpheniramine maleate and theophylline tablet formulations and tablet characteristics (standard deviation, $n = 6$)

	CPM tablets	Theophylline tablets
Tablet formulations (%)		
API	15	
Avicel® PH 101	46.25	
Lactose monohydrate	35	
Kollidon® 30	3	
Cab-O-Sil® M-5P	0.25	
Magnesium stearate	0.5	
Tablet characteristics ($n = 6$)		
Diameter (d) [mm]	5.0 ± 0.0	5.0 ± 0.0
Height (h) [mm]	4.2 ± 0.0	4.2 ± 0.0
Weight [mg]	81.2 ± 0.5	82.6 ± 0.3
Hardness [kg]	7.8 ± 0.6	7.8 ± 0.4
Disintegration time [min]	21	1
Tablet friability [%]	0.04	0.01

3.4. Powder coating process

Powder coating of the tablets was performed according to the method reported by Cerea et al. and Zheng et al. in a modified laboratory scale spheronizer (Model 120, G.B. Caleva, Dorset, UK) [11,12]. The batch size was 40 g of tablets. The rotation speed of the spheronizer was set to 220 rpm. The bed temperature was dependent on the plasticizer content of the coating mixture and maintained at 80–85 °C, 70–75 °C, or 70–75 °C using coating powders containing either 20%, 30%, or 40% TEC based on the polymer weight, respectively. The temperature of the coating bed was monitored by measuring the surface temperature of the tablets using a Fluke 61 Infrared Thermometer (Fluke Corporation, Everett, WA). Both talc and PEG 3350 were added in a 10% ratio to the coating powder based on the weight of the ground extrudate. The feeding rate of the coating powder onto the tablets cores was dependent on the capacity of the coating powder to adhere, which decreased with increasing coating levels. Following the application of the primer subcoat, the polymer mixture containing pre-plasticized Eudragit® L 100-55 was fed onto the tablet surfaces at a feeding rate of about 3 g/min until a polymer weight gain of 7% was obtained. The powder-feeding rate was then reduced to 0.5 g/min. Due to the poor flow properties of the coating formulation, the powder mixture was manually fed onto the tablet cores. After completion of the coating process, the tablets were subsequently cured either in the operating spheronizer for 6 h

or in a static oven on Teflon trays at 60 °C for 24 h. To prevent sticking during the stability test at 25 °C/60% RH and 40 °C/75% RH, the cured tablets were over-coated with 2% talc based on the weight of the coated tablets in the spheronizer.

3.5. Contact angle measurements

Polymer sample compacts were prepared at a 500 kg compression force using a Carver Laboratory Press (Model M, ISI Inc., Round Rock, TX). Three microliters of water was placed onto the surface of polymer compacts using a microsyringe. The contact angle was determined by measuring the tangent to the curve of the droplet on the surface of the compact using a Goniometer (Model No. 100-00-115, Ramé-Hart Inc., Mountain Lakes, NJ). The measurements were performed in triplicate at 20 °C.

3.6. Drug release study

The drug release rate of CPM and theophylline from powder-coated tablets was investigated using a modified USP 29 Drug Release Standard for Enteric-Coated Articles, Method B. *In vitro* dissolution testing was performed in 900 mL of 0.1 N HCl for the first 2 h, followed by 4 h in 900 mL, pH 6.8, 50 mM phosphate buffer solution maintained at 37 °C and agitated at 50 rpm using a USP 29 Apparatus 2 (Vankel VK 7000; VanKel Industries Inc., Cary, NC). The dissolution properties of the coated tablets were determined by placing three tablets into each of either three or six dissolution vessels, respectively ($n = 3 \times 3$ tablets/vessel or $n = 6 \times 3$ tablets/vessel). Samples were withdrawn by an autosampler over a 6 hour period (Vankel VK 8000; VanKel Industries Inc., Cary, NC). Samples were analyzed for CPM content using a HPLC system with a photodiode array detector (Model 996, Waters, Milford, MA) at a wavelength of 260 nm. Prior to analysis, the samples were filtered using 0.45 μm nylon filters. The autosampler (Model 717plus) was set to inject 50 μL samples. The data were collected and analyzed using Empower® Version 5.0 software. An ODS-3 3 μm, 150 mm × 4.6 mm column (Alltech Inertsil™, Deerfield, IL, USA) was used. The column temperature was kept at 40 ± 2 °C. The mobile phase contained a mixture of water/methanol/triethylamine in volume ratios of 675:325:4.5. The retention time of the CPM was 9.5 min. Linearity was demonstrated from 2 to 50 μg/mL ($R^2 \geqslant 0.9994$). The quantitative analysis for theophylline was conducted using the HPLC method described by Zheng et al. [12]. The same equipment was used as for the quantitative analysis of CPM. The injection volume was 40 μL. The mobile phase consisted of water:acetonitrile:glacial acid in volume ratios 845:150:5 and 1.156 g/L of sodium acetate trihydrate. The flow rate was 1 mL/min, and the retention time was 4 min. Linearity was confirmed from 1 to 60 μg/mL ($R^2 \geqslant 0.9999$).

3.7. Film preparation

The ground extrudate containing varying amounts of PEG 3350 was pressed into polymeric films in Teflon coated aluminum dishes with a Teflon coated lid by applying a small weight. A compression force of 45 g/cm^2 during the curing process was used to prepare the polymeric film to facilitate polymer particle fusion and film formation. This pressure minimized the formation of voids in the film due to an increase in the packing density of the polymer powder. The films were stored at 60 °C in a static oven for 24 h.

3.8. Scanning electron microscopy

The morphology of the surface and cross-section of powder-cast films and coated tablets was analyzed by scanning electron microscopy (SEM) using a Hitachi, Model S-4500 FE (Hitachi, London, UK) operated at 10 kV and 20 mA. The samples were sputter coated with gold/palladium (60:40) using a Ladd Benchtop Sputter Coater (Ladd Research, Winston, VT) at 2.5 kV and 20 mA for 75 s.

4. Results and discussion

4.1. Coating powder preparation

Due to the high glass transition temperature of the bulk polymer and to reduce the melt viscosity, the Eudragit® L 100-55 was pre-plasticized with up to 40% TEC using hot-melt extrusion. The pre-mixing of polymer and plasticizer under high shear conditions allowed for a homogeneous distribution of the plasticizer in the extrudate. The temperature in the metering zone of the extruder (zone 3) was maintained at 115 °C. Processing temperatures for Eudragit® L 100-55 should generally not exceed 130 °C as a decrease in functional groups was reported above temperatures of approximately 130 °C, with depolymerization occurring at temperatures exceeding 300 °C [15].

The TEC content recommended for aqueous coating dispersions of Eudragit® L 100-55 is 10–15% based on the dry polymer weight. In previous reports, Obara et al. and Pearnchob et al. demonstrated that dry powder coating of tablets and pellets required polymers with higher plasticizer levels than normally employed in aqueous coating processes [6–9]. The extrusion of Eudragit® L 100-55 containing 10% TEC (based on the polymer weight) was unsuccessful due to the high melt viscosity of the polymer. A thermal glidant could be used to aid in processing, but may impact dissolution. Thus, the current study investigated plasticizer ratios of 20%, 30%, and 40% TEC.

The glass transition temperature of the polymer was dependent on the amount of plasticizer in the extrudate, as seen in Table 2. A homogeneous distribution of the plasticizer throughout the polymer was verified for all TEC concentrations, as evidenced by the low standard deviation of the TEC recovery values. The higher the plasticizer level,

Table 2
Coating powder characteristics: TEC recovery, inflection glass transition temperature (T_g) (standard deviation, $n = 3$), and particle size distribution

TEC content	0 (bulk)	20	30	40
TEC recovery	–	98.5 ± 0.3%	97.5 ± 0.2%	97.5 ± 0.3%
T_g	123.7 ± 0.6 °C	73.7 ± 0.6 °C	61.3 ± 3.1 °C	37.0 ± 2.2 °C
Loss on drying	4.50 ± 0.05%	3.07 ± 0.08%	3.77 ± 0.18%	3.25 ± 0.09%
T_g after addition of 10% PEG 3350	122.2 ± 3.0 °C	47.4 ± 9.0 °C	29.2 ± 0.9 °C	11.1 ± 2.9 °C
Particle size distribution				
D_v10 (μm)	0.37	0.33	35.13	38.42
D_v50 (μm)	43.63	74.18	77.50	81.94
D_v90 (μm)	83.25	148.33	147.58	151.07
Span	1.900	1.995	1.451	1.375

Span index: $(D_v90 - D_v10)/D_v50$.

the more difficult was the feeding of the polymer–plasticizer mixture from the hopper into the extruder barrel due to the poor flow properties of the powder–plasticizer mixture. The low glass transition temperatures of the pre-plasticized polymeric extrudates required a cryogenic grinding process to obtain a fine powder suitable for powder coating applications.

The loss on drying of the coating powder was analyzed to determine the moisture content since water is a known plasticizing agent for acrylic polymers [16] and adsorbed moisture has been shown to significantly impact the glass transition temperature for Eudragit® L 100-55 [13]. The loss on drying of the processed polymer ranged from 3.1% to 3.8%, which was slightly lower than the value of 4.5% for the bulk polymer (Table 2). Before the analysis, it was demonstrated by thermogravimetric analysis that TEC was not volatile at the 110 °C storage temperature used in this study (data not shown). However, TEC exhibited a distinct weight loss at temperatures above 200 °C.

The particle size distributions of the unprocessed Eudragit® L 100-55 and ground, pre-plasticized polymer after sieving are presented in Table 2. The particle sizes of the processed polymers were significantly higher than that of the commercially available Eudragit® L 100-55 powder but equivalent to those of particles used in previous powder coating studies [12]. Due to identical processing conditions and the same sieving process, no influence of the plasticizer level on the particle size distribution of the cryogenic ground powders was observed.

4.2. Powder coating

The coating powder mixture was composed of the processed polymer, 10% talc, and 10% PEG 3350. Both the weight of talc and the weight of PEG 3350 were based on the weight of the ground extrudate. A talc content of 10% effectively prevented tablet aggregation during the powder coating process with pre-plasticized Eudragit® L 100-55. Comparably low levels of talc as an anti-tack agent were sufficient due to the absence of liquids during the coating operation, and low talc levels had previously been successfully employed in a powder coating process with Eudragit® E PO and Eudragit® RS/RL PO [11,12].

Powder adhesion to the core tablets of pre-plasticized Eudragit® L 100-55 combined with 10% talc was not possible without the presence of a primer subcoat. Several primers were investigated including cetyl alcohol, poloxamer 407, and PEG 3350. All investigated priming agents had a melting point below the coating temperature in order to generate a liquid priming layer covering the core tablets. The interfacial interactions between the tablet surface and the pre-plasticized polymer particle are complex and are dependent on interfacial tension, wetting and adhesion [17]. The fluid layer reduces the surface tension of the tablet surface and results in an improved adhesion of the coating powder to the tablet surface. The work of adhesion between two materials is reduced with decreasing surface tension [18]. Another factor influencing the adhesion of the coating powder is the hydrophilicity of the tablet surface. PEG 3350, which is characterized by a small contact angle with purified water, increases the hydrophilic surface properties of the tablet [12]. The use of low melting point hydrophobic primers, such as cetyl alcohol, was not effective in powder-coating with pre-plasticized Eudragit® L 100-55, although they were successfully employed for Eudragit® RS/RL PO [12]. Since Eudragit® L 100-55 was characterized by a contact angle with water of 61.0 ± 2.6° ($n = 3$), while the contact angle of Eudragit® RS PO and RL PO was determined to be 87.7 ± 2.1° and 86.7 ± 0.6°, respectively ($n = 3$), Eudragit® L 100-55 is a more hydrophilic polymer which required a more hydrophilic priming agent.

PEG 3350 was not only employed as a priming agent, but it was also incorporated into the coating powder at the 10% level based on the weight of the ground extrudate. When PEG 3350 was utilized as the priming agent but was not present in the powder coating formulation the maximum polymer weight gain that could be achieved was 5%, which was insufficient to pass the gastric phase of the USP enteric test for all TEC levels investigated. To investigate the miscibility of PEG 3350 and Eudragit® L 100-55 and to study the influence of PEG 3350 on the thermal properties of Eudragit® L 100-55, polymeric films were powder-cast and cured for 24 h at 60 °C. The presence of the PEG 3350 at the 10% level reduced the glass transition temperature of Eudragit® L 100-55 by about 30 °C for all

TEC levels as shown in Table 2. The thermograms indicated complete miscibility of Eudragit® L 100-55 and PEG 3350 at this ratio, as evidenced by a single detectable glass transition and the absence of the distinct melting peak of PEG 3350. These findings correlate well with previously published solubility parameters, which suggest a high affinity between PEGs and the Eudragit® L polymers [19].

The influence of PEG 3350 on film formation was additionally investigated in a second free film study. The SEM micrographs of cross-sections of Eudragit® L 100-55 films containing 30% TEC and various levels of PEG 3350 are presented in Fig. 1. PEG 3350 levels of 5% and 10% promoted polymer particle fusion and facilitated film formation during the curing process at 60 °C for 24 h. However, the addition of 5% PEG 3350 to the coating powder in combination with a primer did not promote polymer adhesion. In contrast, a 3% weight gain of PEG 3350 as primer and the additional incorporation of 10% PEG 3350 into the coating powder allowed high coating levels with polymer weight gains above 15% for all employed TEC levels.

The bed temperatures for the powder coating process were 80–85 °C, 70–75 °C, or 70-75 °C for powder blends containing 20%, 30%, and 40% TEC, respectively. These temperatures are above the glass transition temperature of the pre-plasticized Eudragit® L 100-55 for the respective TEC concentrations.

The influence of TEC content and coating level on the release rate of CPM from powder-coated tablets is presented in Fig. 2. Tablet samples were withdrawn during the coating process after each designated coating level was reached and cured for 24 h in a static oven. The applied polymer weight gain had a significant impact on the drug release properties of the powder-coated tablets. The USP 29 Drug Release Standard for Enteric-Coated Articles requires a drug release of less than 10% after 2 h dissolution testing in 0.1 N HCl. In addition, the gastric stability was found to be significantly dependent on the TEC concentration in the film coating. A coating level of 10% polymer weight gain on powder-coated CPM tablets met the USP dissolution specifications at a TEC content of both 30% and 40%. However, a polymer weight gain of 15% was needed to maintain the release of CPM in acid below the 10% level for a TEC content of 20%. Higher plasticizer levels will enhance the coalescence between the polymer particles and were previously demonstrated to decrease drug release rates [20]. This trend was observed both in the gastric as well as the buffer phase of the enteric test.

To investigate the surface morphology of the coating, powder-coated tablets with a 15% polymer weight gain were subjected to microscopic examination as seen in Fig. 3. The highest coating level was chosen to evaluate the dependence of film formation on the plasticizer level in the coating powder. All TEC concentrations resulted in the formation of a dense polymer film as seen in the micrographs of the cross sections. The surfaces of all films, however, were characterized by the presence of voids and non-fused large particles of polymer. The number of flaws in the film coating decreased with increasing TEC levels,

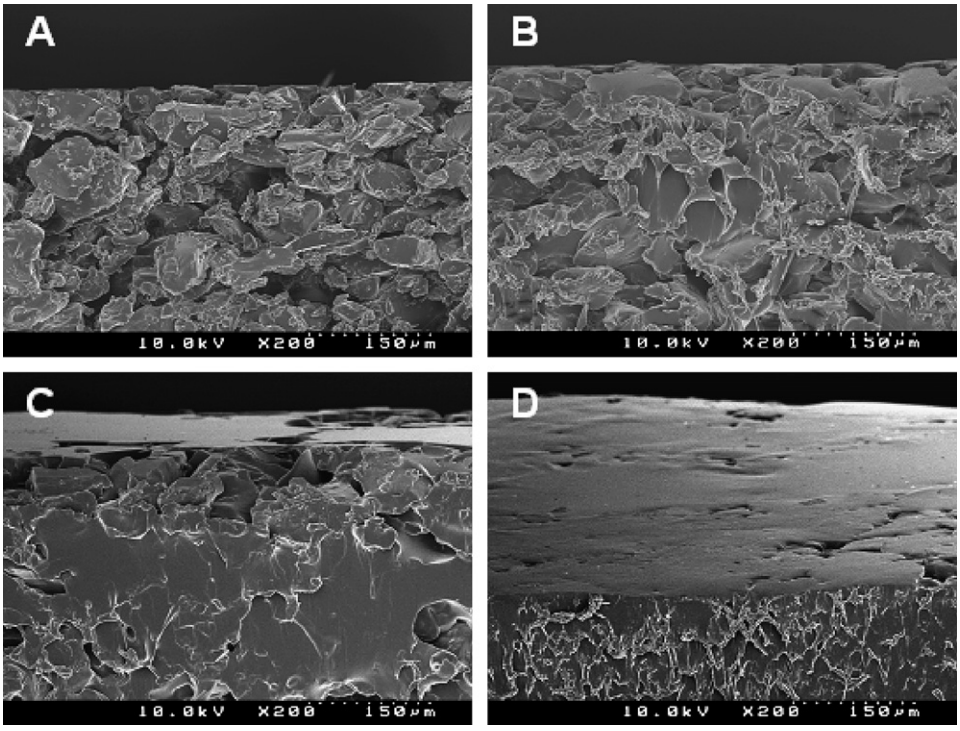

Fig. 1. Influence of PEG 3350 content on morphology of free films prepared from HME processed Eudragit® L 100-55 pre-plasticized with 30% TEC (based on the polymer weight) after curing at 60 °C for 24 h. (A) 0% PEG 3350. (B) 1% PEG 3350. (C) 5% PEG 3350. (D) 10% PEG 3350.

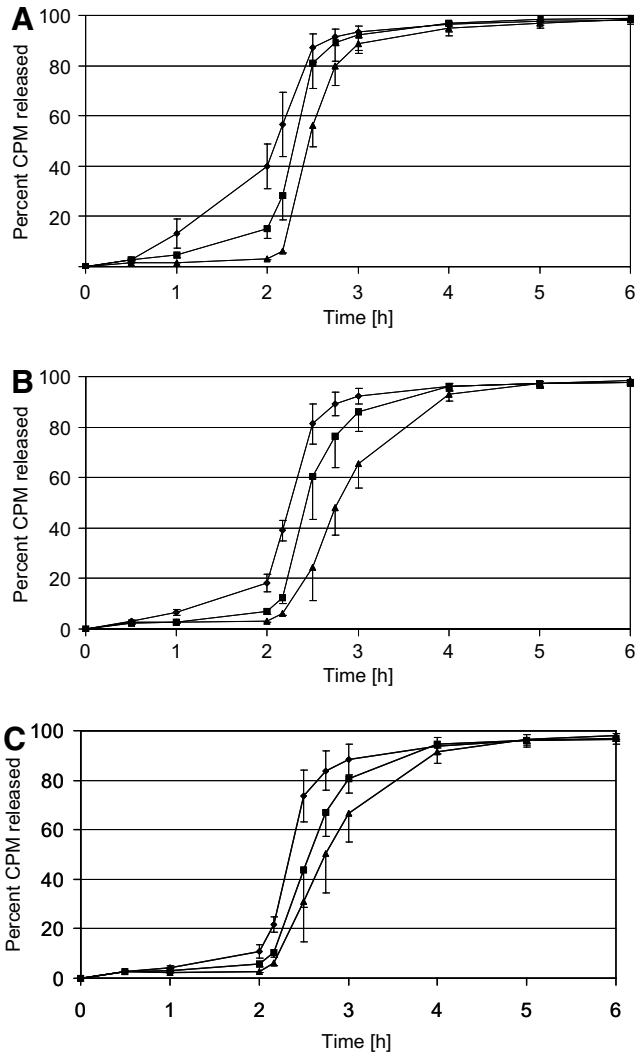

Fig. 2. Influence of TEC content and coating level on the release of CPM from tablets powder-coated with pre-plasticized Eudragit® L 100-55 using USP 29 apparatus 2. Dissolution in 900 mL of 0.1 N HCl for 2 h followed by 4 h in 900 mL, pH 6.8, 50 mM phosphate buffer at 37 °C and 50 rpm. ◆, 7% polymer weight gain. ■, 10% polymer weight gain. ▲, 15% polymer weight gain (standard deviation, $n = 6 \times 3$ tablets/vessel). (A) 20% TEC based on the polymer weight. (B) 30% TEC based on the polymer weight. (C) 40% TEC based on the polymer weight.

thereby demonstrating improved film formation at elevated plasticizer concentrations in the polymeric film. The results of the microscopic analysis support the observed differences in CPM dissolution rates at different plasticizer levels.

Swelling of the enteric coating was observed for the powder-coated CPM tablets during dissolution testing after immersion in 0.1 N HCl for 2 h. Following the acid stage of the enteric test, the tablets were characterized by an increase in size and a soft consistency compared to the dry tablets. These results may be partially attributed to the high level of water-soluble components in the film coating. TEC has been shown to be slowly released from Eudragit® L film coatings due to strong interactions with Eudragit® L compared to other plasticizers [21]. PEGs have been studied by other researchers to increase the permeability of poly(meth)acrylate films. Due to its high water solubility, PEG can act as a pore forming agent during dissolution testing depending on the miscibility with the polymer and can cause an increase in the drug diffusion rate [22–24]. Since water molecules are strongly bound to the ether groups in the PEG molecule by hydrogen bonds [19], the PEG remaining in the polymeric film causes swelling of the polymer coating, resulting in the release of a small amount of CPM during the acid stage of the enteric test. This level of drug release did not exceed the maximum allowance of the USP test for enteric-coated articles at coating levels of 10% polymer weight gain and above.

High levels of plasticizer also increase the tackiness of a polymeric film. This effect improves adhesion of the polymer film to the tablet core, but represents an undesired phenomenon in coating operations and during storage, and may result in agglomeration of coated dosage-forms [25,26]. Increasing tackiness with high TEC levels (40%) was also observed for the powder coating of tablets with pre-plasticized Eudragit® L 100-55 following curing. Tackiness was eliminated with the application of a 2% talc overcoat in the spheronizer after the curing step.

A TEC content of 30% in the processed polymer and a coating level of 10% polymer weight gain were determined to be the ideal coating parameters for CPM tablets since tablets coated with Eudragit® L 100-55 containing 20% TEC required high coating levels, while a TEC content of 40% resulted in slightly tacky tablets. Tablets powder-coated using these conditions were further studied to investigate the optimal curing conditions and the physical stability of the powder-coated tablets at accelerated storage conditions. This formulation was also used to coat tablets containing theophylline, a less soluble drug.

4.3. Curing conditions

In Fig. 4, the scanning electron micrographs are presented which show the surface and cross-section of an uncured tablet that was powder-coated with pre-plasticized Eudragit® L 100-55. Film formation was incomplete following the application of the coating material using the dry powder coating process. The upper layer of the polymer film is characterized by separate polymer particles, while the lower layer exhibited a dense polymeric film. Without curing, the quantity of drug released in the acidic medium was higher than 10%, which is the maximum allowance by the USP 29 Release Standard for Enteric-Coated Articles, and exhibited a large standard deviation. Since a curing time of 24 h in a static oven resulted in a continuous polymeric film in previous powder-coating studies [11,12], all tablets used in the dissolution studies presented in Fig. 2 were cured for 24 h at 60 °C. Curing at 80 °C resulted in yellow discoloration of the tablets, due to the oxidation of PEG at this high temperature [27,28]. A curing condition at 60 °C for 24 h prevented the discoloration. A curing study was performed to

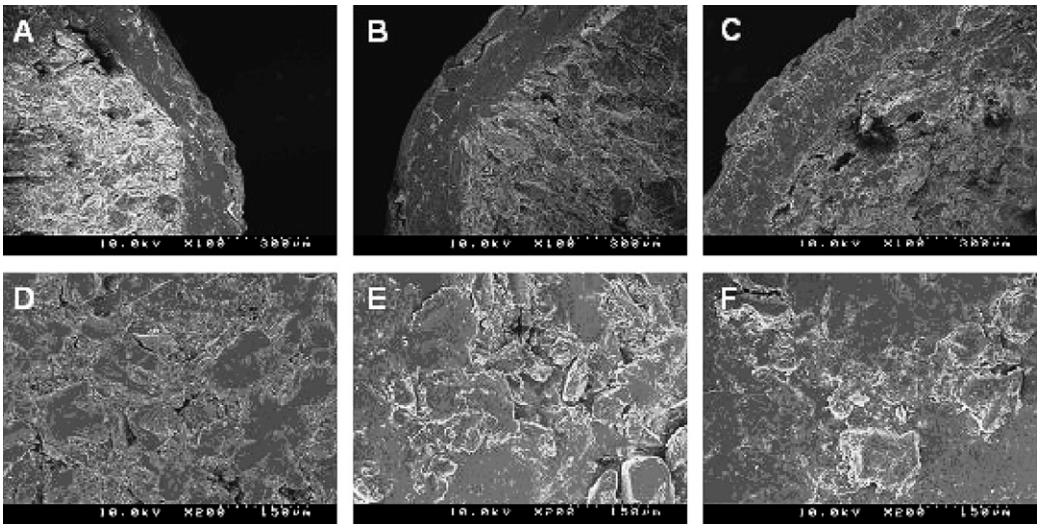

Fig. 3. SEM micrographs of cross-section (CS) and surface (SF) of powder-coated tablets (15% polymer weight gain) after curing in a static oven at 60 °C for 24 h. (A) 20% TEC based on the polymer weight (CS). (B) 30% TEC based on the polymer weight (CS). (C) 40% TEC based on the polymer weight (CS). (D) 20% TEC based on the polymer weight (SF). (E) 30% TEC based on the polymer weight (SF). (F) 40% TEC based on the polymer weight (SF).

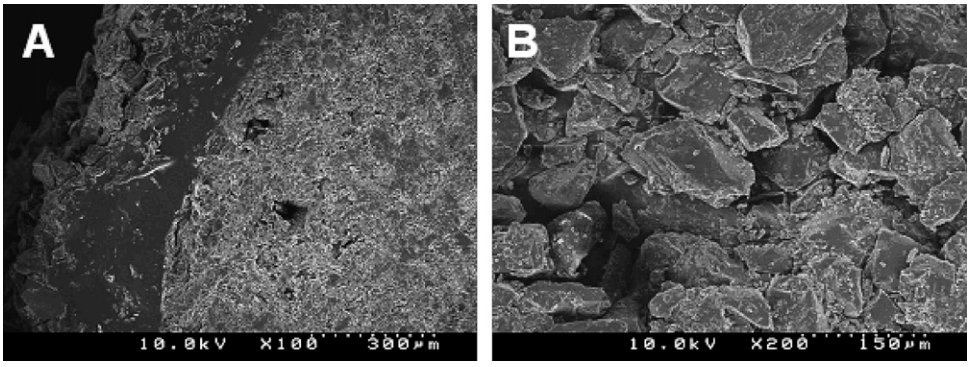

Fig. 4. SEM micrographs of cross-section (A) and surface (B) of tablets powder-coated with Eudragit® L 100-55 containing 30% TEC based on the polymer weight before curing.

determine the necessary curing time at 60 °C to reduce the drug release in 0.1 N HCl to less than 10%.

The tablets were coated with pre-plasticized Eudragit® L 100-55 containing 30% TEC based on the polymer weight with a 10% polymer weight gain. After the completion of the coating process, the tablets were either cured in a static oven at 60 °C or were tumbled in the spheronizer at 60 °C at 220 rpm. The gastric stability of the powder-coated tablets was investigated, which was characterized by the percent of CPM released in 0.1 N HCl after 2 h using USP 29 Apparatus 2. The data in Fig. 5 show the influence of curing time and conditions on the CPM release rate from tablets powder-coated with pre-plasticized Eudragit® L 100-55.

Curing of powder-coated CPM tablets at 60 °C improved gastric stability and decreased the variability in the dissolution data since curing eliminated the residual voids between the polymer particles. In prior studies, curing was shown to be an essential step in a dry-powder coating process to improve polymer particle fusion and complete film formation [6–9,11,12]. Curing in the spheronizer was demonstrated to be an efficient curing method with a small standard deviation and a lower average CPM release rate in the acidic medium than the oven cured tablets. Due to the strong centrifugal forces and the resulting impact of the tablets on the spheronizer wall, the polymer particles were compressed, deformed, and fused. The surface was leveled and defects were corrected faster resulting in a shiny surface compared to the oven cured tablets, even after short curing times. Curing in the spheronizer also reduced the influence of gravity on the polymer flow during film formation. Generally, the flow of polymeric films with a thickness of 25–75 μm or above is controlled by gravity [29]. In the case of powder-coated tablets, this effect caused the direction of flow of the polymer to the bottom of the tablet. As a result, tablets stored on trays at 60 °C for 24 h developed a flat base which resulted in the loss of the round tablet shape. After rotating for 12 h, tablets cured in the spheronizer showed signs of deformation and grey discoloration of the tablet edges. Curing in the spheronizer should therefore generally not exceed 6 hours to prevent this phenomenon.

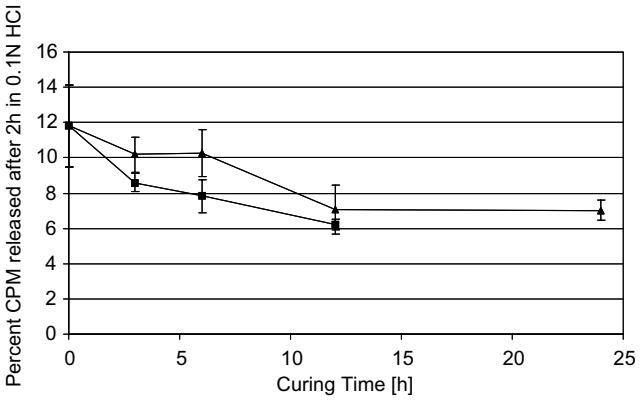

Fig. 5. Influence of curing time and conditions on the release of CPM from powder-coated tablets (30% TEC based on the polymer weight, 10% polymer weight gain) in 900 mL of 0.1 N HCl using USP Apparatus 2 at 50 rpm and 37 °C after 2 h. ▲, 60 °C, static oven. ■, 60 °C, revolving spheronizer at 220 rpm (standard deviation, $n = 3 \times 3$ tablets/vessel).

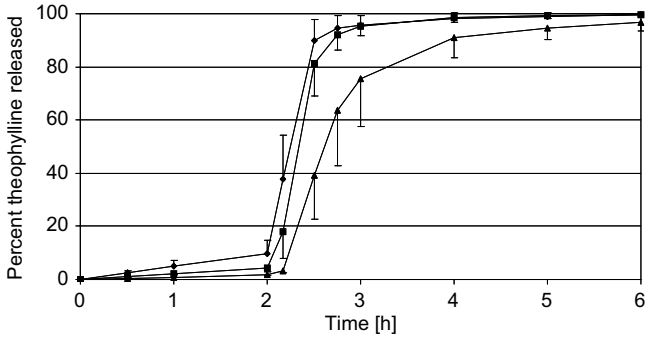

Fig. 6. Influence of coating level on the release of theophylline from tablets powder-coated with pre-plasticized Eudragit® L 100-55 containing 30% TEC based on the polymer weight using USP 29 apparatus 2. Dissolution in 900 mL of 0.1 N HCl for 2 h followed by 4 h in 900 mL, pH 6.8, 50 mM phosphate buffer at 37 °C and 50 rpm. ◆, 7% polymer weight gain. ■, 10% polymer weight gain. ▲, 15% polymer weight gain (standard deviation, $n = 6 \times 3$ tablets/vessel).

Curing in both a static oven and the spheronizer was shown to be effective for tablets powder-coated with pre-plasticized Eudragit® L 100-55, to achieve sufficient gastric stability. However, curing in the spheronizer reached equilibrium faster than curing the powder-coated tablets in a static oven.

4.4. Properties of powder-coated theophylline tablets

Dosage forms containing theophylline were shown to require a lower Eudragit® L 30 D-55 coating weight gain applied from an aqueous dispersion compared to those containing CPM to provide sufficient gastric stability [2]. This phenomenon was attributed to the lower water solubility of theophylline and decreased migration rate of the API into the film. Thus, theophylline was selected for this study to compare and characterize its release rate from tablets powder coated with pre-plasticized Eudragit® L 100-55 using the same parameters as for CPM.

Theophylline containing tablets (Table 1) were powder-coated with a pre-plasticized blend of Eudragit® L 100-55 containing 30% TEC. The tablets were coated to polymer weight gains of 7%, 10%, and 15% and then subsequently cured in a static oven for 24 h. The static oven and not the spheronizer was used for curing to compare the results to the CPM tablets. The influence of weight gain on the release rate of theophylline from tablets powder-coated with pre-plasticized Eudragit® L 100-55 containing 30% TEC based on the polymer weight is seen in Fig. 6. A polymer weight gain of 7% provided gastric stability with the amount of drug released after 2 h in 0.1 N HCl being approximately 10%. A 10% and 15% polymer weight gain reduced the amount of drug released after two hours in 0.1 N HCl to less than 5% and 2%, respectively. The drug release from theophylline tablets could be controlled with a lower polymer weight gain. The differences in the drug release rates are mainly caused by the higher water solubility of CPM and higher drug diffusion from CPM tablets compared to the theophylline tablets in acidic media. It has been reported that the drug release rate from theophylline tablets was slower compared to tablets containing a more water soluble API [30]. Drug release during the acid phase is a result of swelling of the film coating, water penetration into the core, drug dissolution, and subsequent diffusion through the hydrated polymeric film [31]. Penetrated water increases the polarity and molecular mobility inside the tablet [30]. Both water influx and drug solubility are factors which increase the drug release rate through enteric polymer films [31]. The transfer of drug through polymeric films is not only controlled by diffusion, but is also modulated by osmotic pressure [32]. Osmotic forces that are generated by the dissolution of drug and excipients in the tablet matrix increase the influx of water and the diffusion of electrolyte, which result in faster drug release [33].

The theophylline core tablets were characterized by a significantly shorter disintegration time compared to the CPM tablets. The tablet size, weight, hardness, and friability were similar for both formulations. To investigate possible API migration into the polymer film during the powder coating process or curing, the interactions between the model drugs and the molten PEG 3350 were studied using conventional DSC. The first heating cycle was used to investigate the effects of the molten PEG 3350 on each crystalline drug. The DSC profiles of the raw materials were characterized by distinct melting peaks as seen in Fig. 7. PEG 3350 melted at a temperature of 61 °C. The melting points of CPM and theophylline occurred at 136 and 274 °C, respectively, which were above the coating and curing temperature conditions. The melting point as well as the heat of fusion of PEG 3350 was not influenced by the presence of either CPM or theophylline. In contrast, the DSC profiles of the physical mixtures exhibit lower or no distinct melting points for both APIs, depending on the mixing ratio. Additionally, PEG 3350 influenced the heat of fusion of both APIs. Table 3 shows the heat of fusion values of the individual components calculated based on the mixing ratio of the model drug and PEG 3350. All physical mixtures exhibited a lower heat of fusion

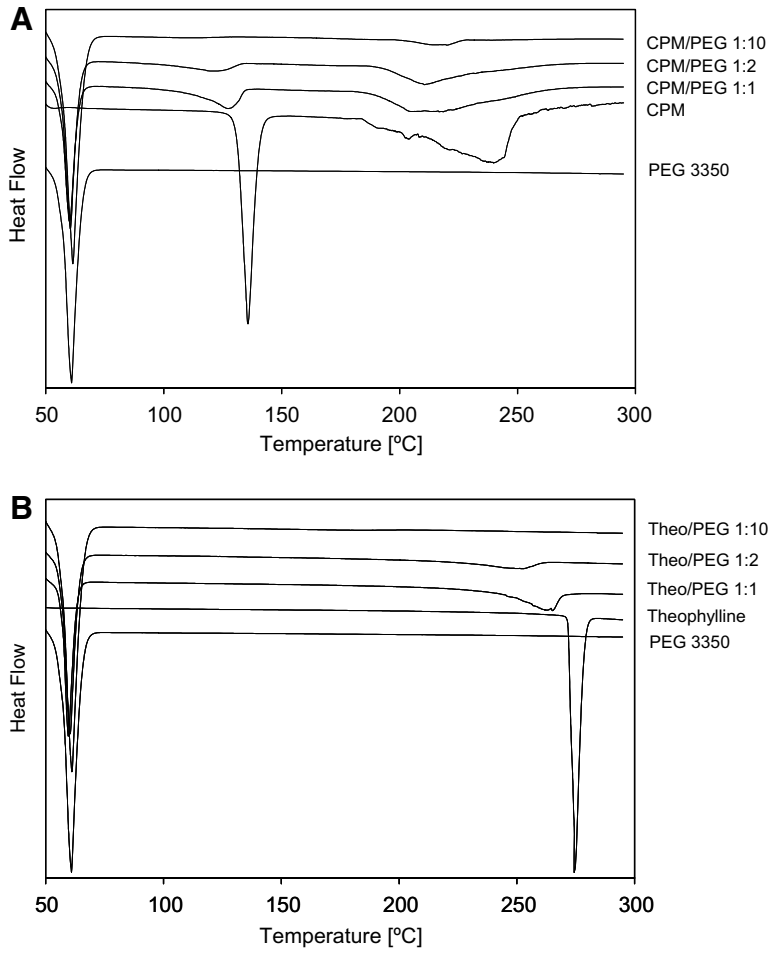

Fig. 7. DSC profiles of CPM (A) and theophylline (B) and their physical mixtures in ratios of 1:1, 1:2, and 1:10 PEG 3350.

Table 3
Heat of fusion of CPM, theophylline, and PEG 3350 and their mixtures

	CPM/PEG mixtures		Theophylline/PEG mixtures	
	CPM	PEG 3350	Theophylline	PEG 3350
Heat of fusion [J/g] Bulk	121.2	194.6	167.1	194.6
1:1	86.5	194.2	79.0	206.6
1:2	73.7	196.4	69.8	202.5
1:10	33.1	193.7	19.3	200.9

for both CPM and theophylline in a physical mixture compared to the pure drugs, indicating changes in the crystal lattice of the model compounds. Both theophylline and CPM were shown to interact with PEG 3350. The melting point of CPM is lower than that of theophylline and hence closer to the processing conditions. Consequently the effect of PEG 3350 could be more pronounced on CPM than on theophylline.

The theophylline release rate in buffer was faster compared to the CPM release rate. The dissolution of enteric polymeric films during the buffer phase of the enteric test was demonstrated to occur primarily at the polymer/bulk interface rather than by bulk erosion throughout the coating layer [31]. As a result, the thickness of the polymeric film was shown to decrease under simulated intestinal conditions. The drug CPM was previously shown to adsorb to Eudragit® L 30 D-55 as a function of the pH of the dissolution medium [2]. Consequently the theophylline release rate in pH 6.8 buffer was expected to be faster and less dependent on the coating level.

4.5. Stability of powder-coated CPM tablets

Powder-coated tablets have been reported to demonstrate excellent physical stability during storage [6–8,12]. The physical stability of CPM tablets powder-coated with a 10% weight gain of pre-plasticized Eudragit® L 100-55 containing 30% TEC based on the polymer weight was determined. These tablets were cured in the rotating spheronizer at 170 rpm for 6 h. After the completion of the curing step, a 2% talc overcoat was applied onto the coated tablets in the spheronizer to reduce the tackiness of the film coating. The powder-coated tablets were stored in induction-sealed HDPE containers with desiccant to exclude the influence of humidity during storage at both 25 °C/60% RH and 40 °C/75% RH. Before dissolution testing, the samples were equilibrated to ambient temperatures for 24 h.

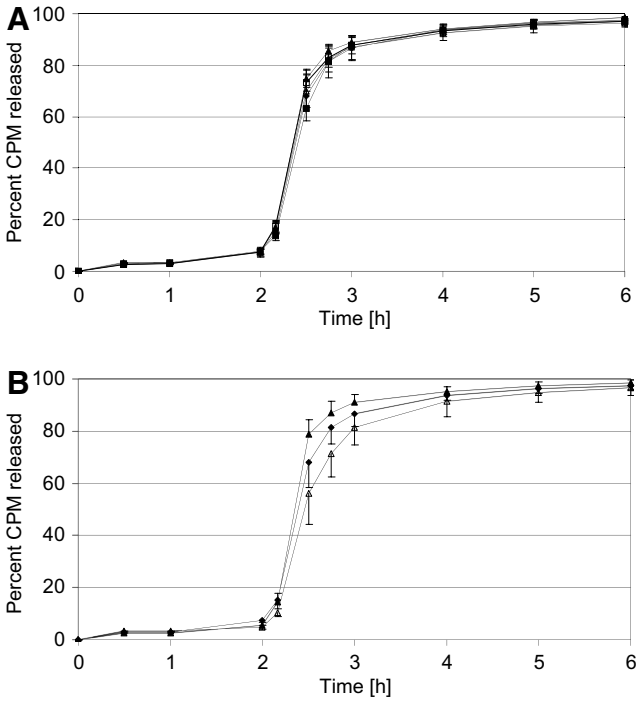

Fig. 8. Twelve week stability of CPM tablets powder-coated with pre-plasticized Eudragit® L 100-55 containing 30% TEC based on the polymer weight using USP 29 apparatus 2. Dissolution in 900 mL of 0.1 N HCl for 2 h followed by 4 h in 900 mL, pH 6.8, 50 mM phosphate buffer at 37 °C and 50 rpm. Polymer weight gain: 10%. ◆, initial. ■, 1 week. ▲, 4 weeks. □, 8 weeks. Δ, 12 weeks (standard deviation, $n = 6 \times 6$ tablets/vessel). (A) 25 °C/60% RH. (B) 40 °C/75% RH.

As shown in Fig. 8, CPM powder-coated tablets demonstrated excellent stability over 12 weeks at 25 °C/60% RH with no detectable difference in the drug release profiles. The drug release rate from powder-coated tablets stored at 40 °C/75% RH was characterized by an initial increase over 4 weeks followed by a slight decrease after 8 and 12 weeks. The drug release profiles that were obtained from tablets stored at 40 °C/75% RH after one and eight weeks were excluded from Fig. 8(B) for better clarification between the single profile curves. Both deleted graphs were similar to the initial drug release curve. This aging phenomenon was attributed to the additional plasticization of the Eudragit® L 100-55 by PEG 3350 during storage. The glass transition temperature of the coating powder containing 30% TEC based on the polymer weight and 10% PEG based on the ground extrudate was approximately 28 °C as shown in Table 2. This temperature was below the storage temperature. The changes in dissolution rate during storage can be explained by changes in the permeability of the coating that resulted from increased molecular mobility.

5. Conclusions

Dry powder coating, a completely liquid free process, was demonstrated to be an efficient method to enterically coat tablets with Eudragit® L 100-55. Unlike aqueous coating, powder coating minimized partitioning of the drug into the film coating during the coating process. The choice of primer significantly impacted the film formation and drug release properties. PEG 3350 was determined to be an ideal priming material for powder coating of tablets with pre-plasticized Eudragit® L 100-55. Curing is a necessary step to ensure the complete film formation and drug release stability. The drug release properties of powder-coated tablets were dependent on the curing time, coating level and plasticizer content. Higher TEC levels in the acrylic polymer reduced the polymer weight gain required to control the drug release in 0.1 N HCl. The drug release rate from powder-coated theophylline tablets was controlled with slightly lower coating levels. The stability of the powder-coated CPM tablets was confirmed at 25 °C/60% RH over a storage time of 12 weeks.

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