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Characterization and performance assessment of solid dispersions prepared by hot melt extrusion and spray drying process

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ABSTRACT

The present study investigated effect of manufacturing methods such as hot melt extrusion (HME) and spray drying (SD) on physicochemical properties, manufacturability, physical stability and product performance of solid dispersion. Solid dispersions of compound X and PVP VA64 (1:2) when prepared by SD and HME process were amorphous by polarized light microscopy, powder X-ray diffractometry, and modulated differential scanning calorimetry analyses with a single glass transition temperature. Fourier transform infrared (FT-IR) and Raman spectroscopic analyses revealed similar molecular level interactions between compound X and PVP VA64 as evident by overlapping FT-IR and FT Raman spectra in SD and HME solid dispersions. The compactibility, tabletability, disintegration and dissolution performance were similar for solid dispersions prepared by both processing techniques. Differences in material properties such as surface area, morphological structure, powder densities, and flow characteristics were observed between SD and HME solid dispersion. The SD solid dispersion was physically less stable compared to HME solid dispersion under accelerated stability conditions. Findings from this study suggest that similar product performance could be obtained if the molecular properties of the solid dispersion processed by two different techniques are similar. However differences in material properties might affect the physical stability of the solid dispersions.

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1. Introduction

Amorphous solid dispersion is an increasingly important formulation approach to improve the dissolution rate and apparent solubility of poorly water soluble compounds (Fahr and Liu, 2007; Leuner and Dressman, 2000; Vasconcelos et al., 2007). A successful solid dispersion formulation should be easily processable to final dosage form and remain chemically as well as physically stable upon storage. Identification of appropriate formulation components is important to develop a successful amorphous solid dispersion with desired release profile. In addition, methods used to prepare amorphous solid dispersion can also influence each of these important properties of the dispersion.

Commonly used methods for preparation of solid dispersions includes the fusion or solvent processes such as hot melt extrusion (HME) (Miller et al., 2007; Zheng et al., 2007; Zhu et al., 2006), spray drying (SD) (Chauhan et al., 2005; Takeuchi et al., 2004), solvent co-precipitation (CP) (El-Gazayerly, 2000), and supercritical fluid process (Moneghini et al., 2001). Often one method of preparation for solid dispersion is arbitrarily selected and then the formulation scientist modifies the formulation until desired product performance is achieved. However, solid dispersions prepared by different methods can have differences in physicochemical properties, which might affect product performance (Patterson et al., 2007; Sethia and Squillante, 2004) and manufacturability. Hence, during early stage of development it could be important to understand the influence of processing technique on the solid dispersion performance to ensure selection of an appropriate formulation and processing technique. Limited studies have been conducted so far to understand the influence of a solid dispersion manufacturing technique on the physicochemical properties and performance of the solid dispersion (Badens et al., 2009; Guns et al., 2011; Patterson et al., 2007; Sethia and Squillante, 2004). HME and SD are the most common processing techniques used to prepare amorphous solid dispersion. The objective of the current study was to systematically investigate the effect of solid dispersion manufacturing methods such as HME and SD on physicochemical properties and understand how these properties can affect manufacturability, physical stability and product performance of solid dispersions.

In this investigative study, a weakly basic drug (referred to in this article as compound X), which belongs to BCS class II category was used. The compound X has poor aqueous solubility (intrinsic solubility estimated 18 μg/ml), moderate hydrophobicity (log *P*

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of 2.6) and pK_a of 2.5 (shows pH dependant solubility). The compound X has melting point of 207.6 °C and decomposes above 275 °C. Compound X was selected as model compound because it is difficult to convert to amorphous form and has high inherent tendency to crystallize. Polyvinylpyrrolidone-co-vinyl acetate 64 (PVP VA64) was selected as a suitable polymeric crystallization inhibitor to prepare solid dispersion based on preliminary screening studies, during which various extrusion polymers at different ratios were evaluated by hot stage microscopy, DSC analysis, and accelerated physical stability studies. Based on initial screening, a 1:2 compound X and PVP VA64 formulation was selected to prepare solid dispersions. The solid state and physicochemical properties of the solid dispersions prepared by HME and SD process were thoroughly characterized to understand their influence on product performance, physical stability, and manufacturability of solid dispersions.

2. Materials and methods

2.1. Materials

Compound X was supplied by the Chemical Development department of Boehringer Ingelheim Pharmaceuticals, Inc. (Ridgefield, Connecticut, U.S.A.). PVP VA 64 (Kollidon® VA64) and Crospovidone (Kollidon® CL) were obtained from BASF (Ludwigshafen, Germany). Microcrystalline cellulose (Avicel® PH 112) was obtained from FMC BioPolymer (Philadelphia, PA). Colloidal silicon dioxide (Aerosil® 200 P) was obtained from Evonik Degussa Corporation (Parsippany, NJ). Magnesium stearate was purchased from Mallinckrodt (Phillipsburg, NJ). Organic solvent of reagent grade and pharmaceutical excipients of compendial grade were used as received.

2.2. Preparation of solid dispersion by hot melt extrusion

Preliminary screening was conducted by hot stage microscopy to screen several ratios of compound X and PVP VA64 as well as to identify appropriate temperature at which drug dissolves in the polymer matrix.

A binary physical mixture of compound X with PVP VA 64 (1–2 ratio, w/w) was prepared by blending in a Turbula mixer for 5 min. This physical mixture was extruded using a 9 mm mini extruder (Three-tech, Seon, Switzerland), which was equipped with twin screws and heated barrel. The extruder was heated to 180 °C with thermostatic control at the front and rear end of barrel to maintain desired barrel temperature. The system was allowed to heat soak for ~15 min. The twin screws were rotated to a desired speed and the powder blend was added in small amounts to the extruder. The cooled extrudates were milled by passing through 18 mesh screen in a quadro co-mill (Waterloo, Canada) at 500 rpm. Milled extrudates were stored in a sealed aluminum pouch to keep them moisture free.

2.3. Preparation of solid dispersions by spray drying

The PVP VA64 polymer and compound X (2:1 ratio) were dissolved in acetone to prepare feed solution (2.5%, w/v) for spray drying process. Formulation was spray dried using a Buchi B290 mini spray dryer with inert loop (Buchi Labortechnik AG, Flowil, Switzerland). The solution was sprayed at a flow rate of 10 mL/min using 40 psi atomizing pressure. The aspirator pump was set at 100% and N_2 gas pressure was set at 4.5 bar. The inlet temperature was adjusted appropriately to achieve an outlet temperature around 70 °C. All spray dried material was kept in vacuum oven for overnight drying at 25 °C. The dried solid dispersions were stored in a sealed vial in a desiccator to keep them moisture free.

Approximately 2 g of spray dried solid dispersion slugs were prepared by applying 35 kN of compressional force on carver press, followed by milling to minimize the differences in particle size of solid dispersions obtained by spray drying and hot melt extrusion technique as well as to facilitate handling of spray dried solid dispersions. X-ray powder diffractogram of spray dried dispersion before and after slugging showed no difference indicating no change in material due to slugging and milling operation.

2.4. Preparation of solid dispersion tablets

The milled solid dispersions prepared by spray drying and hot melt extrusion process were blended with 40% extragranular components in a turbula mixer for 5 min. The final blend with composition given in Table 1, was compressed into 11 mm round shape tablets using single station carver press. The compression force for each formulation was adjusted to achieve disintegration time of not more than 15 min and tablet hardness of ≥7 kP.

2.5. Characterization of solid dispersions and tablets

2.5.1. Chemical purity analysis

Quantitative assay and purity analysis of samples was done using an gradient HPLC method where the eluent (A) comprised of 45 mM ammonium hexafluorophosphate in water/methanol 95/5 (v/v) and eluent (B) comprised of methanol/water 95/5 (v/v). The analytical column Atlantis T3 C18, 3 μm, 150 mm × 4.6 mm was operated at 40 °C with a flow rate of 1.0 ml/min and UV detection at 250 nm. The injection volume was 12 μl and the data acquisition time was 57 min.

2.5.2. Powder flow

Powder flow was assessed by determining the Carr index. Bulk density was determined by measuring known volume of mass occupied by the drug substance. Tap density was determined by mechanically tapping (raising the cylinder and allowing it to drop 1250 times a specified distance under its own weight) the cylinder (Vankel, Cary, NC) and measuring the volume. Carr index was determined from the bulk and tap density.

Table 1
Composition of solid dispersion formulation and dispersion tablets.

Components	Dispersion formulationmg/tablet (w/w %)	Process stage
BI proprietary compound X	100 (20%)	Part of the dispersion preparation by SD or HME
PVP VA64	200 (40%)	
Microcrystalline cellulose-PH 112	140 (28%)	Extra granular components blended with dispersion to make tablets
Colloidal silicon dioxide	5 (1%)	
Magnesium stearate	5 (1%)	
Crospovidone	50 (10%)	
Total	500 (100%)	