



Application of X-ray microtomography for the characterisation of hollow polymer-stabilised spray dried amorphous dispersion particles



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ABSTRACT

The aim of this study was to investigate the capability of X-ray microtomography to obtain information relating to powder characteristics such as wall thickness and solid volume fraction for hollow, polymer-stabilised spray dried dispersion (SDD) particles. SDDs of varying particle properties, with respect to shell wall thickness and degree of particle collapse, were utilised to assess the capability of the approach.

The results demonstrate that the approach can provide insight into the morphological characteristics of these hollow particles, and thereby a means to understand/predict the processability and performance characteristics of the bulk material. Quantitative assessments of particle wall thickness, particle/void volume and thereby solid volume fraction were also demonstrated to be achievable. The analysis was also shown to be able to qualitatively assess the impact of the drying rate on the morphological nature of the particle surfaces, thus providing further insight into the final particle shape.

The approach demonstrated a practical means to access potentially important particle characteristics for SDD materials which, in addition to the standard bulk powder measurements such as particle size and bulk density, may enable a better understanding of such materials, and their impact on downstream processability and dosage form performance.

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1. Introduction

The use of dissolution enhancing approaches during pharmaceutical formulation development activities is now increasing in utility and a range of mature technologies are available. This is particularly so when more traditional approaches such as size reduction (Rabinow, 2004) and the use of salts (Berge et al., 1977) or pro-drugs (Rautio et al., 2008) are unable to give sufficient increases in solubility/bioavailability in order to make the crystalline drug substance viable for use in a standard solid dosage form. As the number of compounds with low solubility (BCS class II and IV) increases, the use of amorphous solid dispersions (Bhugra and Pikal, 2008; Chiou and Riegelman, 1971; Ford, 1986; Hancock and Parks, 2000; Leane et al., 2013; Leuner and Dressman, 2000; Serajuddin, 1999) is correspondingly becoming more common. Spray drying and hot melt extrusion, to produce

stabilised amorphous systems, is becoming a standard means to achieve the necessary dissolution.

Spray drying involves the rapid drying of an atomised feed solution consisting of organic solvent(s) containing an active pharmaceutical ingredient (API) plus any additional components such as polymers used to provide a stabilised amorphous systems (Paudel et al., 2013; Tobyn et al., 2009; Wegiel et al., 2013; Yoshioka et al., 1995). In such stabilised amorphous systems the role of the polymer can be to increase the glass transition temperature of the intermediate material and inhibit mobility of the constituents (kinetic stabilization) (Hancock et al., 1995), provide a matrix in which the amorphous active is soluble (thermodynamic stabilization) (Baird and Taylor, 2012; Van den Mooter et al., 2000), improve wetting during dissolution, and following dissolution to form a super-saturated solution to inhibit crystallization from solution (Alonzo et al., 2010; Graeser et al., 2009; Vandecruys et al., 2007). The polymer can also play a role in the chemical stabilization of the drug within the spray dried dispersion (SDD) matrix (Patterson et al., 2015).

Particle formation during spray drying is achieved by atomizing the feed solution to form droplets, the size of which is dependent

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on the nozzle design, spray pressure, and feed solution viscosity (Elversson et al., 2003). As the droplets begin to dry a film is formed around the outer edges of the droplet following which the exterior dimension of the particle remains relatively fixed. As drying progresses, the remaining solvent is driven off thereby creating a void space within the SDD particle. Dependent on the rate of drying, these voids can be expressed in multiple ways, from a single central void space at one extreme, to a porous honeycomb type structure at the other (Maher et al., 2015; Vehring, 2008; Vehring et al., 2007). The thickness of the particle wall will define the amount of solid present within a particle rather than the volume of the particle, and may also control the rate of drying in subsequent secondary drying steps (Hsieh et al., 2015). Hollow SDD particles may additionally undergo partial collapse forming raisin-like particles with the final morphology being dependent on the drying conditions used (Vicente et al., 2013).

In previous work, the use of mercury intrusion (Yates et al., 2015), imaging technologies such as cryogenic scanning electron microscopy (SEM) and image based particle characterization (Gamble et al., 2014) have been applied to understand the impact of spray drying parameters on particle attributes such as wall thickness and solid volume fraction. In the latter work it was demonstrated that the use of tests such as bulk density did not adequately describe the particle characteristics as the measurement, in addition to particle size and the packing of the particles, was also affected by variations in the volume of the internal void space within the particles. Whilst the measurements made were shown to be informative, the methodology applied was inherently prone to bias, due to the low number of particles analysed, and very labour intensive, making the approach practically infeasible for routine analysis.

The above approach also utilised a number of assumptions, a key assumption being the particles (and the void spaces) were spherical in nature, which excludes application of the approach to SDD particles which have undergone some degree of collapse during drying, a feature commonly observed for many polymer stabilised SDD materials.

In an attempt to overcome these limitations, X-ray microtomography (XRM) was assessed as an alternative approach to elucidate the morphological nature of SDD particles. XRM has been previously demonstrated to be able to measure the internal structure of SDD materials (Wong et al., 2014a) due to the sensitivity of the technique to density differences within samples.

The aim of this work was to investigate the feasibility of XRM to characterize SDD materials. For the purposes of this feasibility study, samples of SDD materials with as wide a range of morphological characteristics were analysed in order to fully assess the ability of the XRM to deal with varying wall thicknesses and extent of particle wall collapse. SDD material of varying wall thickness which had previously been characterised and reported (Gamble et al., 2014) were analysed to assess the feasibility of XRM.

In addition, samples of SDD showing varying levels of wall collapse were also analysed to assess the ability of the approach to characterize the 3-dimensional internal pore volume characteristics and wall thicknesses of such particles. As a consequence of the sample selection process, an in-depth investigation of the inter-relationship between spray drying conditions and particle characteristics was out of scope for this initial study.

2. Materials

The materials used during this study were:

- A spray dried amorphous dispersion consisting of 90.9% BMS-817399 (Bristol-Myers Squibb, USA) (Santella et al., 2014), and 9.1% PVP K-30 (Ashland Inc., Covington, KY, USA). The drug substance has a melting point of 210 °C and a glass transition temperature of 123 °C. The three batches used, batches B, D and E, were obtained using the methods previously reported (Gamble et al., 2014) and the same batch references are used to provide clarity across both pieces of work.
- Batch F was a spray dried amorphous dispersion consisting of 40% BMS-708163 (Bristol-Myers Squibb, USA) (Gillman et al., 2010), and 60% HPMC-AS (ShinEtsu Chemical Co. Ltd., Japan). The drug substance has a melting point of 160 °C and a glass transition temperature of 45 °C. The batch was subsequently tray dried to remove residual solvent.
- Batch G was a spray dried amorphous dispersion consisting of 100% HPMC-AS (ShinEtsu Chemical Co. Ltd., Japan). The batch was subsequently tray dried to remove residual solvent.

3. Methods

3.1. Spray drying process

The spray dried dispersions used in this study were all manufactured on a GEA Niro PSD-1 or PSD-2 spray dryer (GEA Niro, Columbia, USA). The API and polymer were first dissolved in the selected solvent system before being sprayed; the spray drying conditions for all lots studied are detailed in Table 1. The relative saturation at the outlet (%RS_{out}) for the three BMS-817399 SDD lots was calculated based upon the approach reported by Dobry et al. (2009) as shown in Eq. (1):

$$\%RS_{out} = 100 \cdot \left(\frac{P_{chamber}}{P_{*T_{out}}} \right) \cdot \frac{M_{soln} (1 - \chi_{solids}) / MW_{solvent}}{\left(\frac{M_{soln} (1 - \chi_{solids})}{MW_{solvent}} + \frac{M_{gas}}{MW_{gas}} \right)} \quad (1)$$

where M_{soln} is the solution feed rate, M_{gas} is the drying-gas flow rate, T_{out} is the drying-gas outlet temperature, χ_{solids} is the mass fraction solids in solution, $MW_{solvent}$ and MW_{gas} are the molecular weights for the respective species, $P_{chamber}$ is the absolute pressure

Table 1
Spray drying conditions for investigatory batches.

Material	Batch reference	Polymer	API load (%)	Spray solvent	Spray dryer	Solids concentration in solution (%w/w)	Solution temperature (°C)	Atomizing pressure (psi)	Inlet temperature (°C)	Outlet temperature (°C)	Solution feed rate (g/min)
BMS-817399	Batch B	PVP K-30	90.9	Methanol	PSD-1	35	Ambient	150	113	40	140
	Batch D					35	150	143	60		
	Batch E					25	125	124	40		
BMS-708163	Batch F	HPMC-AS	40	Acetone	PSD-2	16	Ambient	400	98	31	1167
Placebo SDD	Batch G	HPMC-AS	0	90:10 Methanol: water	PSD-1	7.5	121	248	151	88	145

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