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Novel application of hot-melt extrusion for the preparation of monolithic matrices containing enteric-coated particles

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ABSTRACT

The objective was to investigate a novel application of hot-melt extrusion for the preparation of multiparticulate matrices comprising delayed-release particles. Multiparticulates of different mechanical strengths (theophylline granules, wet-mass extruded/spheronized pellets and drug-layered microcrystalline cellulose spheres) were coated with Eudragit® L30D-55 and characterized regarding potency, moisture content, dissolution properties and tensile strength. The coated particles were incorporated into a water-soluble matrix using hot-melt extrusion. Six hydrophilic polymers including polyethylene glycols, poloxamers and polyethylene oxides were studied as the carrier material for the extrusion. Dissolution testing showed that the maintenance of the delayed-release properties of the incorporated particles was independent of the particle tensile strength, but influenced by the nature of the carrier polymer. High miscibility between the carrier and the coating polymer correlated with increased film permeability and higher drug release in acidic media. Of the materials tested, poloxamer 407 exhibited lower miscibility with the Eudragit® L polymer and matrices containing up to 40% enteric pellets were compliant with the USP dissolution requirements for delayed-release dosage forms. The potential advantages of hot-melt extrusion over direct compression for the processing of soft drug granules coated with Eudragit® L polymer were demonstrated.

1. Introduction

Oral dosage forms providing controlled drug delivery can be classified as monolithic or multiple unit systems. Biopharmaceutical advantages of multiple unit dosage forms include less variation in gastric transit time, reduction of food effects and a more uniform distribution along the intestinal tract (Ghebre-Sellassie, 1994). With regard to the final dosage form, monolithic systems are preferred to ensure patient compliance and dosing accuracy. Processing technologies to convert multiparticulates into monolithic dosage forms include pellet compression into tablet compacts or filling into capsules. Tableting of functionally coated particles has experienced increasing popularity as these systems can be manufactured at lower costs and higher output rates, are less sensitive to moisture or susceptible to tampering and may be divided to increase dosing flexibility when compared to capsules (Bodmeier, 1997).

The tableting of functionally coated particles, however, is technologically more challenging than the compression of traditional powder blends. The exertion of unidirectional compaction forces on film-coated particles including pellets, granules or microspheres may induce their deformation and/or fragmentation and ultimately damage the coating during the compaction process. Fracture of the coating during tableting results in the loss of the controlled release properties and has been reported for particles coated with brittle polymers including ethylcellulose (Bechard and Leroux, 1992; Bansal et al., 1993; Cantor et al., 2009), Eudragit® RS/RL mixtures (Aulton et al., 1994) or enteric polymethacrylates (Beckert et al., 1996; Mount and Schwartz, 1996; Dashevsky et al., 2004). Strategies to maintain the functionality of the film during compression include the application of films of high flexibility (Chang and Rudnic, 1991; Beckert et al., 1996; Dashevsky et al., 2004) or increased thickness (Beckert et al., 1996; Wagner et al., 2000a; Sawicki and Lunio, 2005), reduction in the tablet surface area (Wagner et al., 2000b) or use of appropriate cushioning excipients (Mount and Schwartz, 1996; Torrado and Augsburger, 1994; Vergote et al., 2002). However, particles with highly flexible films are more difficult to prepare, tend to agglomerate during compression and are more susceptible to storage instabilities (Zheng and McGinity, 2003). Partial film fusion of coated pellets during tableting can further interfere with tablet disintegration (Wagner et al., 2000a). The requirement for controlled release particles to remain intact during compression implies that these particles do not contribute to tablet hardness in the form of plastic deformation,

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densification or brittle fragmentation. Tablet strength has been shown to decrease while tablet friability increased when high particle loads were present in the tablet (Debunne et al., 2004). Large amounts of cushioning and highly compressible tableting excipients can absorb compaction forces, physically separate the particles during compression and produce tablets of acceptable hardness and low friability, but limit the load of particles in the tablet. Moreover, blend segregation during tableting can result in poor tablet content uniformity due to differences in particle size and density between pellets and tableting excipients.

Hot-melt extrusion has been recognized as a valuable technology for the preparation of a large variety of pharmaceutical dosage forms including matrix tablets and pellets, films and implants (Crowley et al., 2007; Repka et al., 2007). The objective of this study was to investigate a novel application of hot-melt extrusion as an alternative method to tableting for the preparation of multiparticulate monolithic matrices. Our hypothesis was that the challenges associated with pellet compaction technologies may be overcome using hot-melt extrusion due to the absence of compaction forces. Three types of particles exhibiting different mechanical strengths (theophylline granules from BASF, self-made theophylline-loaded pellets and theophylline-layered microcrystalline cellulose spheres) were enterically coated with Eudragit® L30D-55 and characterized regarding tensile strength and dissolution properties. Relevant formulation and processing factors for the incorporation of the coated particles into soluble matrices by hot-melt extrusion were investigated. Six hydrophilic polymers were studied as thermoplastic carriers, and the thermal miscibility of these carriers with the coating polymer was analyzed by differential scanning calorimetry to evaluate potential film solubilization during the extrusion process. The influence of the type of carrier polymer, particle load and the strength of the coated particles on the maintenance of the enteric particle properties following hot-melt extrusion was investigated. The release properties of a hot-melt extruded tablet system were compared to a directly compressed tablet, and the storage stability was evaluated.

2. Materials and methods

2.1. Materials

Anhydrous theophylline, glycerol monostearate (powder, food grade) and polysorbate 80 (Tween® 80, NF) were purchased from Spectrum Chemicals (Gardena, CA). Avicel® PH-101 (NF) and Ac-Di-Sol® were donated by FMC BioPolymer (Newark, NJ), and hypromellose E3 (Pharmacoat® 603) was obtained from Shin-Etsu (Tokyo, Japan). Kollidon® K25, theophylline granules, poloxamer 188 (Lutrol® F 68) and poloxamer 407 (Lutrol® F 127) were kindly provided by BASF Corp. (Ledgewood, NJ). Polyethylene glycols (PEG 4000 and 8000, Carbowax Sentry™), polyethylene oxide 100K (PEO 100K, Sentry Polyox™ WSR N-10 NF) and polyethylene oxide 200K (PEO 200K, Sentry Polyox™ WSR N-80 NF) were donated by Dow Chemical Company (Midland, MI). Microcrystalline cellulose spheres (MCC spheres, Ceolus™ CP-305) and powder (Ceolus™ KG-802) were kind gifts from Asahi Kasei America, Inc. (New York, NY). Triethyl citrate (TEC) was provided by Vertellus (Greensboro, NC), and Eudragit® L30D-55 and Eudragit® L100-55 were donated by Evonik Pharmapolymers (Piscataway, NJ).

2.2. Preparation of theophylline-loaded pellets

Pellets containing 30% theophylline were prepared by wet-mass extrusion and spheronization. The drug and Avicel® PH-101 (62.5%) were premixed in a Kitchen Aid mixer® (St. Joseph, MI), and an aqueous Kollidon® K25 solution (12.5%, equivalent to 7.5% Kollidon® K25 in the final dry formulation) was added under stirring to form a wet mass of appropriate consistency. After manual pre-kneading, the mass was processed with a Benchtop granulator (LCI Corp., Charlotte, NC) equipped with a 0.6 mm screen and operated at a blade rotation speed of 50 rpm. The extruded strands were transferred into a spheronizer (Caleva Model 120, Dorset, UK) and spheronized at 700 rpm for 3 min.

2.3. Active layering of MCC spheres

Microcrystalline cellulose (MCC) spheres were loaded with theophylline using a layering technique. A binder solution (2%) was prepared by dissolving hypromellose E3 in deionized water under magnetic stirring. Theophylline (10%) was added to the binder solution under high-shearing with a Polytron mixer (Brinkmann Instruments, Westbury, NY), and the obtained suspension was homogenized for another 10 min. The theophylline-binder dispersion was sprayed onto MCC seed cores (Ceolus™ CP-305, particle size 300–500 μm, 200 g) in a Strea-1 fluidized-bed coater (Aeromatic-Fielder, Bubendorf, Switzerland) with bottom-spray and Wurster column. The dispersion was stirred during the process and applied with a peristaltic pump through a 1.0 mm nozzle at an atomizing air pressure of 1.5 bars. The inlet temperature was 75 °C and the outlet temperature was 50–51 °C. The dispersion was sprayed at 10 g/(min kg) to obtain MCC spheres with a potency of 10% theophylline.

2.4. Moisture content

The moisture content of the particles was determined after equilibration at 25 ± 1 °C and 50 ± 5% RH for 24 h and prior to enteric coating using a moisture analyzer AND MF-50 (A&D Engineering, Inc., Milpitas, CA). In accordance with the USP loss on drying method, 1 g of particles was accurately weighed into a dried aluminum dish and maintained at 110 °C until a constant weight was achieved (weight loss below 0.02%/min). The average percent weight loss of three measurements was reported as the moisture content.

2.5. Functional film coating

Three different types of theophylline-loaded particles were used for the enteric coating trials (Table 1): theophylline granules, self-made pellets and drug-layered MCC spheres. The particles were coated in the above described fluid bed coater using an aqueous dispersion of Eudragit® L30D-55. The composition of the coating dispersion is shown in Table 2, and the dispersion was prepared as recommended by the polymer manufacturer (Evonik, 2009). The process parameters are detailed in Table 3. The polymeric dispersion was stirred continuously throughout the coating process to prevent the sedimentation of solids. The film-coated particles were dried and sieved, and the 300–500 μm fraction was selected for further analysis and processing.

Table 1
Core materials used for the preparation of enteric film-coated particles.

Core material	Theophylline content[a] [%]	Moisture content[b] [%]
Drug granules	96.3	2.15 ± 0.13
Pellets	28.2	3.52 ± 0.08
MCC spheres	10.8	3.50 ± 0.25

[a] The theophylline content was determined for the uncoated particles using HPLC ($n = 3$).
[b] The moisture content of the particles was determined as the loss on drying after equilibration at 22 ± 1 °C and 50 ± 5% RH for at least 24 h ($n = 3$).

Table 2
Formulation used for the enteric coating of theophylline particles (50% weight gain, amounts are presented for 1000 g coating dispersion).

Formulation	Amount [g]
Eudragit® L30D-55	400
Triethyl citrate	12
Glyceryl monostearate	9
Tween 80	3.6
Water	575.4

Table 3
Conditions used for the enteric coating of theophylline particles in a Strea-1 fluidized-bed coater.

Parameter	Condition
Inlet temperature	36–38 °C
Exhaust temperature	32–33 °C
Nozzle diameter	1.0 mm
Spray rate	10 g/(min kg)
Drying conditions	Oven at 40 °C, 48 h

2.6. Mechanical strength testing

The tensile strength of the three different types of particles before and after enteric coating was determined with a Chatillon Universal Tension/Compression Tester Model TCD-200 (Ametek, Largo, FL) as previously described (Wang et al., 1996; Felton et al., 1997). Briefly, a flat circular steel plate was fitted onto a DFGS 50 digital force gauge and lowered in diametral direction towards an individual pellet at a crosshead speed of 2.5 mm/min. The load-deflection data was collected using Chatillon Nexygen TCD force testing software, and the mechanical strength was reported as the average tensile strength (σ) of 20 specimens as calculated with the Hiramatsu-Oka equation:

$$\sigma = \frac{2P}{\pi d^2}$$

The diameter (d) of each individual particle was obtained from the distance of the crosshead plate from the base at the moment of load buildup, and the maximum load (P) at which brittle fragmentation of the pellets occurred was used for the calculation of the tensile strength. Statistical analysis was performed with JMP® 7 software (SAS Institute Inc., Cary, NC) considering an α-level of $\leq$0.05 statistically significant. One-way ANOVA and post hoc Tukey–Kramer test were employed to evaluate the influence of the particle type on the mechanical strength. The mechanical strength before and after enteric coating was compared using the two-sided t-test for dependent data.

2.7. Hot-melt extrusion of multiparticulate matrices

Functionally coated particles (30%, unless stated otherwise) were blended with a hydrophilic carrier polymer (70%) and extruded into circular strands using a single screw Randcastle extruder (model RCP 0750 Microtruder, Nitralloy 135M screw, Cedar Grove, NJ) equipped with a 6 mm rod shaped die. Six polymers were studied as the thermoplastic carriers including PEG 4000 and 8000, poloxamer 188 and 407 and PEO 100K and 200K. The temperature settings in the three heating zones and in the die zone were selected based on the melting point and the viscosity of the individual polymers and are listed in Table 4. The extruded strands were cooled to room temperature and cut with a razor blade into cylindrical tablets comprising 200 mg enteric particles (667 mg tablets when particle loading was 30%).

2.8. Differential scanning calorimetry

The miscibility between the enteric polymer and the carrier polymers was investigated by differential scanning calorimetry (DSC) to evaluate the potential for solubilization of the enteric film during hot-melt extrusion. Samples weighing 15 ± 3 mg were crimped sealed in aluminum pans and placed inside the furnace of a Thermal Advantage Model 2920 (TA Instruments, New Castle, DE). The carrier polymers were heated either alone or in the presence of an equal amount of Eudragit® L100-55 at 10 °C/min to a temperature of 10° above the extrusion temperature and kept isothermal at this temperature for 10 min to simulate the hot-melt extrusion process. After quench cooling to 0 °C, a second run was performed using the same heating rate. The melting points of the carrier polymers are listed in Table 4, and the melting enthalpies were calculated by peak integration using TA Universal analysis 2000 software. The fraction of melting enthalpy remaining in the second run relative to the first run was used to express the percentage of relative polymer crystallinity after thermal processing. The term "relative crystallinity" was used since the actual degree of crystallinity of the untreated semi-crystalline polymers was unknown.

2.9. Direct compression of multiparticulate tablets

Enteric-coated granules (30%), microcrystalline cellulose (Ceolus™ KG-802, 65%) and superdisintegrant (Ac-Di-Sol®, 5%) were blended and directly compressed into round tablets (333 mg, equivalent to 100 mg particles) using a single station manual Carver Press (Fred Carver, Menomonee, WI) equipped with a concave, 10 mm diameter die (04-04, #91459, Natoli Engineering, Saint Charles, MO). The compression force was 5 kN and the tablet hardness was 17.1 ± 1.6 kPa as determined with a Varian VK 200 tablet hardness tester (Cary, NC).

2.10. Dissolution studies

The dissolution properties of the enteric-coated particles before and after hot-melt extrusion or direct compression into multiparticulate matrices were studied in a paddle apparatus (Vankel VK 7000, Varian, Cary, NC) according to the USP chapter ⟨724⟩ method A for delayed-release articles. The bath temperature was maintained at 37.0 ± 0.5 °C, and the paddle rotation speed was set to 100 rpm. Specimens equivalent to 200 mg particles (one hot-melt extruded tablet or two compressed tablets, n = 3) were initially

Table 4
Carrier polymers and temperature settings used for the hot-melt extrusion of enteric pellets into multiparticulate matrices.

Polymer	Supplier and grade	Melting point [°C]	Extrusion temperature [°C]			
			Zone 1	Zone 2	Zone 3	Die
Poloxamer 188	BASF, Lutrol F68 NF Prill	57.1 ± 0.3	40	45	47	47
Poloxamer 407	BASF, Lutrol F127 NF Prill	58.9 ± 0.2	40	45	50	48
Polyethylene glycol 4000	Dow, Carbowax Sentry PEG 4000	63.8 ± 0.3	40	45	50	50
Polyethylene glycol 8000	Dow, Carbowax Sentry PEG 8000	64.3 ± 0.5	40	50	55	55
Polyethylene oxide 100K	Dow, Sentry Polyox WSR N-10	69.7 ± 0.2	55	70	75	75
Polyethylene oxide 200K	Dow, Sentry Polyox WSR N-80	69.9 ± 0.8	55	70	75	75

tested in 750 ml simulated gastric fluid pH 1.2 (SGF without pepsin) for 2 h, followed by an additional 2 h in phosphate buffer pH 6.8 after adding 250 ml of 0.2 M tribasic phosphate buffer. Samples were withdrawn at selected time intervals using a Vankel VK 8000 auto sampler and assayed for theophylline content by HPLC.

2.11. Theophylline assay

The amount of theophylline released during dissolution testing was determined by HPLC analysis using a Waters HPLC system (Waters Inc., Milford, MA) equipped with a C18-reversed phase column (Capcell PAK 3 mm × 100 mm, Shiseido Co, Japan). The mobile phase consisted of 20 mM phosphate buffer and acetonitrile (9:1) and was delivered at a flow rate of 0.5 ml/min. Theophylline was eluted after 3.5 min, detected with a UV detector extracting at 271.5 nm (996-PDA, Waters Inc.) and quantified by peak area integration using Empower version 5.0 software (Waters Inc.). Linear correlation was confirmed between 0.1 and 100.0 μg/ml ($R^2 = 0.99997$) and multiple injections yielded good reproducibility with RSD values between 0.08% (100.0 μg/ml) and 1.77% (0.1 μg/ml).

3. Results and discussion

3.1. Characterization of multiparticulates

Three different types of theophylline-loaded particles (theophylline granules, pellets and layered MCC spheres) were prepared and characterized regarding potency, moisture content and mechanical strength before and after functional coating with Eudragit® L30D-55. The potency and moisture content of the different particles before enteric film coating are given in Table 1. As can be seen in Fig. 1, the tensile strength of the granules was low and increased significantly when enterically coated (7.31 ± 2.18 MPa before coating versus 9.53 ± 2.75 MPa after coating, paired *t*-test, $p = 0.0036$). The tensile strength of wet-massed pellets was significantly higher when compared to coated or uncoated granules (one-way ANOVA and post hoc Tukey–Kramer with $\alpha < 0.05$), and remained unchanged after enteric film coating (21.52 ± 3.03 MPa before coating versus 20.03 ± 3.38 MPa after coating, paired *t*-test, $p = 0.1329$). Drug-layered MCC spheres exhibited the highest tensile strength which decreased significantly after enteric coating (33.58 ± 5.36 MPa before coating versus 24.05 ± 4.49 MPa after coating, $p < 0.0001$).

The differences in mechanical strength between the different types of particles were attributed to their composition and manufacturing process. The degree of material compression during particle formation influenced the particle porosity and hence the tensile strength. High particle strength was further promoted by MCC in the formulation due to the high plasticity of this material. The influence of enteric film coating with Eudragit® L30D-55 on the mechanical properties was dependent on the tensile strength of the core material. The mechanical robustness of the soft theophylline granules could be enhanced by the application of the film coat, and increases in mechanical strength after film coating have been previously reported for spheres coated with Eudragit® RS 30D/RL 30D (Aulton et al., 1994) or Eudragit® L30D-55 (Mount and Schwartz, 1996). Pellets prepared by wet-mass extrusion and spheronization exhibited an intermediate tensile strength before functional coating, and the application of a polymeric film did not alter their resistance to diametral compression forces. These results were in agreement with previous reports demonstrating that film coating did not change the mechanical strength of pellets (Lundqvist et al., 1998; Abbaspour et al., 2008). These findings further indicated that fracture of the pellet core was the dominating failure mechanism during tensile testing, and that the core and the film exhibited similar mechanical properties. On the other hand, the tensile strength values of enteric MCC spheres were decreased following functional coating. In this case, the mechanical properties were mainly dictated by the high strength of the core material. Application of a film did not alter the load that was required for particle crushing, but increased the particle size, so that the calculated tensile strength values decreased. Overall, it was demonstrated that the effects of functional coatings on the mechanical properties of particles were dependent on the mechanical strength of the core material in relation to the film strength.

3.2. Influence of carrier polymers on the dissolution properties of enteric pellets after hot-melt extrusion

Hot-melt extrusion requires the presence of a thermoplastic carrier in the form of a malleable or meltable polymer, wax or lipid (Crowley et al., 2007). The behavior of the carrier in dissolution media in terms of dissolution rate and swelling characteristics controls the release rate of the active ingredient, and in the case of particle extrusion, the liberation of the multiparticulates from the matrix. For this reason, carrier polymers should exhibit high aqueous solubilities and refrain from forming highly viscous gels in dissolution media. In contrast, conventional multiparticulate tablets prepared by compaction methods are generally formulated with a superdisintegrant to ensure rapid tablet disintegration and particle release in the stomach after ingestion.

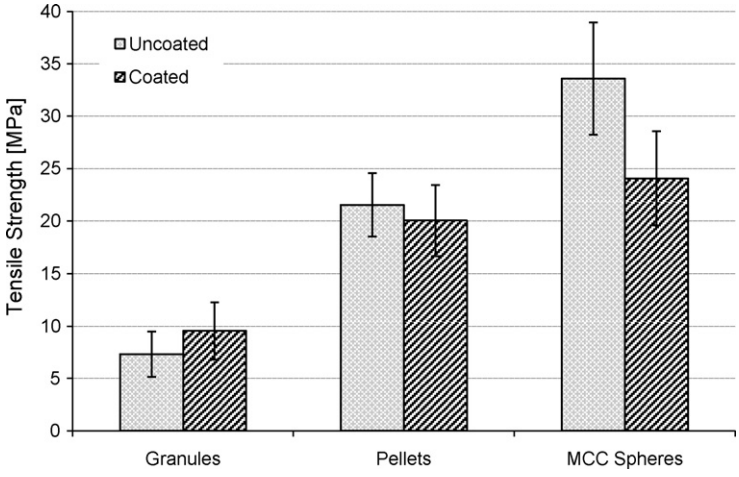

Fig. 1. Mechanical strength of three different types of particles before and after film coating with Eudragit® L30D-55 (diametral compression analysis, $n = 20$).

Carriers for hot-melt extrusion applications should also exhibit low glass transition temperatures or melting points to allow hot-melt extrusion at moderate temperatures and avoid the thermal degradation of blend components. Semi-crystalline polymers with low melting points are advantageous since they can be extruded at high output rates, solidify quickly and show negligible elastic recovery (die swell) upon extruder exit. In the melt extrusion of coated multiparticulates, it is further important that the carrier exhibits low miscibility with the coating polymer. High polymer miscibility and elevated processing temperatures could potentially promote solubilization of the enteric film during the extrusion process.

Six water-soluble polymers exhibiting low melting points and semi-crystalline properties were studied as potential carrier materials (Table 4). The poloxamers and PEGs melted between 57 and 65 °C and could be extruded at temperatures below their melting points (47–55 °C) since shearing of the material under elevated pressure promoted polymer softening. In a similar manner, other groups demonstrated that lipids could be extruded at temperatures below their melting ranges, with 80–90% of the thermal binder remaining in the solid state during the extrusion process (Reitz and Kleinebudde, 2007). In contrast, polyethylene oxides needed to be processed above their melting point (70 °C) and showed pronounced elastic recovery (die swell), likely due to their higher molecular weights and higher percentage of amorphous regions within these polymers.

Differential scanning calorimetry was employed to investigate the influence of thermal processing on the crystallinity of the carrier polymers and their miscibility with Eudragit® L. All specimens were cycled twice, and the melting enthalpies of the carrier polymers were determined by integration of the melting peak areas. The formation of miscible phases with the highly viscous acrylic polymer was expected to hinder the carrier recrystallization during the cooling period, resulting in reduced enthalpy values for the second cycle. The results in Fig. 2 show that the crystallinity of the poloxamers and PEGs decreased only slightly when heated alone (92–96%). In contrast, PEOs exhibited a more significant decrease in crystallinity to 77–78% after thermal treatment which was in agreement with previous reports (Blanton et al., 2003). The relatively low molecular weights and melt viscosities of the poloxamers and PEGs allowed a quick rearrangement of the disordered chains into ordered crystalline structures during the cooling period, while the recrystallization process was presumably hindered within the highly viscous PEO melts.

The melting enthalpies of physical mixtures with Eudragit® L100-55 (1:1) in the first run were equivalent to those of the pure carrier polymers. The melting enthalpies in the second cycle were lower indicating reduced carrier crystallinity in the presence of the coating polymer due to partial polymer miscibility (Fig. 2). This phenomenon was most distinctive for the low molecular weight PEG (relative crystallinity of 9% in second run), and least for the PEOs (61–62%). The miscibility with poloxamer 188 or PEG 8000 was also high (21–24%), while poloxamer 407 yielded only moderate miscibility with the coating polymer (46% relative crystallinity in second run). These results suggested that the PEOs and poloxamer 407 were more suitable carriers for the melt extrusion of particles coated with Eudragit® L30D-55 than the PEGs or poloxamer 188. However, all carriers exhibited some miscibility with the coating polymer which might encourage film solubilization and compromise the gastric resistance of the particles following hot-melt extrusion.

The dissolution profiles of matrix systems containing 30% coated pellets are shown in Fig. 3. The release properties in acid were controlled by the permeability of the enteric film and, to a lesser extent, by the dissolution rate of the carrier. The PEG 4000 matrix yielded increased drug release rates in acid, with 14.6% theophylline released after 2 h. As demonstrated by DSC, PEG 4000 and the enteric polymer were at least partially miscible, and the film integrity of particles was compromised after extrusion in a PEG 4000 matrix. In a previous study, lower molecular weight PEGs were demonstrated to be unsuitable carriers for Eudragit® L30D-55 coated pellets in congealed matrices since they increased the film permeability by dissolving the film coating (Schmidt and Bodmeier, 2001). The high miscibility between Eudragit polymers and PEGs was expected since PEGs are commonly used plasticizers for polymethacrylic polymers (Skalsky and Petereit, 2008). Matrices prepared with poloxamer 188, PEG 8000 or the PEOs released the drug to a similar extent in acid (9.9–11.2% after 2 h). The lowest drug release in acid was obtained for the poloxamer 407 matrix, with 7.4% theophylline released after 2 h.

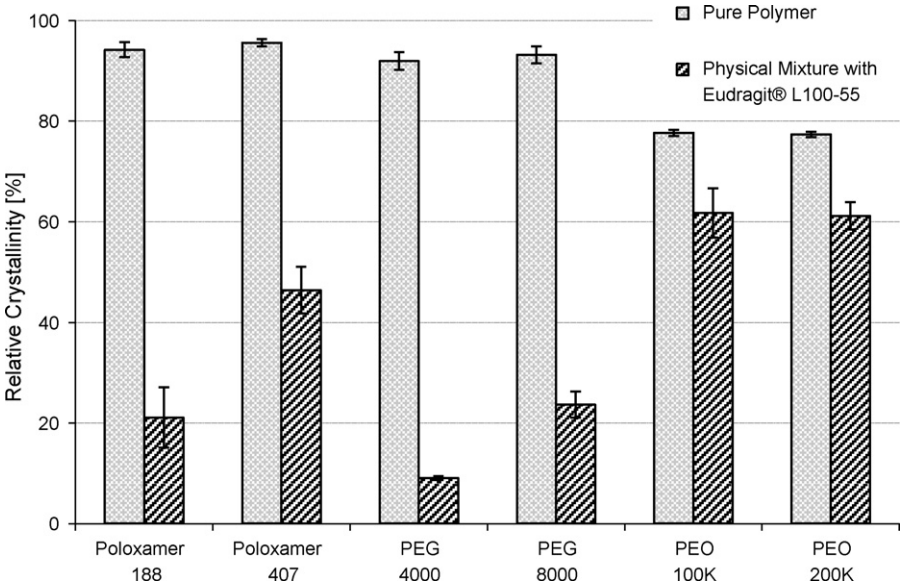

Fig. 2. Influence of thermal processing and Eudragit® L in a 50:50 physical mixture on the degree of crystallinity of the carrier polymers (DSC, heating rate 10°/min, samples: 15 ± 3 mg, crimp-sealed in aluminum pans, cycled twice, $n = 3$. The relative crystallinity was calculated as the ratio of the melting enthalpies in the second run divided by the first run).

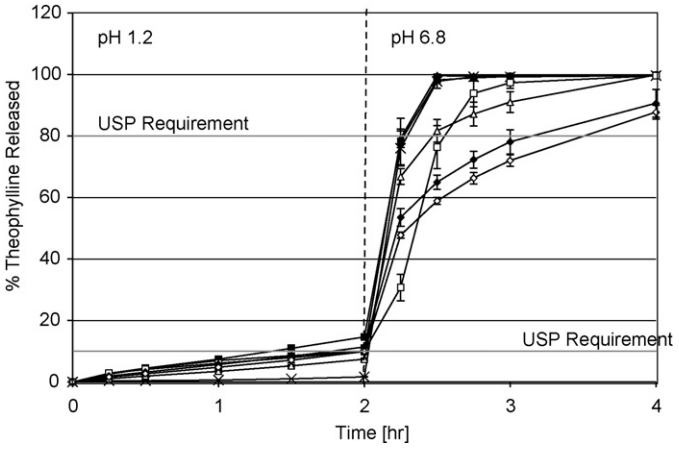

Fig. 3. Influence of carrier polymer on the drug release properties of hot-melt extruded matrix tablets containing 30% enteric pellets. (×) Original enteric pellets, (▲) pellets in poloxamer 188, (△) pellets in poloxamer 407, (■) pellets in PEG 4000, (□) pellets in PEG 8000, (♦) pellets in PEO 100K, (◊) pellets in PEO 200K. Dissolution: USP paddle apparatus, 100 rpm, 37 ± 0.5 °C, $n = 3$, 2 h in 750 ml simulated gastric fluid pH 1.2 (without pepsin), after 2 h pH change to pH 6.8 by addition of 250 ml 0.2 M tribasic phosphate buffer.

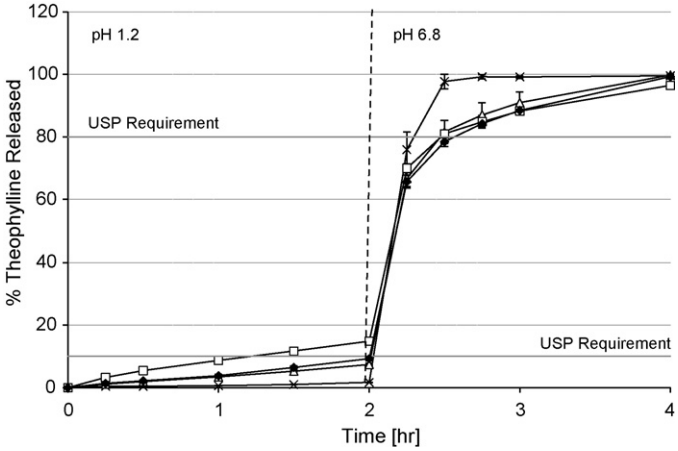

Fig. 4. Influence of pellet loading on the drug release properties of hot-melt extruded poloxamer 407 matrices. (×) Original enteric pellets, (△) 30% pellets in poloxamer 407, (♦) 40% pellets in poloxamer 407, (□) 50% pellets in poloxamer 407. Dissolution: USP paddle apparatus, 100 rpm, 37 ± 0.5 °C, $n = 3$, 2 h in 750 ml simulated gastric fluid pH 1.2 (without pepsin), after 2 h pH change to pH 6.8 by addition of 250 ml 0.2 M tribasic phosphate buffer.

The drug release in buffer pH 6.8 from the hot-melt extruded matrices containing the coated pellets was mainly governed by the dissolution kinetics of the carriers. Polyethylene oxide matrices formed highly viscous gels that acted as barriers towards penetrating water and diffusing drug, which resulted in the slowest drug release after 45 min in buffer (72.2% for PEO 100K and 66.3% for PEO 200K). The release profiles of the poloxamer 188 and PEG 4000 matrices were superimposable with those of the original coated pellets before hot-melt extrusion (>98.8% released after 45 min), demonstrating that the polymer matrix dissolved quickly so that the theophylline release rate was only controlled by the dissolution kinetics of the enteric film. The release from the PEG 8000 matrices yielded an approximate 15–20 min lag time in buffer, after which the drug was rapidly released to reach 93.4% after 45 min. Hot-melt extruded poloxamer 407 tablets provided dissolution rates in between the fast dissolving carriers and the highly viscous PEOs with 87.1% theophylline released after 45 min in buffer pH 6.8. The retarded matrix dissolution of poloxamer 407 compared to poloxamer 188 was attributed to the slightly higher molecular weight (9840–14,600 versus 7680–9510) and a higher percentage of less hydrophilic polypropylene oxide units (PEO: PPO ratio of 1.8:1 versus 3.0:1 for poloxamer 188). Poloxamer 407 was selected as the carrier for the remaining extrusion trials since the produced matrices were the only system that fulfilled the USP requirements for the minimum drug release in acid (<10% after 2 h) and the release in buffer pH 6.8 (>80% after 45 min).

3.3. Influence of pellet loading on the properties of hot-melt extruded matrices

The properties of compressed tablets containing multiparticulates have been demonstrated to be influenced by the pellet-to-filler ratio. High amounts of pellets in the formulation increase the number of inter-particle contacts, leading to pellet deformation and film damage not only on the tablet surface, but also in the interior of the tablets. The drug release rate from pellets coated with Eudragit® L30D-55 was shown to increase as a function of the pellets content (Beckert et al., 1996; Mount and Schwartz, 1996). Partial film fusion and pellet agglomeration during compaction may compromise rapid tablet disintegration as demonstrated for tablets containing large amounts of Eudragit® FS 30D film-coated pellets (Wagner et al., 2000a). High pellet loads may further decrease the mechanical strength and increase the friability of the multiparticulate tablets (Debunne et al., 2004).

Poloxamer 407 matrices containing increasing amounts of pellets (30, 40 and 50%) were prepared by melt extrusion and their release characteristics were studied. Increasing the pellet load to up to 50% did not compromise the processibility, and all formulations could be prepared using the same extrusion conditions. The hardened strands were not friable despite the high amount of non-meltable material in the formulation. The influence of the pellet content on the delayed-release properties is shown in Fig. 4. Poloxamer 407 matrices containing 30% or 40% enteric pellets were compliant with the USP requirement to release less than 10% of their drug content after 2 h in acid (7.4 and 9.2%, respectively). However, tablets prepared with 50% pellets failed this criterion with 14.8% theophylline released. Drug dissolution at the buffer stage was independent of the pellet loading and higher than 80% within 45 min (84–87%).

3.4. Influence of type of particles on the maintenance of the release properties after hot-melt extrusion

Previous studies by Beckert et al. have shown that pellets with high mechanical strength were better able to withstand compression forces during tableting than soft particles (Beckert et al., 1996). Excessive deformation or fragmentation of the particle core will result in stretching and eventual rupture of the functional film. As demonstrated in Fig. 1, the three different types of particles (granules, pellets and MCC spheres) displayed significant differences in mechanical properties, with granules yielding the lowest and MCC spheres yielding the highest tensile strength. In contrast to compression technologies, high unidirectional forces were absent during the hot-melt extrusion process, while shear forces whose magnitude depends on the carrier viscosity, screw design and rotation speed (Crowley et al., 2007) could potentially compromise the particle integrity. Preliminary studies on pellets of different particle sizes demonstrated that the particle conveyance through the extruder was hindered and resulted in increased drug release in acid above 10% when pellets with diameters larger than 500 μm were extruded (Schilling and McGinity, 2009). Fig. 5 shows the influence of the particle type on the percentage of theophylline released after 2 h from melt extruded poloxamer 407 matrix tablets containing 30% enteric particles (300–500 μm). All formulations

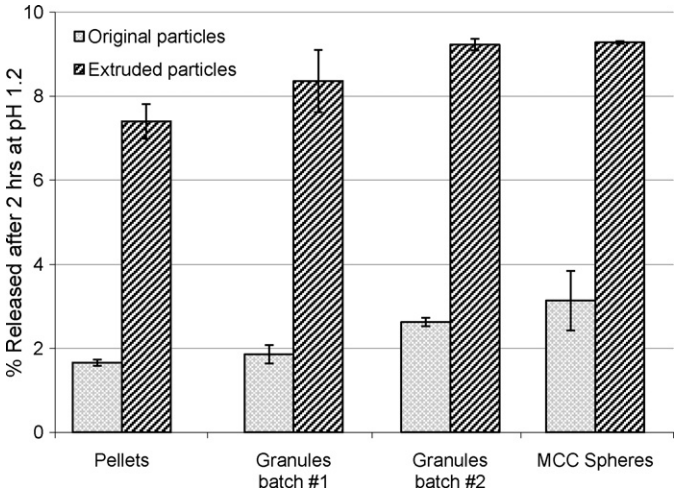

Fig. 5. Influence of the particle type on the drug release in acid after 2 h for extruded poloxamer 407 matrices comprising 30% particles. Dissolution: USP paddle apparatus, 100 rpm, 37 ± 0.5 °C, $n = 3$, 750 ml simulated gastric fluid pH 1.2 (without pepsin).

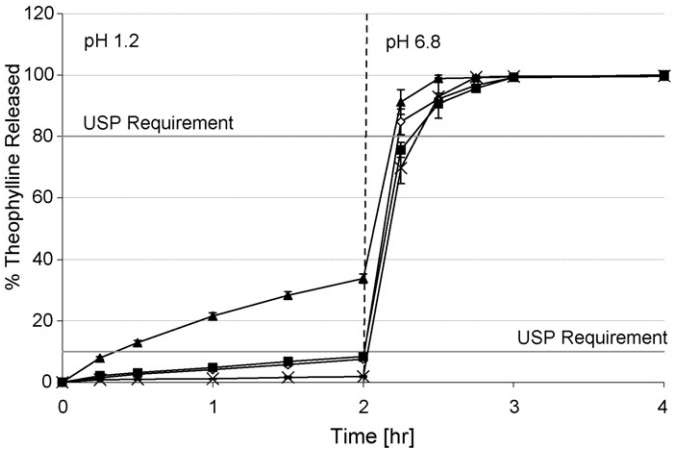

Fig. 6. Influence of tablet manufacturing method and storage on the release properties of enteric-coated theophylline granules. (×) Original enteric granules, (■) fresh prepared hot-melt extruded matrix tablets containing 30% granules in poloxamer 407, (◊) hot-melt extruded matrix tablets containing 30% granules in poloxamer 407 after one year of storage at room temperature and ambient humidity, (▲) directly compressed tablets containing 30% granules in Ceolus™ KG 802. Dissolution: USP paddle apparatus, 100 rpm, 37 ± 0.5 °C, $n = 3$, 2 h in 750 ml simulated gastric fluid pH 1.2 (without pepsin), after 2 h pH change to pH 6.8 by addition of 250 ml 0.2 M tribasic phosphate buffer.

were compliant with the USP criteria for the release in acid and in buffer pH 6.8. All multiparticulate matrices exhibited a similar increase in percent drug released after extrusion (between 5.7 and 6.6%), which was independent of the mechanical strength of the enteric particles. These findings provided evidence that hot-melt extrusion is a suitable process to convert particles of low mechanical strength into monolithic dosage forms. Furthermore, the slight increase in drug release was more likely a result of partial solubilization of the film in the carrier polymer during extrusion due to partial polymer miscibility as demonstrated in the DSC study, than a result of mechanical rupture of the film.

3.5. Comparison of multiparticulate matrices prepared by hot-melt extrusion versus direct compression and investigation of storage stability

Our hypothesis was that hot-melt extrusion technology would be advantageous over direct compression for the preparation of multiparticulate-containing tablets, especially when the particles were of low mechanical strength and coated with tough but brittle polymeric films. As the processing of granules was expected to be most challenging due to their low tensile strength, enteric-coated theophylline granules were selected to compare hot-melt extrusion and direct compression.

Tablet compacts containing 30% enteric granules were prepared by direct compression at low compaction force (5 kN) using a highly compressible MCC grade (Ceolus™ KG-802) as the filler material. The release properties of these tablets were compared to melt extruded poloxamer 407 matrices comprising the same amount of enteric granules (Fig. 6). Direct compression resulted in a significantly increased drug release from the enteric granules in acid, with 33.8% released after 2 h compared to 8.4% for the melt extruded formulation. This loss in gastric protection was presumably attributed to partial film rupture during compaction. Similar observations have been reported by other groups for pellets coated with Eudragit® L30D-55 (Beckert et al., 1996) or Kollicoat® MAE (Dashevsky et al., 2004) when flexible polymers were absent in the coating formulation. The drug release in acid from the poloxamer 407 matrix was less than 10%, demonstrating that the enteric film remained to a large extent intact during hot-melt extrusion, and that increased film flexibility and high particle strength were not required to maintain the enteric release profile of the particles.

Furthermore, the stability of the enteric release properties of the poloxamer 407 matrix was investigated after one year of storage at room temperature and ambient humidity. As shown in Fig. 6, the drug release after 2 h in acid decreased only insignificantly from 8.4 to 7.5%. Changes in dissolution properties of extruded dosage forms may be due to aging of the enteric film, aging of the carrier polymer, or migration of the carrier into the enteric coating during storage. The latter mechanism was proposed to explain the faster drug release from pellets that were coated with plasticized Eudragit® RS and embedded in a PEG 4000 matrix after storage at room temperature (Schmidt and Bodmeier, 2001). The good storage stability of the Eudragit® L30D-55 coated particles in hot-melt extruded poloxamer 407 matrices was presumably due to the high glass transition temperature of the enteric polymer and its low affinity to the poloxamer 407.

4. Conclusions

Enteric particles were prepared by fluidized-bed coating of three different core materials, theophylline granules, pellets and layered MCC spheres, with an aqueous Eudragit® L30D-55 dispersion, and then processed into multiparticulate matrix systems by hot-melt extrusion using low melting polymers with high aqueous solubility as carrier materials. The maintenance of the delayed-release profile was demonstrated to be independent of the mechanical strength of the extruded particles, but dependent on the nature of the carrier polymer. These results indicated that the enteric film was susceptible to solubilization by the carrier polymer during the hot-melt extrusion process, while particle fragmentation and film rupture due to shear forces were less significant. Poloxamer 407 showed only moderate miscibility with the enteric polymer and produced tablets with optimized dissolution properties when used as the thermoplastic carrier for the particle extrusion, and matrices containing up to 40% enteric pellets in poloxamer 407 fulfilled the USP requirements for delayed-release dosage forms. In contrast to directly compressed tablets, the enteric properties of soft theophylline granules that were coated with brittle Eudragit® L30D-55 could be successfully preserved when hot-melt extrusion was used for the preparation of the multiparticulate matrices. The release properties of poloxamer 407 matrices were further demonstrated

to be stable for one year when stored at room temperature, presumably due to the low tendency of the carrier to migrate into the enteric film.

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