Compression Effects on the Phase Behaviour of Miconazole–Poly (1-Vinylpyrrolidone-Co-Vinyl Acetate) Solid Dispersions—Role of Pressure, Dwell Time, and Preparation Method

ABHISHEK SINGH,[1] CATHÉRINE DE BISSCHOP,[1] HENK SCHUT,[2] JAN VAN HUMBEECK,[3] GUY VAN DEN MOOTER[1]

[1]Drug Delivery and Disposition, KU Leuven, Leuven, Belgium
[2]Faculty of Applied Physics, Delft University of Technology, Delft, The Netherlands
[3]Department of Metallurgy and Materials Engineering, KU Leuven, Leuven, Belgium

Received 1 April 2015; revised 4 May 2015; accepted 13 May 2015

Published online 17 June 2015 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.24540

ABSTRACT: Compression of miconazole–poly (1-vinylpyrrolidone-co-vinyl acetate) (PVPVA64) solid dispersions prepared by spray drying and hot-melt extrusion was performed to gain insights into effect of compression pressure, dwell time, and preparation method on compression-dependent phase behavior. The solid dispersions prepared by spray drying were initially phase-separated showing two glass transition temperature (T_g), whereas the extruded samples showed one single T_g indicating better mixing. Compression caused mixing of spray-dried solid dispersions at high compression pressures and especially high dwell times. The extruded systems showed no statistically significant differences. However, physical mixtures made up from extruded samples containing 20% and 40% of active pharmaceutical ingredient underwent mixing upon compression. Coincidence Doppler measurements were performed to quantify the free volume of PVPVA64 which is a major contributor to the free volume in the solid dispersion matrix. A small but significant difference was found between the open free volume of the pure polymer subjected to varied manufacturing processes. Compression-induced plastic deformation and plastic flow enhances molecular mobility leading to mixing of different domains in solid dispersions. Different manufacturing methods may result in products with similar free volume, thereby showing similar molecular mobility. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 104:3366–3376, 2015

Keywords: solid dispersions; tableting; compression; mixing; glass transition; spray drying; extrusion; calorimetry (DSC); X-ray diffractometry; spectroscopy

INTRODUCTION

Despite concerted efforts by the drug discovery teams worldwide, the problem of poor solubility remains a serious impediment to the entry of effective formulations in the market. Amorphous solid dispersions (ASD) are a promising and increasingly utilized formulation tool in development research to formulate the complicated poorly soluble organic molecules.[1–3] In this formulation strategy, the active pharmaceutical ingredient (API) is dispersed in the polymer matrix either by processes such as spray drying or hot-melt extrusion (HME). In spray drying, both the API and the carrier are solubilized in a common solvent followed by evaporation of solvent leading to a powder. On the contrary, in HME, the API and polymer are heated above the glass transition temperature (T_g) of the polymer and/or the melting point of the API and mixed via shear forces imparted through the screws of the extruder. Out of the various solid dispersion subtypes, ASD are the most popular. This is because of the lack of energy obligation to break the crystal structure because of the presence of the API and the polymer in amorphous state and resulting in a solubility advantage.[4]

It is reported that various unit operations can affect the stability of formulations.[5,6] The most utilized delivery platform for administration of solid dispersions are tablets or capsules, and our research group is involved in exploring the effect of compression on the phase behavior of solid dispersions.[7,8] Worku et al. investigated the effect of compression on a pure amorphous system wherein amorphous indomethacin was used as a model system. Compression resulted in the induction and increased extent of crystallization because of enhanced molecular mobility and microcrack formation.[9] The stabilization of solid dispersions takes place because of antiplasticization effects and intermolecular interactions between the API and the carrier.[10] Therefore, it can be envisaged that the absence/presence of H-bonding can determine the impact of compression on phase behavior of solid dispersions. In H-bonded Naproxen-polyvinylpyrrolidone K25 (PVP K25), binary solid dispersions compression caused demixing of the metastable compositions because of weakening and/or disruption of intermolecular hydrogen bonding between Naproxen and PVP.[11] Interestingly, compression resulted in the mixing of miconazole–PVPVA64 solid dispersions devoid of any H-bonding that was attributed to molecular level mixing because of plastic deformation.[12] As viscoelastic/viscoplastic flow was envisaged to be responsible for mixing, variation in factors affecting plastic deformation can be expected to affect the mixing behavior. Consolidation and plastic deformation are affected by the applied stress and dwell time. Hence, in this study, we

Abbreviations used: API, active pharmaceutical ingredient; ASD, amorphous solid dispersions; HME, hot-melt extrusion; MDSC, modulated differential scanning calorimeter; T_g, glass transition temperature; T_g width, width of the glass transition temperature; PVP K25, polyvinylpyrrolidone K25; PVPVA64, poly (1-vinylpyrrolidone-co-vinyl acetate); XRD, X-ray diffraction.

Correspondence to: Guy Van den Mooter (Telephone: +32-16-330-304; Fax: +32-16-330-305; E-mail: guy.vandenmooter@pharm.kuleuven.be)

This article contains supplementary material available from the authors upon request or via the Internet at http://wileylibrary.com.

Journal of Pharmaceutical Sciences, Vol. 104, 3366–3376 (2015)

investigated the effect of various compression pressures and dwell times on miconazole–PVPVA64 solid dispersions.

Previous investigations have proven that the manufacturing method can impact the mixing capacity and the phase behavior of solid dispersions. HME resulted in better mixed miconazole–poly(ethylene-g-vinylalcohol) solid dispersions as compared with those prepared by spray drying.[13] In another study, HME, spray drying, and ball milling were compared as a preparation method for glass solutions. The method of manufacture had no influence on the physical stability, but did affect the dissolution characteristics.[14] The manufacturing method may also result in differences in powder parameters critical for the tableting process such as porosity, particle surface, and density. In a comparative study between coprecipitation and HME methods, it was found that extruded products had a lower specific surface area because of its lower porosity and smooth particle surface.[15] As compression-induced mixing/demixing is dependent not only on the presence/absence of the H-bonding but may also be affected by differences in macrolevel properties such as porosity, particle surface, density, and microlevel properties such as phase composition, mixing, and solid state characteristics, we investigated in this paper the effect of compression on the phase behavior of miconazole–PVPVA64 solid dispersions prepared by two different manufacturing methods: spray drying and HME.

MATERIALS AND METHODS

Materials

Miconazole was a gift sample from Janssen Pharmaceutica (Beerse, Belgium). Poly (1-vinylpyrrolidone-co-vinyl acetate) (PVPVA64) was acquired from BASF (Ludwifshafen, Germany). Solvents and chemicals used were of analytical or HPLC grade and were used as received.

Methods

Preparation of Solid Dispersions

Miconazole–PVPVA64 solid dispersions were manufactured using two different techniques.

Spray Drying. In the first method, solid dispersions were prepared using a Buchi mini spray-dryer B191 (Buchi, Flawil, Switzerland) with 20%, 30%, and 40% (w/w) loading of miconazole in PVPVA64. The process parameters used were: inlet temperature 60°C, outlet temperature 40°C, drying air flow rate 0.56 m^3/min, nozzle air flow rate 25 L/min, feed rate 6.8 mL/min, diameter nozzle tip 0.5 mm, and feed concentration 5% solids in dichloromethane. The spray-dried material was dried at 25°C in vacuum oven for 7 days prior to being used for further investigations.

Hot-Melt Extrusion. In the second method, solid dispersions were manufactured using a twin screw extruder type MP19PC (APV Baker Limited, Newcastle-U-Lyme, England). Two compositions were prepared with 20% and 40% (w/w) drug loading. The physical mixtures of API and PVPVA64 were prepared and fed through the feeding system with screws rotating at 300 rpm. The mixture was constantly mixed and tapped in the feed hopper in order to ensure uniform feed rate and avoid arching. The feeding speed was controlled by a speed controllable rotating screw.

The hot-melt extruder consists of three zones. The zone where the feed material enters is water-cooled, whereas the other two zones, through which material subsequently passes, are heated. The temperature at which the two heated zones were kept was decided based on the T_g of the 20% and 40% solid dispersions. The second and third zones were heated to T_g+20°C. Modular dies were used in which the feed screws were placed in Zone 1, that is, the location at which material enters into the barrel. This was followed by mixing paddles in Zone 2 and 3. The overall screw configuration of MP19PC extruder with a L/D ratio of 25/1 consisted of conveying elements in Zone 1 followed by five 30° forwarding paddles, followed by four 60° forwarding paddles, followed by six 90° alternating paddles, and finally three 60° reversing paddles in Zone 2. In the end, the conveying elements in Zone 3 push the molten material out through a die with 5 mm circular hole. The relative screw length of the kneading elements was 0.3 and the paddle width was 1.9 cm. Even though the die is not heated, its temperature is high owing to the conductive heat flow from the heated zones and friction as well. The three temperatures, which were registered, were those from Zone 2 (T2), Zone 3 (T3), and in between the heated zones (T1). Out of 400 g feed material, the first 100 g material was discarded to avoid contamination and inhomogeneity. Upon cooling, extrudes were converted into fine powder using a milling machine (Janke and Kunkel GmbH and Company, Staufen im Breisgau, Baden-Württemberg, Germany). Ten gram material was milled for 1 min and was subsequently dried at 25°C in vacuum oven for 24 h before being used further. This drying step was incorporated in order to remove the moisture that might have been taken up by the extrudates during and after milling.

Thermal Analysis

Powder samples and tablets were analyzed in triplicate using a Q2000 modulated differential scanning calorimeter (MDSC) (TA Instruments, Leatherhead, UK) connected to a refrigerated cooling system (RCS90) unit and purged with 50 mL/min of inert dry nitrogen gas. The instrument was calibrated for two temperature points using standard indium and *n*-octadecane. Indium was also used to calibrate and validate enthalpy. Sapphire disks were used to calibrate and validate the heat capacity (validation at 66.85°C). The modulation parameters applied were an amplitude of 0.636°C every 40 s. The underlying heating rate used for all the samples was 2°C/min. The powdered samples were analyzed in crimped TA Instruments standard aluminum pans. The tablet analysis was performed by isolating a part of the 13-mm tablet and crimping it in standard TA pans. Universal Analysis software (version 4.4; TA Instruments) was used to analyze the acquired data. Origin 8.6 (OriginLab Corporation, Northampton, Massachusetts) was also used to plot thermograms wherever required.

Powder X-Ray Diffraction

Samples were analyzed using an automated X'pert PRO diffractometer (PANalytical, Almelo, The Netherlands). A Cu X-ray radiation source (Kα radiation, $\lambda = 1.541874$ Å) tube and generator set at 45 kV and 40 mA were employed. The sample was placed between Kapton films and analyzed between 2θ of 4°