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Downstream processing of a ternary amorphous solid dispersion: The impacts of spray drying and hot melt extrusion on powder flow, compression and dissolution

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ABSTRACT

Downstream processing aspects of a stable form of amorphous itraconazole exhibiting enhanced dissolution properties were studied. Preparation of this ternary amorphous solid dispersion by either spray drying or hot melt extrusion led to significantly different powder processing properties. Particle size and morphology was analysed using scanning electron microscopy. Flow, compression, blending and dissolution were studied using rheometry, compaction simulation and a dissolution kit. The spray dried material exhibited poorer flow and reduced sensitivity to aeration relative to the milled extrudate. Good agreement was observed between differing forms of flow measurement, such as Flow Function, Relative flow function, Flow rate index, Aeration rate, the Hausner ratio and the Carr index. The stability index indicated that both powders were stable with respect to agglomeration, de-agglomeration and attrition. Tablet ability and compressibility studies showed that spray dried material could be compressed into stronger compacts than extruded material. Blending of the powders with low moisture, freely-flowing excipients was shown to influence both flow and compression. Porosity studies revealed that blending could influence the mechanism of densification in extrudate and blended extrudate formulations. Following blending, the powders were compressed into four 500 mg tablets, each containing a 100 mg dose of amorphous itraconazole. Dissolution studies revealed that the spray dried material released drug faster and more completely and that blending excipients could further influence the dissolution rate.

1. Introduction

Amorphous solid dispersions (ASD) have received a surge in research interest over recent decades, due to the large and increasing number of poorly soluble drugs on today's market (Brouwers et al., 2009; Leuner and Dressman, 2000). Although several examples of commercial ASDs exist (Huang and Williams III, 2017), the technology has sometimes lost out to other bioavailability enhancement strategies, often due to problems with recrystallisation or perceived difficulties in downstream processing. Although publications addressing recrystallisation issues are manifold, far less research has been reported addressing the issues of flow and compression (Demuth et al., 2015).

Efficiency of flow and compression can affect processing times and tablet quality. Bridging, arching or rat-holing for instance, can lead to increased processing times, inaccurate die fill and unacceptable dose variation. Compression issues can cause sticking, picking or flaking of tablets and ultimately reduction in patient compliance (Jain, 1999; Leuenberger and Rohera, 1986; Patel et al., 2006). In an age of greater focus on quality by design (QbD), global manufacturing competition and 'right first time' demands, the need to resolve or minimise such issues at the research stage is stronger than ever.

The purpose of this study was to assess the impacts of spray drying (SD) and hot melt extrusion (HME) on the flow, compression and dissolution characteristics of an ASD containing itraconazole (ITZ). Comparisons between properties of amorphous dispersions prepared by SD and HME are popular, (Davis and Walker, 2018) although most of these do not specifically deal with downstream processing issues. We have recently reported the preparation of a novel ternary ASD using both SD (Davis et al., 2017) and HME (Albadarin et al., 2017). Ternary dispersions have become increasingly popular (Davis and Walker, 2018) in the struggle to meet the sometimes competing demands of ASDs: increased bioavailability, adequate stability, efficient processing, the use of existing plant equipment and bearable costs. The formulations, containing drug and excipient polymers Soluplus® and HPMCP, displayed excellent stability and enhanced dissolution in both studies (Albadarin et al., 2017; Davis et al., 2017). The following is an account of the impact of preparation on the downstream processing of one of those formulations.

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2. Materials and methods

2.1. Materials

ITZ (> 99%) was purchased from Xi'an Lyphar Biotech Ltd. Accurate analytical standard of itraconazole (99.8%) for HPLC calibration was purchased from Sigma Aldrich. Polymers Soluplus® & HPMCP HP-55 (HPMCP) were donated by BASF and Shin Etsu respectively. Excipients Avicel 101 & Avicel PH 200 LM were donated by FMC and Mannogem granular was donated by SPI Pharma. Solvents and chemicals were purchased from Sigma-Aldrich and were of HPLC and reagent grade.

2.2. Spray drying

Spray drying was conducted using a Büchi B-290 mini spray dryer connected to a B-295 inert loop. A 2-fluid pneumatic nozzle (0.7 mm) was fitted and liquid feedstock was pumped at 4 mL/min (15%). Drying nitrogen was set at maximum by fixing the aspirator at 100% (35 m^3/h). A solution of ITZ-Soluplus®-HPMCP (30–40-30 w/w) in dichloromethane-methanol 7–10 (v/v) (1.0 L, 10.0% w/v) was pumped through the nozzle at inlet temperature 100 °C, producing an outlet temperature of 65 ± 2 °C. High yields (88.6%) were achieved by using high spray gas rates (670 L/h) and attaching the high efficiency cyclone option. Powdered product was immediately transferred into a stainless steel pan and dried overnight in a vacuum oven at 40 °C and 10^{-2} mBar to ensure complete removal of residual levels of solvent. Powder was then stored in a sealed glass bottle in a desiccator over anhydrous molecular sieves.

2.3. Hot melt extrusion and milling

Itraconazole, Soluplus® and HPMCP 30:40:30 (w/w) (50 g) were pre-mixed by hand in a polythene bag, having first removed larger particles of HPMCP, by passing through a 435 μm sieve. The pre-mixed powders were then manually fed into a Three-Tec twin-screw extruder (Three-Tec GmbH, Germany) with a barrel diameter of 12 mm and an L/D ratio of 40:1. The set points of the six heating zones, from feed to die, were 80, 110, 120, 140, 150 and 150 °C, respectively and screw speed was maintained at 15 rpm throughout. Following extrusion the material was milled for 1 min at 20 Hz using a 25 mL stainless steel jar attached to a Retsch Mixer Mill MM 400 ball mill (Retsch GmbH, Germany). Milled extrudate was sieved through 435 and 90 μm sieves and the 90–435 μm and < 90 μm fractions were stored separately in sealed glass bottles in a desiccator over anhydrous molecular sieves.

2.4. Scanning electron microscopy (SEM)

Drug polymer formulations were attached to double sided carbon tape and sputter coated with a thin layer of gold followed by imaging using a Joel CarryScope JCM-5700 scanning electron microscope. Micrographs were recorded at various magnifications, using a beam acceleration voltage of 5 kV, a spot size of 40 and a working distance of 12.

2.5. Powder rheometry

Powder flow was analysed using an Freeman FT4 powder rheometer in a manner previously reported (Freeman, 2007). Stability and Variable flow rate was performed in the 25 mm vessel, Aeration in the 25 mm vessel and Shear in the 10 mL and 1 mL vessels.

2.6. Compaction simulation

Powders were tableted using a Gamlen R-series tablet press containing a 500 kg load cell and 6 mm punch and die. The material was subjected to uniaxial compression tests to form flat-face cylindrical tablets with a target weight of 90 mg. Punch load and displacement were measured during compression and the effect of compaction forces from 0.5 to 5 kN, equivalent to pressures of 17–173 MPa, was studied. Tablet hardness, defined as the diametral force required to break the compact, was investigated using a PharmaTest hardness tester (Pharma Test Apparatebau AG, Germany) immediately after tabletting.

2.7. True density

The true density of the extruded and spray dried products and powder blends was measured under ambient conditions using an helium pycnometer (AccuPyc II 1340, Micromeritics Inc., Norcross, GA). The volume of the pycnometer was verified with a standard before carrying out analysis. During sample analysis five purge cycles were recorded for samples and the reported result is an average of measurements made on three different days.

2.8. Formulation and tabletting

ASD products and excipients were accurately weighed as described in Table 4 and the individual components were vortex mixed for 2 min in 10 mL vessels. The resultant prototype tablet formulations were pressed according to scalable parameters determined through small scale compaction simulation performed on 90 mg material. Blends were weighed into a 0.5 in. (12.7 mm) diameter die and then pressed at 1000 kg pressure on a manual hydraulic tablet press to form flat-face cylindrical tablets with a target weight of 500 mg.

2.9. In-vitro dissolution studies

Drug release studies were carried out using non-sink conditions, in a USP type II apparatus, PharmaTest dissolution tester (Pharma Test Apparatebau AG, Germany), with 900 mL 0.1 *N* HCl buffer (pH 1.2) per well, a paddle speed of 100 rpm and a temperature of 37 ± 0.2 °C. Formulated tablets of mass 500 mg, equivalent to 100 mg of drug were added to the dissolution vessel (n = 3), with start times staggered by 2 min. 5 mL aliquots of media were withdrawn at predetermined intervals (0.25, 0.5, 0.75, 1, 2, 3, 4, and 6 h), filtered through a 0.45 μm polytetrafluoroethylene (PTFE) syringe filter and then the first 1 mL of filtrate was discarded. 500 μL of the filtrate was subsequently added to 500 μL of HPLC mobile phase in 2 mL HPLC vials. 5 mL of fresh medium was immediately replaced following each withdrawal.

2.10. High performance liquid chromatography (HPLC)

Dissolution samples were analysed using an Agilent (Agilent, Little Island, Cork) 1260 Infinity II high performance liquid chromatography system, comprising of quaternary pump G1311B and diode array detector G1315D set at wavelength 263 nm. The thermostated column compartment G1316A was set at 25.0 °C and equipped with a Kromasil 100 C18 5 μm 250 × 4.6 mm (Kromasil, Mainz, Germany) RP-HPLC column. The system was operated under isocratic flow at 1 mL/min using, a mobile phase of acetonitrile:water:diethanolamine (69.95/30/0.05, v/v/v). Samples were injected from autosampler G1329B in volumes of 20 μL and data was collected and analysed by Agilent OpenLAB CDS Chemstation software. Standards of ITZ (99.8% purity) were prepared from a stock solution of 1 mg/mL in methanol, to quantify the levels of drug in the dissolution media.

3. Results and discussion

3.1. Preparation of amorphous solid dispersions by spray drying and hot melt extrusion

In our previous studies we discovered that it was possible to prepare