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Influence of polymeric subcoats on the drug release properties of tablets powder-coated with pre-plasticized Eudragit® L 100-55

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ABSTRACT

The aim of the study was to investigate the properties of sodium valproate tablets that were dry powder-coated with pre-plasticized Eudragit® L 100-55. Polyethylene glycol 3350 (PEG 3350) was used as primer to facilitate initial coating powder adhesion. Solubility parameters were employed to determine the wetting properties of the PEG 3350 primer. Additional PEG 3350 within the powder coating formulation was required to enable powder adhesion to the tablet cores. The application of a subcoat of either Eudragit® E PO or Eudragit® RL PO facilitated adhesion of the enteric polymer to the tablet cores and reduced the amount PEG 3350 required in the coating formulation. Since reduction of the PEG 3350 content produced less water-vapor permeable films, the enteric coating level necessary to control the drug release was decreased. PEG 3350 and Methocel® K4M were incorporated in both Eudragit® E PO and Eudragit® RL PO subcoating formulations as pore forming agents. The influence of the pore forming excipients on physicochemical properties of free powder-cast films was investigated. The miscibility of the PEG 3350 and Methocel® K4M in the film coating was correlated with their ability to function as pore forming agent.

1. Introduction

Dry powder coating of pharmaceutical dosage forms was first investigated by Obara et al. in the late 1990s (Obara et al., 1999). The process was later modified by Kablitz et al. (2006) and Pearnchob and Bodmeier (2003). Recently, a new liquid free coating technique for tablets was developed by Cerea et al. and Zheng et al. using the acrylic polymers Eudragit® E PO and mixtures of Eudragit® RL PO and RS PO (Cerea et al., 2004; Zheng et al., 2004). The process did not require the use of organic solvents or water. Powder coating is a suitable technique for water-sensitive drugs and can reduce interactions between the API and functional polymers in aqueous coating applications. Powder coating has been shown to significantly reduce processing times (Pearnchob and Bodmeier, 2003), prevent aging of polymer films (Zheng et al., 2004), and reduce the migration of drugs into functional coatings (Sauer et al., 2007).

Sodium valproate is a very water-soluble, heat-stable, deliquescent salt with a p*K*a of 4.8 (Chang, 1979). It has been reported that sodium valproate tablets and pellets required high coating levels of an enteric polymer, even with the application of either a Methocel® E5 or Opadry® AMB subcoat (Bruce et al., 2003b). Several mechanisms have been proposed in the literature to explain why cores containing highly soluble model drugs require high coating levels of a functional polymer to control the drug release. In aqueous coating operations, highly water-soluble active pharmaceutical ingredients (APIs) can dissolve and partition into the film coating, which may compromise film integrity during dissolution (Ghebre-Sellassie et al., 1987). In this case, an elevated polymer weight gain is required to control the drug release. Other researchers have found that high levels of an enteric polymer are necessary to delay drug release of an alkaline API in acidic media (Dangel et al., 2000; Deasy and O'Connell, 1984). The presence of a weak base in the core formulation of an enteric-coated dosage form was shown to cause high absorption of simulated gastric fluid and premature drug release at low coating levels (Dangel et al., 2000). Dissociation of the salts at the interface between enteric coating and core due to water penetration through the enteric coating may affect the microenvironmental pH. As a result, active pharmaceutical ingredients or excipients based of a weak acid and a strong base may decrease the stability of the enteric coating in gastric fluid and subcoatings were recommended to prevent this phenomenon (Dittgen et al., 1997).

Subcoating materials have been widely used in combination with enteric polymers to promote adhesion of the functional polymer (Obara et al., 1999), function as a moisture barrier (Felton et al., 1995), and prevent interactions between an API and enteric coating (Bozdag et al., 1999). Other researchers described an increased gastric resistance of enteric-coated dosage forms in the presence

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of a polymeric subcoat (Bruce et al., 2003a; Crotts et al., 2001; Guo et al., 2002). However, the use of powder-layered subcoats has not been described in the literature.

Eudragit® L 100-55 is an anionic copolymer based on methacrylic acid and ethyl acrylate. The ratio of free carboxyl groups to the ester groups is approximately 1:1. The carboxylic groups ionize in aqueous media at pH 5.5 and above. Eudragit® E PO is a copolymer of dimethylaminoethyl methacrylate and neutral methacrylic esters, and, due to its solubility below pH 5.5, is mainly used for taste-masking or moisture protection. Eudragit® RL PO is a water-insoluble polymer based on ethyl acrylate, methyl methacrylate, and trimethylammonioethyl methacrylate chloride in a ratio of 1:2:0.2 and used for sustained release applications. Eudragit® L 100-55, Eudragit® E PO, and Eudragit® RL PO have been used in previous studies of dry powder coating applications (Cerea et al., 2004; Sauer et al., 2007; Zheng et al., 2004).

The objective was to study the influence of the subcoating materials Eudragit® E PO and Eudragit® RL PO on the level of enteric coating required for enteric protection. Both polymers have not been investigated as subcoating materials for Eudragit® L 100-55 in dry-coating applications. The effect of pore forming agents on the permeability and thermal properties of the polymeric subcoats was also studied.

2. Materials and methods

2.1. Materials

Eudragit® L 100-55, Eudragit® RL PO, and Eudragit® E PO were donated by Degussa Corp. (Piscataway, NJ). Sodium valproate USP/NF and magnesium stearate NF were obtained from Spectrum Chemical Mfg. Corp. (Gardena, CA). Triethyl citrate NF (TEC) was supplied by Morflex Inc. (Greensboro, NC). Talc USP (Imperial 500) was donated by Luzenac America Inc. (Centennial, CO). Polyethylene glycol (PEG) 3350 NF and hydroxypropyl methylcellulose (Methocel® K4M) were supplied by The Dow Chemical Company (Midland, MI). Microcrystalline cellulose (MCC, Avicel® PH-200 and 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).

2.2. Methods

2.2.1. Coating powder preparation

Eudragit® L 100-55 and Eudragit® RL PO were pre-plasticized by hot melt extrusion using the method described by Zheng et al. for mixtures of Eudragit® RS and Eudragit® RL PO (Zheng et al., 2004). The process was later adapted for the pre-plasticization of Eudragit® L 100-55 (Sauer et al., 2007). Prior to extrusion, both Eudragit® L 100-55 and Eudragit® RL PO were combined with TEC in a high shear mixer (RSI 3VG, Robot Coupe Scientific-Industrial Division, Joliet, IL). For the extrusion of Eudragit® L 100-55 containing 30% TEC based on the polymer weight, the temperature zones of the single screw extruder (Randcastle Model RC 0750, Cedar Grove, NJ) were set to: zone 1 = 80 °C, zone 2 = 110 °C, zone 3 = 115 °C, die = 120 °C. Eudragit® RL PO with a TEC content of 10% based on the polymer weight was extruded at slightly different temperatures: zone 1 = 80 °C, zone 2 = 105 °C, zone 3 = 115 °C, die = 125 °C. For both extrusion processes, a cylindrical die with an inner diameter of 6 mm was used. A Randcastle RCP-2.0 pelletizer was employed to cut the extrudate into pellets which were subsequently ground into a fine powder using a cryogenic milling process (CF Mikro-Bantam Cryogenic Grinder, Micron Powder Systems, Summit, NJ). The ground extrudate was sieved using mechanical shaking for 15 min to exclude the particle size fractions below 200 and above 100 mesh (below 75 μm and above 150 μm, respectively) as recommended in previous publications (Sauer et al., 2007; Zheng et al., 2004). Eudragit® E PO coating formulations did not require the addition of a plasticizer.

2.2.2. Tablet preparation

Sodium valproate (15%), Avicel® PH-200 (81.25%), and Kollidon® 30 (3%) were blended in a Yoke V-shape blender (Patterson-Kelley Co., East Stroudsburg, PA) for 15 min. The formulation was mixed for an additional 5 min after the addition of the magnesium stearate (0.5%) and colloidal silicon dioxide (0.25%). Tablets with a weight of 74.8 ± 0.3 mg (n = 6, standard deviation) were directly compressed on a single stage press (Stokes F press, Bristol, PA) using deep concave 5 mm punches. A breaking load of 74.5 ± 5.3 N (n = 6, standard deviation) was measured using a WTP-3 tablet tester (Heberlein & Co. AG, Wattwil, Switzerland). The disintegration time was determined to be 22 min, according to USP 29 using a USP Disintegration Tester (VanKel Industries Inc., Chatham, NJ).

2.2.3. Powder coating process

A modified laboratory scale spheronizer (Model 120, G.B. Caleva, Dorset, UK) was used for powder coating of 40 g batches of tablets, as previously described in the literature (Cerea et al., 2004; Sauer et al., 2007; Zheng et al., 2004). The processing conditions varied according to the coating formulation and are presented in Table 1. For formulation A, PEG 3350 was not included in the formulation but fed separately onto the tablet cores. In contrast, formulation B required pre-blending with PEG 3350 and the mixture was fed into the spheronizer. Both formulations contained 10% talc based on the weight of the ground extrudate. Eudragit® E PO and pre-plasticized Eudragit® RL PO were employed as subcoating materials, while pre-plasticized Eudragit® L 100-55 was used as the enteric polymer. The temperature of the coating bed was monitored using a Fluke 61 Infrared Thermometer (Fluke Corporation, Everett, WA). Talc was added as an anti-tack agent at 10% of the ground extrudate weight. The addition of talc considerably affected the adhesion of Eudragit® E PO onto the tablet cores and was thus excluded in formulations of this polymer. Methocel® K4M and PEG 3350 were each added to the coating powder as pore forming agents at 10% of the ground extrudate weight and the mixture was applied to the tablet cores. It was necessary to adjust the feeding rate of the coating powder onto the tablets cores according to the ability of the coating powder to adhere, which decreased with increasing coating levels. Following the application of the molten primer PEG 3350, the polymer mixture adhered well and was therefore applied onto the tablet cores at a feeding rate of about 3 g/min until a polymer weight gain of 5% was obtained. The powder feeding rate was then reduced to approximately 0.5 g/min. Eudragit® E PO formulations did not require a primer and the coating powder was fed at a rate of approximately 0.5 g/min throughout the process. Since all coating formulations exhibited poor flow properties, the powder mixtures were manually fed onto the tablet surfaces using a spatula. After completion of the coating process, tablets were subsequently cured either in the operating spheronizer or in a static oven on Teflon trays. To prevent sticking during storage 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.

2.2.4. Film preparation

Powder-cast films were prepared by placing the ground extrudate into Teflon coated aluminum dishes with a Teflon coated lid. The Eudragit® L 100-55 films were stored in a static oven at 80 °C for 3 h and 24 h at 60 °C to simulate the coating and the curing process.

Table 1
Processing parameters and formulations for the powder-coating of sodium valproate tablets.

	Formulation	Primer	Coating additives	Coating temperature	Rotation speed
Eudragit® L 100-55	A	3% PEG^{++}	10% talc^{+}	70–75 °C	220 rpm
	B		10% talc^{+}, 10% PEG^{+}		
Eudragit® E PO	C	N/A	N/A	55–60 °C	170 rpm
	D		10% PEG^{+}		
	E		10% K4M^{+}		
Eudragit® RL PO	F	3% PEG^{++}	10% talc^{+}	60–65 °C	220 rpm
	G		10% talc^{+}, 10% PEG^{+}		
	H		10% talc^{+}, 10% K4M^{+}		

+: based on the weight of the ground extrudate; ++: weight gain, based on tablet weight.

Eudragit® E PO and Eudragit® RL PO films required higher curing temperatures and were cured at 80 °C for 24 h also in a static oven. A compression force of 9.8 N was applied on 22 cm^2 of film during the curing process to facilitate polymer particle fusion and to reduce the formation of voids in the film.

2.2.5. Drug release study and quantitative TEC analysis

The dissolution test was performed according to the USP Drug Release Standard for Enteric Coated Articles Method A which was recently proven to generate results that are comparable with data that were obtained using Method B (Miller et al., 2007). Following dissolution in 750 mL 0.1N HCl for 2 h, 250 mL of 0.2 M tribasic sodium phosphate solution were added to the dissolution vessel. After the dissolution medium was adjusted to pH 6.8 ± 0.05, the test was continued for two additional hours. The dissolution media were maintained at 37 °C and agitated at 50 rpm using a USP 29 Apparatus 2 (Vankel VK 7000; VanKel Industries Inc., Cary, NC). Six tablets were placed into each of either three or six dissolution vessels, respectively ($n = 3 \times 6$ tablets/vessel or $n = 6 \times 6$ tablets/vessel). Samples were withdrawn by an autosampler over the 4-h period (Vankel VK 8000; VanKel Industries Inc., Cary, NC). All samples were filtered using 0.45 μm nylon filters. A HPLC system with a photodiode array detector (Model 996, Waters, Milford, MA) at a wavelength of 210 nm was employed to analyze the sodium valproate concentration in the dissolution samples. The HPLC method was adapted from a method described by Bruce et al. (2003b). The 50 μL samples were injected using an autosampler (Model 717plus). Data collection and analysis were performed using Empower® Version 5.0 software. A Phenomenex Luna C18(2), 3 μm, 150 mm × 4.6 mm column (Phenomenex Inc., Torrance, CA) was used at a column temperature of 30 ± 2 °C. The mobile phase contained a mixture of sodium phosphate monobasic and acetonitrile in a volume ratio of 63:37. The pH of the mobile phase was adjusted to 2.3 using phosphoric acid. A flow rate of 1 mL/min resulted in a retention time of 18 min for sodium valproate. Linearity was demonstrated from 4 to 100 μg/mL ($R^2 > 0.999$).

The TEC content of the coating powder and powder-cast films was determined with the same equipment used in the quantitative analysis of sodium valproate according to a method previously described in the literature at a detection wavelength of 210 nm (Sauer et al., 2007). 500 mg of the coating powder or powder-cast films were dissolved in 50 mM pH 7.4 buffer and then diluted 1:2 with 50 mM pH 2.5 phosphate buffer to precipitate the polymer ($n = 3$). The samples were then filtered using 0.2 μm nylon filters to remove the polymer from solution. The injection volume was set to 50 μL. 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 and pH 2.5 10 mM phosphate buffer in a volume ratio 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 ($R^2 > 0.999$).

2.2.6. Water-vapor permeability of cast films

The influence of PEG 3350 on the water-vapor permeability of the cast films was determined by casting polymeric films with different PEG 3350 content from an organic solution (ethanol, water 90:10). The water-vapor permeability was tested according to the Desiccant Method of the ASTM guideline E 96/E 96M (ASTM, 2005; Zheng et al., 2005). The average thickness of the film was determined by measuring six points along the film circumference using a micrometer. The film specimen was mounted to the open mouth of an aluminum cup with an inner diameter of 4 cm and a depth of 3 cm that was filled with 20 g Drierite® desiccant. The cups were accurately weighed and stored in a chamber at 85% RH using a saturated potassium chloride solution at 24 °C. The cups were weighed again after 1, 2, and 3 days to determine water uptake. The water-vapor transmission rate (WVT) and permeability (P) were calculated using the following equations (ASTM, 2005),

$$\mathrm{WVT} = \frac{G/t}{A} \quad (1)$$

$$P = \left(\frac{\mathrm{WVT}}{S}\right) \times (R_1 - R_2) \times d \quad (2)$$

where G is the weight change, t the time during which G occurred, A the test area (cup mouth area), S the saturation vapor pressure at test temperature, R_1 the relative humidity in the test chamber, R_2 the relative humidity inside the cup (0% RH for the desiccant method) and d is the thickness of the film. The value for the vapor pressure of a saturated potassium chloride solution (2546 Pa at 24 °C) was obtained from the literature (Apelblat, 1998).

2.2.7. Differential scanning calorimetry

Modulated differential scanning calorimetry (MDSC) was employed to investigate the thermal properties of polymeric films and melt extrudates using a Thermal Advantage Model 2920 (TA Instruments, New Castle, DE) equipped with Universal Analysis 2000 software. The samples were sealed in aluminum pans (Kit 0219-0041, PerkinElmer Instruments, Norwalk, CT). The flow rate of the ultrahigh pure nitrogen purge gas was 150 mL/min. The temperature ramp rate was set to 3 °C/min to characterize the interactions occurring between subcoat and enteric coat or 5 °C/min at a modulation rate of ±1.00 °C every 60 s to study the thermal properties of the subcoating materials containing pore formers. The inflection glass transition temperatures (T_g) were determined using the reverse heat flow of the second heating cycle. The heat of fusion (Q_f) was determined by linear peak integration from 40 to 70 °C. The first heating cycle was used for PEG 3350, the second heating cycle was used for the powder-cast polymer films.

2.2.8. Mechanical testing

The mechanical testing of powder-cast Eudragit® L 100-55 films containing 10% PEG 3350 based on the ground extrudate was performed using a puncture test that was adapted from a method previously described by Bodmeier and Paeratakul (1993). A Chatillon Universal Tension/Compression Tester Model TCD-200 (Ametek, Largo, FL) was used with a DFGS 50 digital force gauge to determine the puncture strength and elongation of powder-cast polymer films as a function of storage time. The film specimen was mounted onto the open mouth of a film holder that consisted of an aluminum cup with an inner diameter of 15 mm and an upper mounting plate. The puncture probe (length, 31 mm; diameter, 6 mm; dome shaped probe end) was lowered toward the center of the film specimen at a crosshead speed of 10 mm/min. The load (N) and deflection (mm) at maximum were used to determine the maximum puncture strength (MPa) and % elongation (puncture strength = F/A_{cs}, where F is the load and A_{cs} is the cross-sectional area in the path of the cylindrical opening; % elongation = $[\{(R^2 + D^2)^{1/2} - R\}/R] \times 100$, where R is the radius of the film and D is the deflection of the probe). SPSS Version 15.0 was used for the statistical analysis of the data.

2.2.9. Scanning electron microscopy

Scanning electron microscopy (SEM) was used to examine the morphology of the surface of powder-cast films and tablet cores at 10 kV and 20 mA (Model S-4500 FE, Hitachi, London, UK). The samples were sputter coated with platinum/palladium (80:20) using a Cressington Sputter Coater 208 HR equipped with a Thickness Controller MTM 20 (Cressington Scientific Instruments Ltd., Watford, UK) at 20 mA until a coating thickness of 15 nm was obtained.

2.2.10. ^1H and ^{13}C Nuclear magnetic resonance spectroscopy and Fourier transform infrared spectroscopy

^1H and ^{13}C Nuclear magnetic resonance spectroscopy (^1H and ^{13}C NMR) as well as Fourier transform infrared spectroscopy (FTIR) were performed to investigate possible interactions between sodium valproate and PEG 3350 after heating at 80 °C for 3 h followed by 24 h at 60 °C to simulate the temperatures occurring during the coating and curing processes. For NMR analysis, 10 mg of sample was dissolved in deuterium dioxide containing 3-(trimethylsilyl)-propionic acid-D4, sodium salt (TSP) as the internal standard. The NMR spectra were obtained using a Varian Inova 500 (Varian Inc., Palo Alto, CA). Prior to FTIR analysis, the single components and the heat-treated physical mixture were compressed with potassium bromide into pellets under vacuum using a compression pressure of 10 tons. A Nicolet Magna IR-560 FT-IR spectrometer was used to acquire the transmittance spectra of the materials.

3. Results and discussion

3.1. Surface properties of sodium valproate tablets

Interfacial properties of polymeric coating materials and the substrate surface such as interfacial tension and wetting have been described as key factors for polymer adhesion (Grundke et al., 1996). Obara et al. demonstrated that the addition of acetylated monoglycerides to the plasticizer significantly improved coating efficiency compared to the plasticizer alone due to a reduced contact angle for the polymer (Obara et al., 1999). Zheng et al. reported that the application of a molten layer of cetyl alcohol enhanced the adhesion of pre-plasticized Eudragit® RS/RL PO mixtures onto the surface of theophylline tablets (Zheng et al., 2004). A PEG 3350 primer and the additional incorporation of PEG 3350 into the coating powder formulation as a low melting, hydrophilic material was necessary to facilitate adhesion of pre-plastiziced Eudragit® L 100-55 (Sauer et al., 2007).

In the current study, the coating process used for chlorpheniramine maleate (CPM) tablets with pre-plasticized Eudragit® L 100-55 (Sauer et al., 2007) did not result in a continuous polymer layer. Insufficient sticking of pre-plasticized Eudragit® L 100-55 to the sodium valproate containing cores was initially thought to be due to less efficient spreading of the molten PEG 3350 primer over microcrystalline cellulose (MCC) compared to more hydrophilic diluents such as lactose. Upon further study, it was shown that coating powder can be successfully applied to CPM tablets containing solely MCC as filler, proving MCC is not limiting adhesion (data not shown).

To exclude the possibility of chemical binding of PEG 3350 and sodium valproate at elevated temperatures, ^1H and ^{13}C NMR as well as FTIR spectroscopy were performed. Both NMR and FTIR spectra of the single components and the annealed physical mixture were identical with no detectable new peaks or peak shifts occurring (data not shown). Consequently, binding interactions of PEG 3350 and sodium valproate were not considered as a cause for the poor coating powder adhesion.

3.2. Prediction of interaction parameters based on solubility parameters

The spreading of the PEG 3350 priming layer on the tablet cores was described to be crucial in the powder coating process (Sauer et al., 2007). The molten priming layer of PEG 3350 promoted liquid bridge adhesion of the polymer particles (Kendall, 2001). The Laplace pressure in the interpenetrating PEG 3350 melt acted on polymer particle and tablet core surfaces, pulling them together (Israelachvili, 1992). Liquid bridges fill gaps between particles and reduce the surface roughness of the tablet core such that capillary attraction, surface tension and viscous resistance of the molten PEG 3350 inhibit rapid separation of the coating powder from the tablet surface (Hotta et al., 1974; McFarlane and Tabor, 1950).

Solubility parameters of materials have been widely used to predict interaction trends between APIs and pharmaceutical excipients (Barra et al., 1996; Rowe, 1988a,b). The method which is based on the Lennard–Jones pair potential function was initially introduced for pharmaceutical applications by Rowe to determine cohesive and adhesive properties using solubility parameters (δ) (Gardon, 1977; Rowe, 1988a,b). The relative strength of interaction (σ) was determined using the following equations where the interaction parameter (Φ) was calculated using the harmonic mean equation derived by Wu (1973):

$$\sigma_{AA} = 0.25\delta_A^2 \quad (3)$$

$$\sigma_{AB} = 0.25\Phi\delta_A\delta_B \quad (4)$$

Eq. (3) was employed to determine the cohesive strength of interaction of PEG 3350 whereas Eq. (4) was used to calculate the adhesive strength of interaction (Rowe, 1988a,b). The Hoftyzer, van Krevelen 3D solubility parameters and the corresponding interaction parameter for theophylline, CPM, valproic acid, and PEG 3350 are presented in Table 2. The solubility parameters were determined using Molecular Modeling Pro™ software. Since it is not possible to calculate the solubility parameters of salts using the group contribution method, the solubility parameter of valproic acid was used in the calculations. According to Rowe, the adhesive strength between materials A and B needs to be larger than the cohesive strength of interaction of B in order to facilitate spreading of substance B over substance A. The calculated values in Table 2 suggest that the spreading of PEG 3350 over dosage forms containing valproic acid is not favored, whereas CPM and theophylline

Table 2
Hoftyzer, van Krevelen 3D solubility parameter and interaction parameter of theophylline, chlorpheniramine maleate (CPM), valproic acid, and PEG 3350. D, P, and H bonding correspond to the dispersive, polar, and hydrogen bonding component of the solubility parameter, respectively.

	PEG3350	Valproic acid	CPM	Theophylline
Hoftyzer, van Krevelen 3D solubility parameter $(J/cm^3)^{0.5}$				
D	17.4	17.1	20.8	24.6
P	1.2	2.8	3.8	16.2
H bonding	9.3	8.1	8.8	13.6
V_m (cm^3/mol)	2803.4	152.3	309.4	109.1
Sol parameter, δ	19.8	19.1	22.9	32.4
Φ with PEG		0.6	0.9	0.9
Strength of interaction, σ (J/cm^3)				
Cohesive (PEG)	98.3	98.3	98.3	98.3
Adhesive (A-B)		59.2	102.9	152.7

promote spreading of the priming agent. The latter two APIs have been previously used in dry powder applications (Sauer et al., 2007).

3.3. Powder coating process

In a method previously used to powder coat with Eudragit® L 100-55, PEG 3350 was incorporated into the coating powder (Sauer et al., 2007). In this study, to overcome adhesion difficulties, the PEG 3350 concentration was increased in the coating formulation, forcing the primer to spread over the tablet cores. Pre-plasticized Eudragit® L 100-55 and PEG 3350 were fed separately onto the sodium valproate containing tablet cores. A modified spheronizer was used for the process as previously described (Cerea et al., 2004; Sauer et al., 2007; Zheng et al., 2004). First, a PEG 3350 priming layer was applied onto the tablet cores with a weight gain of 3% based on the tablet weight. Then the pre-plasticized Eudragit® L 100-55 was blended with talc as an anti-tack agent and fed onto the tablet cores at a rate of approximately 3 g/min in alternation with PEG 3350. High PEG 3350 levels were employed to overcome the spreading difficulties of PEG 3350. The advantage of this modified dry powder coating technique is the high powder feeding rate throughout the coating process.

The drug release profiles of powder-coated tablets that were prepared using the modified method are presented in Fig. 1. A high level of enteric polymer was required to prevent drug release in acidic media. Polymer weight gains up to 20% resulted in a drug release of more than 10% after 2 h in gastric conditions. A polymer

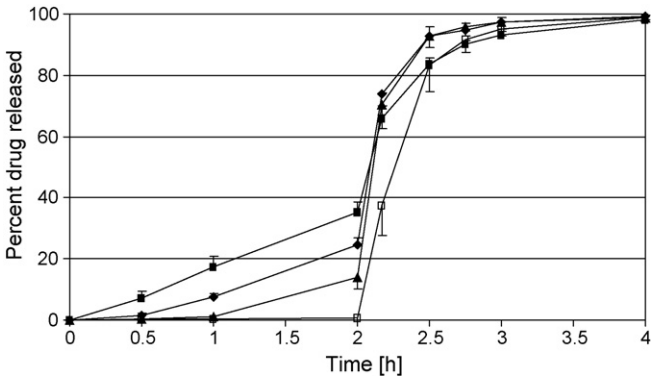

Fig. 1. Influence of coating level on the release of sodium valproate from tablets powder-coated with pre-plasticized Eudragit® L 100-55 containing 30% TEC using USP 29 apparatus 2. Dissolution in 750 mL of 0.1N HCl for 2 h followed by 2 h in 1000 mL pH 6.8 50 mM phosphate buffer after pH adjustment at 37 °C and 50 rpm. (■) 10% polymer weight gain; (♦) 15% polymer weight gain; (▲) 20% polymer weight gain; (□) 28% polymer weight gain (standard deviation, $n = 6 \times 6$ tablets/vessel).

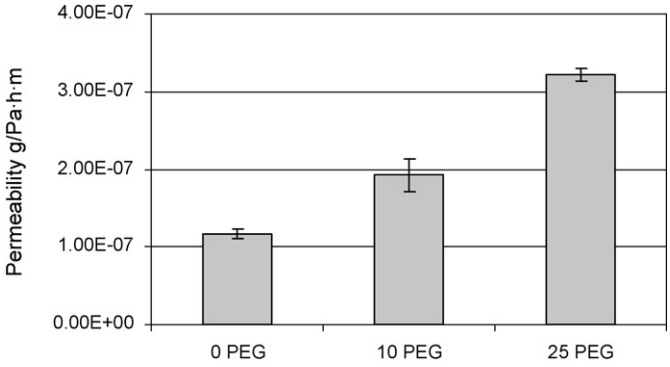

Fig. 2. Influence of PEG 3350 content on the water-vapor permeability of Eudragit® L 100-55 films containing 30% TEC (standard deviation, $n = 3$).

weight gain of 28% Eudragit® L 100-55 delayed drug release in acid and allowed a fast release pH 6.8 buffer.

3.4. Water-vapor permeability of Eudragit® L 100-55 films containing PEG 3350

The PEG 3350 level in the film coating for the 10, 15, 20, and 28% polymer weight gain were approximately 41, 39, 32, and 26% based on the weight of the ground pre-plasticized Eudragit® L 100-55, respectively, compared to 10% that was used in the previous study for chlorpheniramine maleate tablets (Sauer et al., 2007). The PEG level was calculated based on the polymer weight gain and the amount of PEG 3350 applied to the tablet cores. The PEG 3350 content decreased in the polymer film with increasing coating levels due to an increased capacity for the Eudragit® L 100-55/talc mixture to adhere. This phenomenon was presumably caused by an improved ratio between particle size of the coating powder and roughness spacing of the coated tablet surface. The high PEG 3350 levels caused an increased water-vapor permeability of the functional coating and required high coating levels as shown in Fig. 2. The addition of 10% PEG 3350 to the film coating approximately doubled; while the addition of 25% PEG 3350 almost tripled the permeability to water-vapor compared to Eudragit® L 100-55 films with no PEG 3350 due to an increase in the hydrophilicity of the polymer film. PEG 3350 is commonly used as a pore forming agent in coating formulations to increase the drug release (Hennig and Kala, 1987; Jenquin et al., 1992). The increase in water-vapor permeability was associated with a higher uptake of water into the tablet core. Since the permeation of dissolution media through the functional coating causes increased drug dissolution and diffusion as described by Ozturk et al. (1988), highly water permeable coating formulations require higher levels of enteric polymer in order to delay drug release in acid.

3.5. Storage stability of powder-coated tablets

The physical stability of the powder-coated tablets (28% polymer weight gain) was investigated during storage at either 25 °C/60% RH or 40 °C/75% RH for 12 weeks. After curing for 6 h in the spheronizer at 60 °C and 170 rpm, an overcoat of 2% talc, based on the final tablet weight, was applied onto the tumbling tablets. The tablets were sealed in HDPE containers with desiccant. Prior to dissolution testing, all samples were equilibrated to ambient temperature in the sealed container for 24 h to exclude the influence of the tablet temperature on dissolution. The drug release profiles of the enteric-coated sodium valproate tablets are presented in Fig. 3. The powder-coated tablets exhibited excellent storage stability at 25 °C/60% RH with no detectable changes in drug

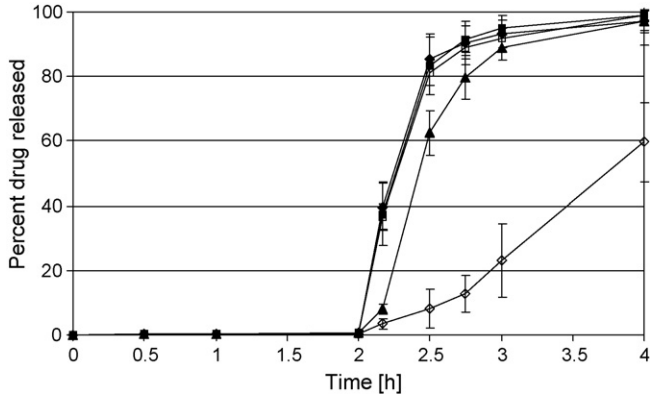

Fig. 3. Four and 12 weeks stability of sodium valproate tablets powder-coated with pre-plasticized Eudragit® L 100-55 containing 30% TEC based on the polymer weight using USP 29 apparatus 2. Dissolution in 750 mL of 0.1N HCl for 2 h followed by 2 h in 1000 mL pH 6.8 50 mM phosphate buffer after pH adjustment at 37 °C and 50 rpm. Polymer weight gain: 28%. (■) Initial; (♦) 4 weeks at 25 °C/60% RH; (▲) 4 weeks at 40 °C/75% RH; (□) 12 weeks at 25 °C/60% RH; (◊) 12 weeks at 40 °C/75% RH (standard deviation, $n = 6 \times 6$ tablets/vessel).

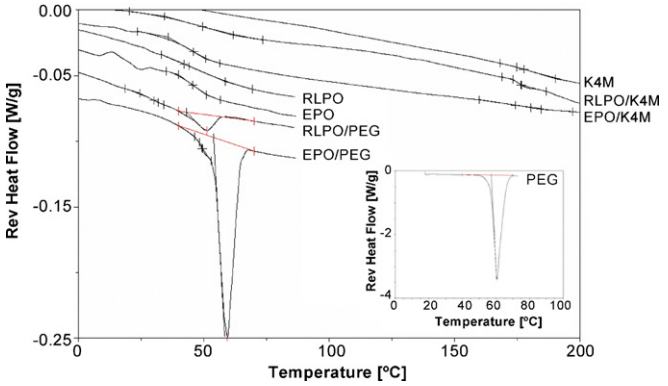

Fig. 5. DSC thermograms of Eudragit® E PO and Eudragit® RL PO, preplasticized with 10% TEC based on the polymer weight containing either PEG 3350 or Methocel® K4M in a 10:1 ratio.

release. In contrast, drug release decreased and became less consistent with a higher standard deviation over time when stored at 40 °C/75% RH.

PEG 3350 is a known plasticizer for Eudragit® L 100-55, therefore, while it functions as a primer, it would also further plasticize the coating polymer during storage. DSC analysis revealed that the T_g of pre-plasticized Eudragit® L 100-55 containing an additional 25% PEG decreased to 13.9 ± 3.8 °C (standard deviation, $n = 3$). The low T_g of the coating formulation was connected with a high molecular mobility of the polymer that resulted in physical instability of the film coating.

3.6. Properties of subcoating materials

In order to avoid large PEG 3350 levels in the Eudragit® L 100-55 coating that required high coating levels, different subcoating materials were investigated. Eudragit® E PO and Eudragit® RL PO were chosen as potential subcoating materials since both polymers were successfully used in previous dry-powder coating applications (Cerea et al., 2004; Zheng et al., 2004). Due to their solubility properties, both polymers would delay drug release in pH 6.8 buffer, a characteristic that is not desired for enteric-coated dosage forms. Consequently, pore forming agents were added to the subcoating to increase water influx and hence drug dissolution in the buffer stage of the enteric test. Methocel® K4M and PEG 3350 were chosen as possible pore formers.

To better understand the influence of pore forming agents on the release of sodium valproate, polymer films were powder cast, cured, and the properties were investigated using dissolution testing, SEM, and DSC. The SEM micrographs of free films before and after 30 min in pH 6.8 buffer are presented in Fig. 4. Both the incorporation of PEG 3350 and Methocel® K4M into Eudragit® E PO films resulted in pore formation after dissolution in pH 6.8 buffer. Since PEG 3350 has a melting point below the processing temperature, PEG 3350 containing films were characterized by numerous small pores while the dissolution of Methocel® K4M generated large openings within the Eudragit® E PO film. In contrast, the addition of PEG 3350 to Eudragit® RL PO did not produce any visible pores after 30 min in the dissolution media (pH 6.8 buffer). Only the combination of Eudragit® RL PO with Methocel® K4M resulted in pore formation after exposure to dissolution media.

Miscibility and compatibility of coating excipients with the functional polymer were shown to influence the permeability of film coatings (Zheng et al., 2005). To further investigate the miscibility of the pore forming agents in the film matrix, the powder-cast films were analyzed using DSC. Eudragit® E PO did not show miscibility with both PEG 3350 and Methocel® K4M. As a result, both materials act as pore former when combined with the polymer. The DSC profiles of the Eudragit® E PO films containing PEG 3350 showed a large endothermic peak due to the melting of the pore former (Fig. 5). The melting peak of PEG 3350 was broadened and

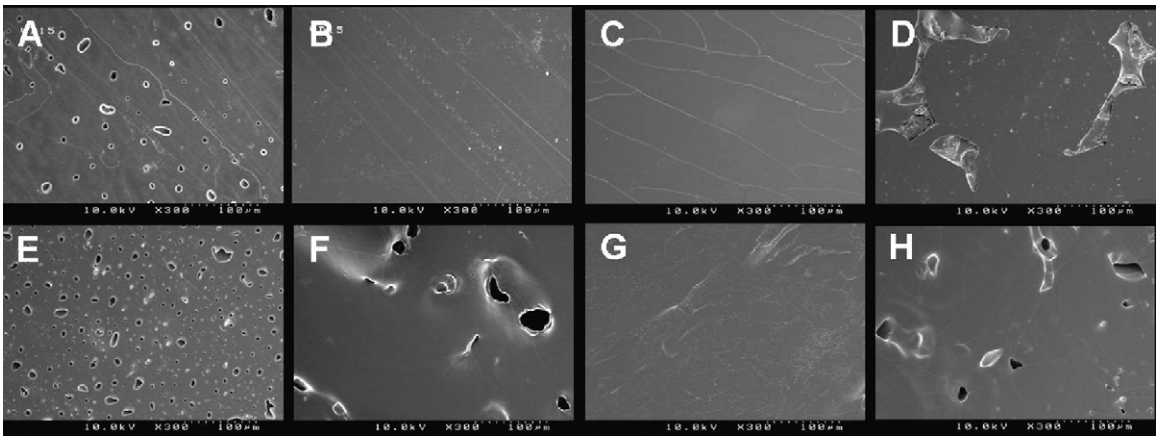

Fig. 4. Surface morphology of powder-cast polymer films before (A–D) and after dissolution in pH 6.8 buffer for 30 min (E–H). A and E: Eudragit® E PO/PEG 3350, ratio 10:1. B and F: Eudragit® E PO/Methocel® K4M, ratio 10:1. C and G: Eudragit® RL PO/PEG 3350, ratio 10:1. D and H: Eudragit® RL PO/Methocel® K4M, ratio 10:1.

slightly shifted from 60.5 ± 0.3 °C (standard deviation, $n = 3$) for bulk PEG 3350 to 55.3 ± 0.2 °C (standard deviation, $n = 3$) when incorporated into Eudragit® E PO. Q_f of PEG 3350 was slightly decreased (160.6 ± 5.8 J/g, standard deviation, $n = 3$) compared to Q_f of bulk PEG 3350 that was determined to be 196.6 ± 24.4 J/g (standard deviation, $n = 3$). PEG 3350 and Methocel® K4M did not produce a significant change in T_g (ANOVA, $p < 0.05$) of Eudragit® E PO (45.4 ± 2.0 °C, standard deviation, $n = 3$). Also the T_g of Methocel® K4M (179.5 ± 2.9 °C, standard deviation, $n = 3$) was not significantly influenced when combined with Eudragit® E PO.

In combination with Eudragit® RL PO, PEG 3350 demonstrated partial miscibility or was present in an amorphous state in the polymer film (Fig. 5). The melting point of PEG 3350 was shifted to 50.7 ± 1.2 °C (standard deviation, $n = 3$). Q_f of PEG 3350 in the polymer films was reduced to 10.0 ± 4.8 J/g (standard deviation, $n = 3$). The T_g of Eudragit® RL PO (pre-plasticized with 10% TEC based on the polymer weight) was slightly decreased from 42.1 ± 0.1 °C (standard deviation, $n = 3$) for the bulk polymer to 33.6 ± 5.9 °C (standard deviation, $n = 3$) when combined with PEG 3350. The miscibility of PEG 3350 in the acrylic polymer affected its function as pore former and improved film formation. DSC thermograms of Eudragit® RL PO films that contained Methocel® K4M showed two T_g and thus no miscibility. The T_g of Methocel® K4M did not change significantly whereas the T_g of Eudragit® RL PO increased to 50.2 ± 1.8 °C (standard deviation, $n = 3$) due to possible interactions of the plasticizer TEC with the hydrophilic pore former.

3.7. Properties of sub- and enteric-coated sodium valproate tablets

Two subcoating formulations at a 5% coating level were chosen for further investigation in an enteric powder-coating process: Eudragit® E PO containing PEG 3350, and pre-plasticized Eudragit® RL PO in combination with Methocel® K4M. In Fig. 6, the drug release profiles of sodium valproate tablets subcoated and subsequently enterically coated using a dry-powder coating technique are presented. Eudragit® E PO subcoated tablets were cured in a static oven at 80 °C for 12 h, while Eudragit® RL PO subcoated tablets were cured in the revolving spheronizer at 60 °C for 2 h prior to application of the enteric polymer. Curing of the Eudragit® E PO tablets in the spheronizer was not possible due to chipping of the functional coating. The Eudragit® L 100-55 film coating was applied using the same technique previously developed for the coating of CPM tablets (Sauer et al., 2007). The process involved the use of pre-plasticized (30% TEC) Eudragit® L 100-55 in combination with a PEG 3350 primer and the incorporation of a small amount of PEG 3350 into the coating formulation. The enteric-coated tablets were subsequently cured in the rotating spheronizer for 6 h.

A coating level of 20% Eudragit® L 100-55 was employed to control the drug release for all formulations. Both the Eudragit® E PO subcoating formulation with PEG 3350 and the Eudragit® RL PO composition with Methocel® K4M resulted in a delay of sodium valproate release in acid and a fast release in buffer. Both formulations passed the USP requirements for enteric-coated tablets when overcoated with adequate levels of Eudragit® L 100-55.

3.8. Stability of sub- and enteric-coated sodium valproate tablets

The physical stability of the sub- and enteric-coated sodium valproate tablets was investigated over 12 weeks at either 25 °C/60% RH or 40 °C/75% RH. Two different subcoating materials were investigated: Eudragit E PO containing PEG 3350 in a 10:1 ratio and Eudragit® RL PO containing Methocel® K4M in a 10:1 ratio. All investigated tablets were subcoated to a polymer weight gain of 5% and enteric-coated to a polymer weight gain of 20%. The tablets

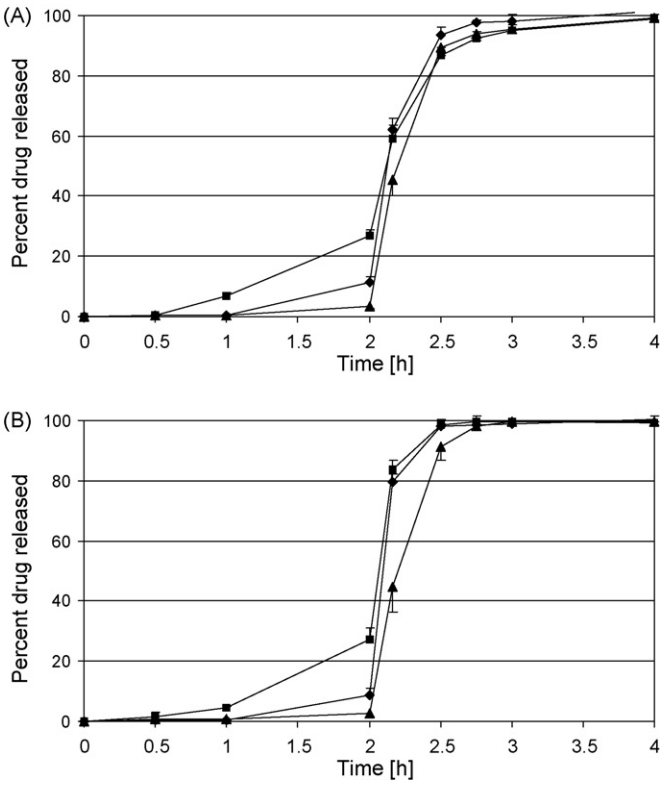

Fig. 6. Influence of coating level on the release of sodium valproate from tablets powder-coated with pre-plasticized Eudragit® L 100-55 containing 30% TEC using USP 29 apparatus 2. Dissolution in 750 mL of 0.1N HCl for 2 h followed by 2 h in 1000 mL pH 6.8 50 mM phosphate buffer after pH adjustment at 37 °C and 50 rpm. (■) 10% polymer weight gain; (♦) 15% polymer weight gain; (▲) 20% polymer weight gain (standard deviation, $n = 6 \times 6$ tablets/vessel). (A) 5% Eudragit® E PO subcoat containing 10% PEG 3350 based on the polymer weight. (B) 5% Eudragit® RL PO subcoat containing 10% Methocel® K4M based on the polymer weight.

were cured in the revolving spheronizer for 6 h before they were overcoated with 2% talc based on the weight of the coated tablets and sealed in HDPE containers with desiccant. Both formulations demonstrated excellent storage stability at 25 °C/60% RH over 12 weeks. The drug release of the Eudragit® E PO subcoat formulation decreased continuously at 40 °C/75% RH over 12 weeks while the drug release of the Eudragit® RL PO subcoat formulation stabilized after 4 weeks (Fig. 7).

Important factors that affect the storage stability of coated dosage forms are plasticizer content and change in the mechanical properties of the polymeric films. The TEC content in the coating powder and in powder-cast films initially and after 4 and 12 weeks is presented in Table 3. Free Eudragit® L 100-55 films containing 30% TEC based on the polymer weight were either stored at 25 °C/60% RH or at 40 °C/75% RH in sealed HDPE containers with desiccant to determine the plasticizer loss. The TEC content in the polymeric films did not change significantly at 25 °C/60% RH. There was a significant decrease in TEC concentration (ANOVA, Tukey's HSD, $p < 0.05$) after storage at 40 °C/75% RH for 4 and 12 weeks. It has been reported that the TEC concentration in polymer coatings decreased during drying processes at elevated temperatures (Thoma and Bechtold, 1999).

To investigate the change in mechanical properties, powder-cast Eudragit® L 100-55 films were stored in desiccators with desiccant to prevent bending of the films at 25 °C or 40 °C. The elongation increased over storage and was significant after 12 weeks of storage compared to the initial value for both storage temperatures (ANOVA, Tukey's HSD, $p < 0.05$). However, there was no significant

Table 3
TEC recovery of coating powder and 12 weeks stability of powder-cast films of Eudragit® L 100-55 pre-plasticized with 30% TEC containing 10% PEG 3350. *Statistical significant difference to initial value (ANOVA, Tukey's HSD, $p < 0.05$).

	Coating powder	Initial	Four weeks		Twelve weeks	
			25 °C	40 °C	25 °C	40 °C
TEC recovery (%)	100.4 ± 0.3	100.1 ± 0.3	99.4 ± 0.3	97.2 ± 0.7*	98.9 ± 0.1	95.3 ± 1.0*
Puncture strength (MPa)	N/A	1.18 ± 0.16	1.04 ± 0.28	1.20 ± 0.18	0.90 ± 0.10	1.05 ± 0.21
Elongation (%)	N/A	112.6 ± 9.6	140.3 ± 24.9	130.7 ± 16.4	164.0 ± 23.0*	160.8 ± 27.5*

difference in elongation between storage at 25 °C compared to storage at 40 °C after 12 weeks. The puncture strength did not change significantly at 25 °C and 40 °C over the investigated storage time (ANOVA, Tukey's HSD, $p < 0.05$).

Another theory included the aging of the subcoating layer and interactions occurring between subcoat and enteric coating. This hypothesis agreed with a previous study that investigated the physico-chemical stability of tablets that were powder-coated using pre-plasticized Eudragit® L 100-55 without prior application of subcoat (Sauer et al., 2007). The drug release fluctuated slightly around the initial profile, but did not drastically decrease over storage. Increased molecular mobility at high storage temperatures and additional plasticization by PEG 3350 were the suggested rationale (Sauer et al., 2007).

DSC was employed to investigate interactions between Eudragit® E PO and pre-plasticized Eudragit® L 100-55. The thermogram of a physical mixture of bulk Eudragit® E PO and pre-plasticized Eudragit® L 100-55 containing 30% TEC was characterized by two T_g, one at 24.9 ± 0.9 °C (standard deviation, $n = 3$) and one at 73.6 ± 7.7 °C (standard deviation, $n = 3$), as presented in Fig. 8. In contrast, the T_g of bulk Eudragit® E PO was 45.4 ± 2.0 °C (standard deviation, $n = 3$), and that of pre-plasticized Eudragit® L 100-55 containing 30% TEC was determined to be 61.3 ± 3.1 °C (Sauer et al., 2007). DSC analysis revealed that the T_g of Eudragit® E PO was lowered by approximately 20 °C, while the transition of Eudragit® L 100-55 was increased by approximately 10 °C. The same phenomenon was observed for physical mixtures of Eudragit® RL PO pre-plasticized with 10% TEC and Eudragit® L 100-55 pre-plasticized with 30% TEC. The DSC profile showed two T_g: one for Eudragit® RL PO at 29.5 ± 4.0 °C and one at 72.0 ± 3.5 °C for Eudragit® L 100-55. This is a shift of approximately 10 °C down for Eudragit® RL PO and 10 °C up for Eudragit® L100-55 compared to the pre-plasticized bulk polymers. TEC can therefore migrate from the enteric coating into the subcoat layer at elevated temperatures, as demonstrated with the TEC loss over storage and change the physico-chemical properties of the powder-coated tablets. An increasing TEC level in the subcoating layer over storage may induce aging within the polymer coating. The influence on dissolution was more pronounced for the unplasticized Eudragit® E PO.

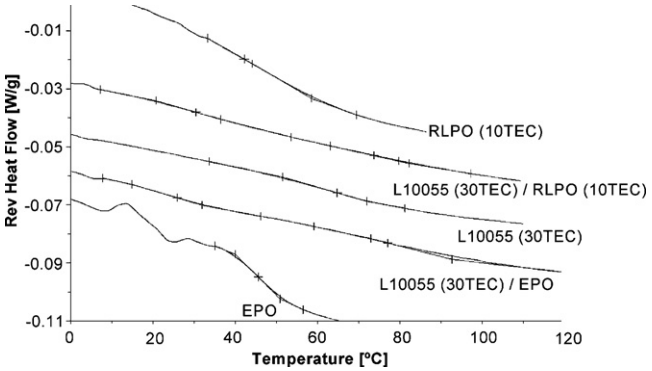

Fig. 8. DSC thermograms of Eudragit® L 100-55, preplasticized with 30% TEC, Eudragit® E PO, and Eudragit® RL PO, preplasticized with 10% TEC and their 1:1 physical mixtures.

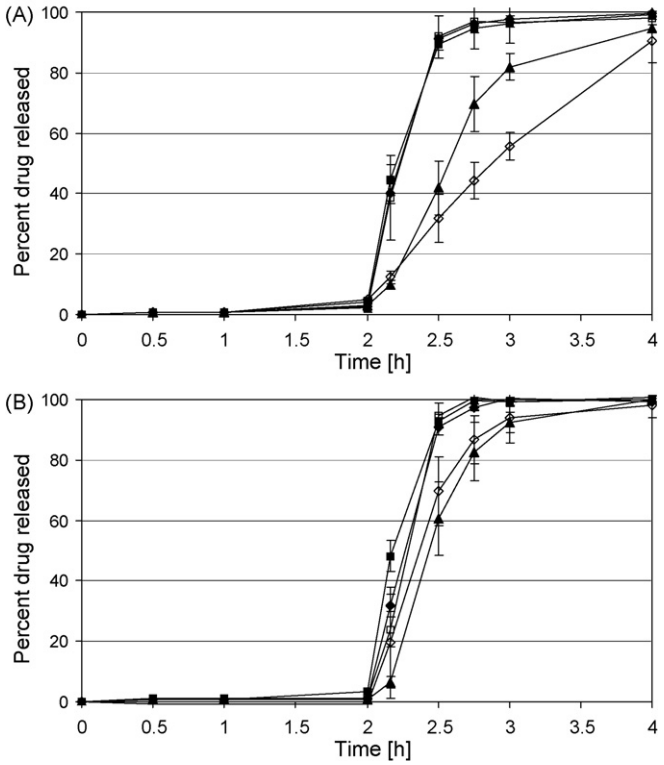

Fig. 7. Twelve weeks stability of sodium valproate tablets powder-coated with pre-plasticized Eudragit® L 100-55 containing 30% TEC based on the polymer weight using USP 29 apparatus 2. Dissolution in 750 mL of 0.1N HCl for 2 h followed by 2 h in 1000 mL pH 6.8 50 mM phosphate buffer after pH adjustment at 37 °C and 50 rpm. Polymer weight gain: 20%. (■) Initial; (♦) 4 weeks at 25 °C/60% RH; (▲) 4 weeks at 40 °C/75% RH; (□) 12 weeks at 25 °C/60% RH; (◊) 12 weeks at 40 °C/75% RH (standard deviation, $n = 6 \times 6$ tablets/vessel). (A) Eudragit® E PO subcoat containing 10% PEG 3350 based on the polymer weight. (B) Eudragit® RL PO subcoat containing 10% Methocel® K4M based on the polymer weight.

4. Conclusion

Sodium valproate tablets required high weight gains of powder-coated Eudragit® L 100-55 and PEG 3350 in order to pass the USP enteric test. The application of a Eudragit® E PO or Eudragit® RL PO subcoat assisted with adhesion of the enteric polymer onto the tablet cores, enhanced film formation, and therefore reduced the amount of enteric polymer required for enteric protection. Poor spreading of the PEG 3350 primer, as demonstrated for valproic acid, was resolved with a subcoating layer of Eudragit® E PO or Eudragit® RL PO. High polymer weight gains of Eudragit® L 100-55, however, were still required for the tablets to pass the USP enteric test. PEG 3350 and Methocel® K4M were added to the subcoat to improve the release of sodium valproate in buffered media. Drug

release was dependent on miscibility of the pore forming agents with the polymers. Storage stability was confirmed for powder-coated sodium valproate tablets at 25 °C/60% RH for all investigated formulations. Storage at 40 °C/75% RH resulted in a decrease in sodium valproate release over 12 weeks. A Eudragit® RL PO subcoat resulted in the smallest change in the drug release over the storage period. A loss of plasticizer in the film coating was shown to affect the storage stability of the powder-coated sodium valproate tablets.

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