The Influence of Drug Physical State on the Dissolution Enhancement of Solid Dispersions Prepared Via Hot-Melt Extrusion: A Case Study Using Olanzapine

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ABSTRACT: In this study, we examine the relationship between the physical structure and dissolution behavior of olanzapine (OLZ) prepared via hot-melt extrusion in three polymers [polyvinylpyrrolidone (PVP) K30, polyvinylpyrrolidone-co-vinyl acetate (PVPVA) 6:4, and Soluplus® (SLP)]. In particular, we examine whether full amorphicity is necessary to achieve a favorable dissolution profile. Drug–polymer miscibility was estimated using melting point depression and Hansen solubility parameters. Solid dispersions were characterized using differential scanning calorimetry, X-ray powder diffraction, and scanning electron microscopy. All the polymers were found to be miscible with OLZ in a decreasing order of PVP>PVPVA>SLP. At a lower extrusion temperature (160°C), PVP generated fully amorphous dispersions with OLZ, whereas the formulations with PVPVA and SLP contained 14%–16% crystalline OLZ. Increasing the extrusion temperature to 180°C allowed the preparation of fully amorphous systems with PVPVA and SLP. Despite these differences, the dissolution rates of these preparations were comparable, with PVP showing a lower release rate despite being fully amorphous. These findings suggested that, at least in the particular case of OLZ, the absence of crystalline material may not be critical to the dissolution performance. We suggest alternative key factors determining dissolution, particularly the dissolution behavior of the polymers themselves. © 2014 The Authors. *Journal of Pharmaceutical Sciences* published by Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:1214–1223, 2014

Keywords: olanzapine; dissolution; solid dispersion; polymer; amorphous; crystallinity; particle size

INTRODUCTION

The oral bioavailability enhancement of poorly soluble active pharmaceutical ingredients (APIs) continues to represent a significant issue in drug development. One strategy to overcome this obstacle is the development of amorphous solid dispersion formulations using hydrophilic polymers. The term "solid dispersion" was described by Chiou and Riegelman[1] as "the dispersion of one or more active ingredients in an inert carrier matrix at solid state prepared by melting (fusion), solvent, or melting–solvent method." This definition is still applicable despite the field having developed considerably to include a wider range of manufacturing techniques [e.g., hot-melt extrusion (HME)] and new concepts in structural characteristics, particularly involving the recognition of complexities of molecular dispersion of drugs in polymers.

The mechanisms underpinning the dissolution increase of these formulations are still not yet clearly understood. Currently, there is a belief that the fundamental critical factor is the molecular dispersion of the drug in the polymer, thereby representing the ultimate in particle size reduction and lattice energy negation. A number of papers have addressed these and associated issues such as wetting and reduction in agglomeration.[2,3] In addition, earlier work in the pre-HME solid dispersion field suggested that the drug dissolution may be controlled by the behavior of the carrier (so-called "carrier controlled dissolution"), by implication suggesting that the physical state of the drug may not be important in such systems.[4,5]

The specific issue of whether full amorphization (in terms of either molecular dispersion or amorphous phase generation) is actually necessary to achieve fast and complete dissolution has been addressed by previous authors. For example, Verheyen et al.[6] observed that the dissolution rate of diazepam and temazepam could be enhanced when formulated into solid dispersions with polyethylene glycol (PEG) 6000, although both drugs remained in a highly crystalline state. The reason for this behavior was attributed to the existence of a microenvironment created by the polymer at the surface of the drug particles leading to a better wetting and solubilization properties.

In this study, we focused on the physical state properties of the dispersions prepared with olanzapine (OLZ) and their influence on the dissolution performance. OLZ was formulated with three hydrophilic polymers, polyvinylpyrrolidone (PVP) K30, polyvinylpyrrolidone-co-vinyl acetate (PVPVA) 6:4, and polyvinyl caprolactam-polyvinylacetate-PEG graft copolymer (Soluplus®, SLP) via HME. HME is a widely used technology in which API and carrier are converted into a product of uniform shape and density by the effect of heat and mechanical stress.[7,8] HME represents a continuous solvent-free manufacturing method and is relatively easy to scale-up, hence

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presenting a commercially viable approach to dosage form development.

Olanzapine is an atypical antipsychotic agent used to treat both negative and positive symptoms of schizophrenia, acute mania with bipolar disorder, agitation, and psychotic symptoms in dementia.[9] According to Biopharmaceutical Classification System (BCS), OLZ is classified as a Class II drug (low solubility, high permeability) with water solubility around 43 mg/L.[10] OLZ has been suggested to crystallize in more than 50 different crystalline forms, including anhydrates, hydrates, and solvates.[11,12] In this study, anhydrous OLZ Form I, the most stable form and currently used in pharmaceutical formulations, was selected for study. In terms of the polymers used in this work, numerous studies have been conducted on the solubility enhancement of water-insoluble compounds, in particular using PVP and its derivatives as carriers,[13–16] with high solubilization effects and the ability to establish hydrogen bonds with APIs being well-recognized properties of these polymers.[17,18] However, there are also issues associated with the use of these materials, for example, PVP K30 has a high glass transition temperature (T_g) and a relatively low degradation temperature (T_{deg}), which can represent an issue during processing via HME because of the narrow temperature window of operation. Moreover, PVP is classified as an extremely hygroscopic substance, which is attributed to the electronegative groups (C=O) in the pyrrolidone structure being able to establish hydrogen bonding with water.[19] The copolymer PVPVA 6:4 has a 40% replacement with lipophilic vinyl acetate functional groups and therefore it is less hygroscopic than the homopolymer system.[20] SLP on the other hand is a synthetic polymer that combines both hydrophilic and hydrophobic components in its structure that facilitates increased solubilization of drugs and thus the preparation of fully amorphous solid dispersions. Moreover, the low T_g (≈70°C) compared with the PVP-based polymers permits easier processing of thermolabile APIs, whereas its low hygroscopicity has favorable stability implications. The chemical structures of OLZ and each polymer are presented in Figure 1.

In this study, the freshly prepared HME systems were characterized with particular reference to the miscibility and crystallinity of OLZ; the influence of drug physical state on the dissolution performance was evaluated accordingly. At first, we evaluated the optimal extrusion temperatures for the OLZ–polymer systems based on the properties of each material (i.e., T_g, T_m, and T_{deg}). In addition, the thermodynamic solubility/miscibility and interaction of OLZ in each polymer were assessed using melting point depression (MPD)[21,22] and solubility parameter[23–25] approaches. The physicochemical properties and the morphology of the extrudates were evaluated using differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD), and scanning electron microscopy (SEM). In this manner, it is intended that the association between the miscibility, processing characteristics, physical structure, and dissolution behavior of OLZ may be determined and compared for three polymer systems, in turn leading to insights into the critical factors determining performance.

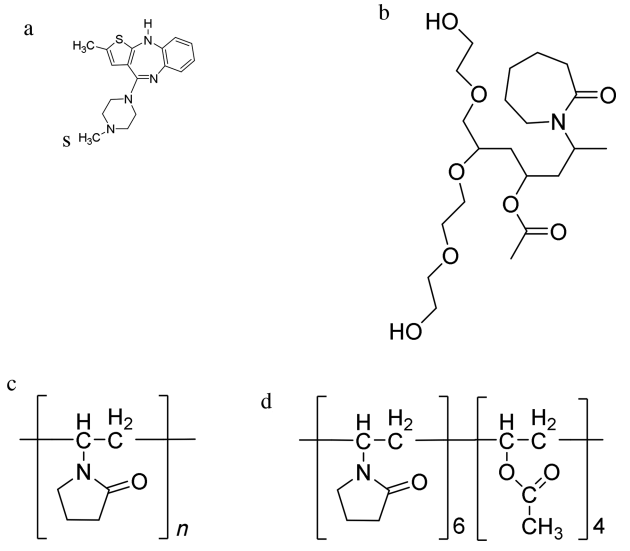

Figure 1. Chemical structures of OLZ (a), SLP (b), PVP K30 (c), and PVPVA 6:4 (d).

EXPERIMENTAL

Materials

Olanzapine [molecular weight (M_w) = 312.43 g/mol, density (ρ) = 1.30 g/cm^3] was purchased from Myjoy Ltd. (India); PVP K30 (M_w = 41.550 g/mol, ρ = 1.16 g/cm^3), PVPVA 6:4 (M_w = 57.500 g/mol, ρ = 1.17 g/cm^3), and SLP (M_w = 118.000 g/mol, ρ = 1.20 g/cm^3) were kindly donated by BASF Chemicals (Germany). Methanol (analytical grade) was obtained from Sigma–Aldrich (UK) . Phosphate buffer, pH 6.8 (Ph Eur), used in the dissolution studies was prepared with potassium dihydrogen orthophosphate (Fischer Scientific, UK) and sodium phosphate dibasic (Sigma–Aldrich).

Methods

Preparation of HME*s*

Hot-melt extrudates were prepared using a corotating twin screw extruder Thermo Scientific HAAKE MiniLab II (Thermo Scientific, UK). Formulations of OLZ with PVPVA and SLP were prepared with ratios of 20:80 and 50:50 (w/w) and extruded at 160°C and 180°C; the OLZ–PVP formulation was only successfully prepared at 50:50 (w/w) and extruded at 160°C. Each system was prepared using a total weight of 5 g at a speed of 100 rotations/min and mixed inside the barrel for 10 min. A round die with a diameter of 2 mm was attached to the extruder.

Drug–Polymer Miscibility Prediction

Melting Point Depression. Olanzapine and polymers were passed through a combination of sieves, and a fraction between 63 and 106 μm was used in all MPD experiments. Polymers were dried over P_2O_5 for 48 h prior to usage. Physical mixtures (PMs) with a drug ratio of 70%, 75%, 80%, 85%, 90%, and 100% (w/w) were prepared at least in triplicate. The melting temperature of OLZ both in the absence and presence of polymers was measured using DSC at a scan rate of 10°C/min in standard pans.

Melting point depression results can be used to predict the drug–polymer Flory–Huggins (FH) interaction parameter, χ, using Eq. (1),

$$\left(\frac{1}{T_m^{mix}}-\frac{1}{T_m^{pure}}\right)=\frac{-R}{\Delta H_{fus}}\left[\ln\phi_{drug}+\left(1-\frac{1}{m}\right)\phi_{polymer}+\chi\phi_{polymer}^2\right]$$