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Production of spherical pellets by a hot-melt extrusion and spheronization process

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Abstract

Controlled-release theophylline containing spherical pellets were successfully produced by a hot-melt extrusion (HME) and spheronization process. A powder blend of anhydrous theophylline, Eudragit® Preparation 4135 F, microcrystalline cellulose and polyethylene glycol 8000 powder was sieved, blended and then melt-extruded in a Randcastle Microtruder®. The hot-melt extruded pellets were prepared by first cutting a thin, extruded composite rod into symmetrical pellets. The pellets were then spheronized in a traditional spheronizer at an elevated temperature. Thermal properties of the pellet formulation components and the hot-melt extrudate were studied to determine suitability of the formulation for HME. Pellets were examined using scanning electron microscopy to determine the effect of spheronization time on surface morphology. The rate of release of theophylline from the hot-melt extruded spherical pellets was characterized using USP 24 Apparatus 2 dissolution testing after initial pellet production and after 1 year storage in sealed HDPE containers at 25 °C/60% RH.

Keywords: Hot-melt extrusion; Spheronization; EUDRAGIT® Preparation 4135 F; Theophylline

1. Introduction

The aim of controlled-release technology is to achieve a predictable and reproducible drug release rate over an extended period of time. Controlled-release delivery systems allow reduced dosing frequency and provide constant drug levels in the blood, thus increasing patient compliance and decreasing adverse drug events (Berner et al., 1992). Pellets are frequently used in controlled-release systems because they are freely dispersed in the gastrointestinal tract and they offer flexibility for further modification. Wet-mass extrusion and spheronization is the more established method of producing spherical pellets, but pellets manufactured by this method are usually film coated to control drug release. Researchers have investigated matrix systems produced by extrusion and spheronization to control drug release and to

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avoid difficulties associated with film coating, but many of these systems only offer limited control of drug release or present processing difficulties (Gandhi et al., 1999).

Hot-melt extrusion (HME) is a widely applied processing technique used in the plastics industry to produce tubes, pipes, wires and films. For pharmaceutical systems, this method has been used to prepare granules, sustained-release tablets and transdermal drug delivery systems (Aitken-Nichol et al., 1996; Repka et al., 1999; McGinity et al., 2000). HME does not require the use of water or solvents and few processing steps are needed, making the process simple, efficient and continuous. The intense mixing and agitation during processing cause suspended drug particles to deaggregate in the polymer melt, resulting in a more uniform dispersion of fine particles.

HME dosage forms are complex mixtures of active ingredients, matrix carrier(s) and functional excipients. These excipients are broadly classified as release-modifying agents, bulking agents, processing agents and miscellaneous additives. The selection and use of various excipients can impart specific properties to HME pharmaceuticals in a manner similar to those in traditional dosage forms (Zheng and McGinity, 1999; Repka and McGinity, 2000).

The purpose of this study was to develop a HME process to manufacture spherical pellets and to examine the controlled drug release properties of the spherical pellets produced by the novel HME process.

2. Materials and methods

2.1. Materials

The polymer Eudragit® Preparation 4135 F (4135 F) is an experimental acrylic polymer that was donated by Röhm GmbH (Darmstadt, Germany). Anhydrous theophylline USP/NF was purchased from Spectrum Quality Products, Inc. (Gardena, CA). Polyethylene glycol 8000 powder (PEG 8000, NF) was supplied by Dow Chemical (Midland, MI), and microcrystalline cellulose (MCC) was provided by FMC (Newark, DE).

2.2. Spherical pellet production

The pellet formulation for melt-extrusion consisted of the thermal polymer, 4135 F (48%), anhydrous theophylline (30%) as the model drug, and functional excipients including PEG 8000 (7%) and MCC (15%). Eudragit® Preparation 4135 F was first ground using a cryogenic grinder since it is supplied as large granules. The powders were passed through a 30-mesh (600 μm) screen and the powder formulation was blended for 5 min at 2000 rpm in a high-shear granulator (Robot Coupe® RSI 3VG; Ridgeland, MS) to assure adequate mixing.

The dry powder blend was extruded using a Randcastle Microtruder® RCP-0750 (Cedar Grove, NJ) single-screw extruder. The extruder temperature controllers were set as follows: Zone 1, 82 °C; Zone 2, 118 °C; Zone 3, 121 °C and Die, 121 °C. The formulation was fed into the hopper after the extruder zones and die had equilibrated to the set temperatures. After exiting the cylindrical die, the polymeric strand with a diameter of 1.22 ± 0.03 mm was fed into a Randcastle® Pelletizer RCP-2.0 and was uniformly cut into cylindrical pellets, 1.22 ± 0.04 mm in length. The pellets were allowed to cool to room temperature under ambient conditions and then a 75 g sample was transferred into a Caleva Model 120 Spheronizer (Dorset, UK). A Milwaukee™ Model 1220 (International Tool Corporation; Davie, FL) heat gun was used to facilitate pellet deformation by circulating hot air through the product exit of the spheronizer. The pellets were spheronized for approximately 45 min at 65–70 °C while dusted with microcrystalline cellulose to prevent agglomeration during spheronization. The HME pellets exhibited a 1.6% w/w loss on drying after lyophilization for 72 h. The spheronized pellets were packaged in sealed HDPE bottles and stored at 25 °C/60% RH and 40 °C/75% RH. A schematic representation of the HME and spheronization process is shown in Fig. 1.

2.3. Thermal analysis of formulation components and pellets

Thermal gravimetric analysis (TGA) of pellet

formulation components was performed with a Perkin Elmer TGA 7 using a heating rate of 10 °C/min from 50 to 600 °C. The polymer glass transition temperatures (T_g) were determined by modulated differential scanning calorimetry (MDSC, TA Instruments Model 2920; New Castle, DE) using a heating rate of 5 °C/min over a temperature range of −20 to 120 °C.

2.4. Pellet morphology

The morphology of gold:palladium (60:40, Ted Bench Top Sputter Coater) coated HME pellets was examined using a Philips Model 515 scanning electron microscope (SEM).

2.5. Dissolution

Dissolution testing of the theophylline containing pellets was conducted using the USP 24 Apparatus 2 (paddle method, VanKel VK6010; Cary, NC) in 900 ml of medium at 37 °C and 100 revolutions per minute (rpm). The pH 1.2 medium was 0.1 N HCl, and the pH 3.0, 6.8 and 7.4 media were 50 mmol phosphate buffer solutions. A VanKel VK8000 auto sampler was used to withdraw 4 ml samples at 0.25, 0.5, 1, 2, 4, 6 and 12 h time points. Filtered samples were assayed by UV spectrophotometry (DU-65, Beckman Instruments; Fullerton, CA) at 272 nm. Dissolution tests were performed in triplicate.

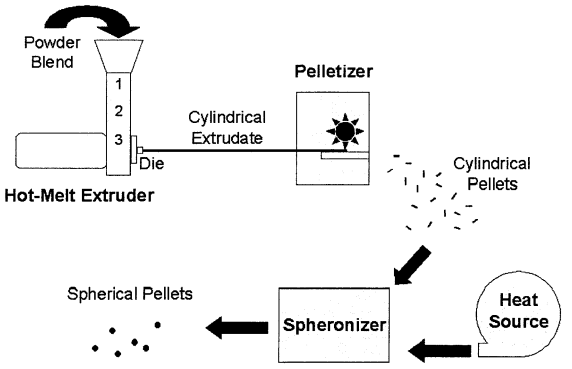

Fig. 1. Diagram of the HME and spheronization technique.

3. Results

Eudragit® Preparation 4135 F is an experimental copolymer composed of methyl acrylate, methacrylic acid and methyl methacrylate. The preparation is ideal for colonic delivery systems since it is soluble in aqueous media at pH 7.0 and above. The copolymer is also an excellent candidate for thermal processing since it is flexible and has a low T_g of 49.2 °C as experimentally determined by MDSC.

A powder formulation composed of theophylline and 4135 F with functional excipients was melt-extruded and spheronized. Functional excipients in HME powder blends may be classified as release-modifying agents, bulking agents, processing agents and miscellaneous additives. MCC was chosen as a HME aid for the powder blend used in this study since it acted as an anti-tacking agent. PEG 8000 was included in the formulation to facilitate HME since it plasticized the 4135 F. The presence of a solid-state plasticizer of the acrylic polymer lowered the T_g of the polymer preparation, which allowed for lower processing temperatures and shorter processing times. Although the experimentally determined T_g of 4135 F was 49.2 °C, the experimentally determined T_g of the plasticized HME product was 23.1 °C. TGA also demonstrated formulation suitability for HME since the formulation components did not experience weight loss at the HME processing temperatures as illustrated in Fig. 2.

The SEM micrographs displayed in Fig. 3 demonstrate the differences in the surface morphologies of the beads as a function of spheronization time. The HME bead manufactured using a 45 min spheronization time exhibits a surface indentation (Fig. 3A). The indentation on either side of the pellet represents the cut surfaces of the unspheronized pellet. Spheronization rounds the pellet ends, thus increasing spheronization time can reduce or eliminate the indentation. The spherical pellet in Fig. 3B illustrates the elimination of the surface indentation with an 80 min spheronization time.

The melt-extruded and spheronized matrix pellets exhibited control of theophylline release as a

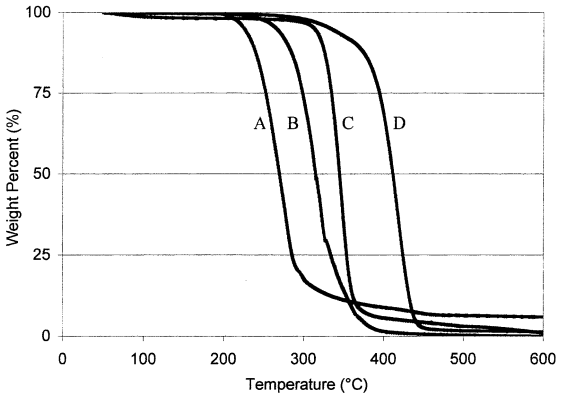

Fig. 2. TGA of pellet formulation components. Key: (A) PEG 8000; (B) theophylline; (C) MCC; (D) EUDRAGIT® Preperation 4135 F.

function of medium pH. The theophylline release profiles in pH 1.2 and 3.0 media are similar with both releasing approximately 52% of the drug after 12 h (Fig. 4). The drug release profiles of the HME beads were characteristic of a diffusion-controlled matrix system. Drug release was governed by solute diffusion within the matrix phase and decreased with time due to a receding drug boundary and to a decreasing area at the diffusion front. Researchers have noted that matrix systems exhibit negligible or no movement of the diffusion front due to swelling or erosion when the matrix polymer is insoluble in the dissolution medium (Lee, 1992). The matrix polymer, 4135 F, of the studied HME beads was insoluble in the acidic aqueous media. Additionally, Follonier and coworkers noted that porosity is an important determinant of drug release from melt-extruded sustained release pellets (Follonier et al., 1994, 1995). Slowed drug release rates from HME beads is further explained by decreased free volume since thermal treatment at elevated pressures decreases polymer free volume in the bead. Free volume is defined as the volume of an amorphous material that is not occupied by molecules of the amorphous material. Available free volume in an amorphous material determines diffusion of other molecules through the matrix material, thus increased degree of packing results in decreased drug release rates (Wicks, 1986). When the HME spherical pellets were tested in pH 6.8 medium, approximately 69% of the theophylline was released after 12 h (Fig. 4). Theophylline release increased in pH 6.8 medium because it was close to the pH at which the polymer starts to dissolve. Complete theophylline release was attained in approximately 4 h when the HME beads were tested in pH 7.4 medium. Drug release behavior in pH 6.8 and 7.4 was diffusion-controlled, but polymer swelling and dissolution also influenced drug release. The early stage of the dissolution process is dominated by polymer swelling as the polymer changes from a glassy to a rubbery state due to water penetration and subsequent plasticization.

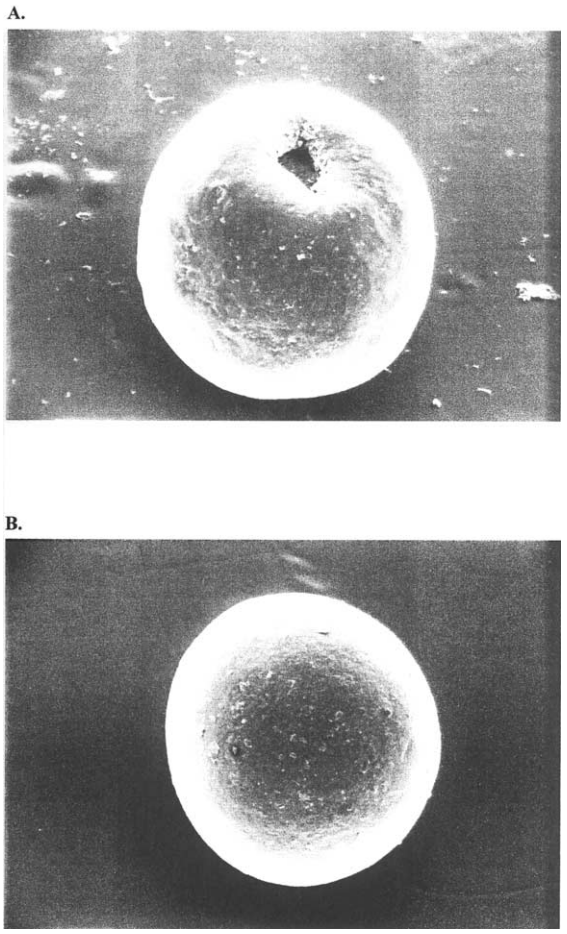

Fig. 3. SEM moicrographs of spherical pellets at ($\approx$ 1.2 mm diameter) Key: (A) spherical pellet produced by HME after spheronization for 45 min; (B) spherical pellet produced by HME after spheronization for 80 min.

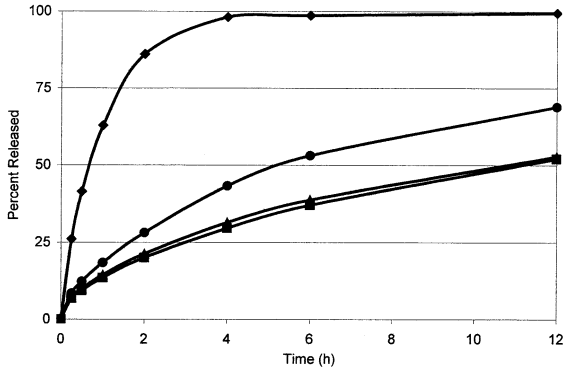

Fig. 4. Influence of medium pH on the release of theophylline from pellets produced by HME and spheronization (USP 24 Apparatus 2, 900 ml 37 °C 100 rpm $n = 3$). Key: pH 1.2 (▲); pH 3.0 (■); pH 6.8 (●); pH 7.4 (◆).

Dissolution of the polymer occurs when the water concentration at the polymer surface exceeds a critical concentration of macromolecular disentanglement (Lee, 1992). HME beads remained intact after dissolution testing for 12 h in pH 1.2, 3.0 and 6.8 media. The matrix beads did not disintegrate in these media due to matrix polymer insolubility and to significant polymer chain entanglement in the core matrix. The HME beads completely dissolved after dissolution testing for approximately 4 h at pH 7.4 where the matrix polymer was soluble.

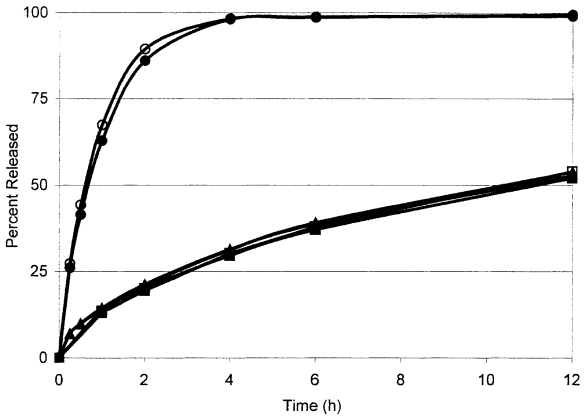

Fig. 5. Effect of 1 year storage at 25 °C/60% RH on the release of theophylline from HME and Spheronized pellets (USP 24 Apparatus 2, 900 ml, 37 °C, 100 rpm, $n = 3$). Key: ▲ initial; pH 1.2; △ stored; pH 1.2; ■ stored; pH 3.0; ● initial; pH 7.4; ○ stored; pH 7.4.

Although the T_g of the HME product was 23.1 °C as determined by MDSC, the pellets exhibited no sticking after storage for 1 week in sealed HPDE containers at 40 °C/75% RH. Furthermore, theophylline release properties of the HME beads did not change after storage for 1 year in sealed HDPE containers at 25 °C/60% RH, as demonstrated in Fig. 5.

4. Discussion

The findings from this study demonstrated that controlled-release spherical matrix pellets could be successfully prepared using a HME and spheronization process. Melt-extruded matrix pellets exhibited diffusion-controlled drug release. Drug release from the acrylic matrix system studied was influenced by the pH of the dissolution medium since the solubility of the matrix polymer, Eudragit® Preparation 4135 F, is pH dependent.

HME pellets are a unique dosage form because they can be used for immediate release or controlled-release applications depending on the properties of the matrix polymer. Conventional pellets must be coated to prevent rapid drug release, even when an insoluble matrix is employed. HME pellets do not require film coating to control drug release, but they can be film coated to further modify drug release in the gastrointestinal tract. Although our study employed Eudragit® Preparation 4135 F to produce spherical pellets, other polymers and thermal agents are currently under investigation to demonstrate the versatility of the HME and spheronization process.

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