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Solid microcrystalline dispersion films as a new strategy to improve the dissolution rate of poorly water soluble drugs: A case study using olanzapine

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ABSTRACT

In this study, we evaluate the dissolution rate enhancement of solid microcrystalline dispersion (SMD) films of olanzapine (OLZ) formulated with four water-soluble polymers namely poly(N-vinylpyrrolidone) (PVP), poloxamer 188 (P188), poloxamer 407 (P407) and Soluplus® (SLP). Prepared formulations were characterised to determine particle size, morphology, hydrogen bonding interactions, thermal characteristics as well as *in vitro* dissolution studies conducted under sink conditions (pH 6.8). Particle size of OLZ in all formulations ranged between 42 and 58 μm. Attenuated Total Reflectance Fourier Transform Infrared spectroscopy (ATR-FTIR), Differential Scanning Calorimetry (DSC) and Hot-Stage Microscopy (HSM) studies confirmed OLZ was well maintained in its crystalline state during the formulation process. *In vitro* dissolution studies showed immediate drug release from all formulation when compared to the drug alone. The greatest increase in *in vitro* dissolution rate was observed in formulations containing P188 most likely due to its enhanced hydrophilic and surfactant properties compared to the other agents used. Overall, this study successfully generated OLZ loaded SMD films with improved *in* vitro dissolution rates which is highly likely to result in improved oral bioavailability *in vivo*.

1. Introduction

Olanzapine (OLZ) is an atypical antipsychotic drug used to treat schizophrenia and other mental health disorders (Roo, 1913). It is a poorly water-soluble drug classified accordingly to the Biopharmaceutics Classification System (BCS), as a class II drug. BCS class II and IV drugs represent a significant challenge in the pharmaceutical industry due to their poor oral bioavailability as a result of their low aqueous solubility (Ku, 2008). Different formulation strategies such as co-crystal (Good and Rodri'guez-Hornedo, 2009), salt formation (Serajuddln, 1999), micronization (Carr et al., 2010; Khadka et al., 2014) and most commonly, solid dispersion (SD) approaches (Chiou and Riegelman, 1971; Craig, 2002; Van Den Mooter, 2009; Raimi-Abraham et al., 2015) have been employed to increase BCS II and IV aqueous solubility and consequently enhance their oral bioavailability. A SD can be described as a delivery system whereby the drug is dispersed in a biologically inert matrix, usually with a view to enhance oral bioavailability (Craig, 2002). There are different types of SDs with the difference between them being the solid state of the polymer-matrix and the active pharmaceutical ingredient (API). A 'glass suspension', as defined by Kolter et al. (2012), is a SD where the drug remains in the crystalline state after being dispersed in an amorphous polymer. More commonly, this term is used to describe a SD where the drug is molecularly dispersed within an amorphous matrix (usually a polymer). Eutectic formulations contain both drug and polymer in the crystalline state (Bikiaris et al., 2005; Kolter et al., 2012; Leuner and Dressman, 2000; Vasanthavada et al., 2005). It is well-known that amorphous materials possess short range molecular order and high kinetic energy. Their weaker attractive intermolecular forces result in bonds which are easily broken that allow molecules to be lost from its surface (in the solid state) into a liquid medium easier compared to their crystalline counterparts, therefore they are more soluble and have faster dissolution rate (Shah et al., 2014). However, amorphous materials

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have low stability and high tendency to recrystallize within pharmaceutically relevant timescales (Michael, 2007; Sinko, 2011). The crystalline state (where molecules possess long range molecular order) is a low energy state which defines its higher stability allowing an adequate physical form control during formulation and storage processes (Michael, 2007; Sinko, 2011).

Micronization is a well-known technique for particle size reduction. The reduction of the particle size of an API increases its surface area, contact regions with the external aqueous environment and consequently its dissolution rate (according to the Noyes-Whitney equation). Decreasing the particle size will increase the saturation solubility (Ostwald-Freundlich) and will also result in a thinned hydrodynamic layer surrounding the particle therefore, increasing its surface-specific dissolution rate (Prandtl equation) (Da Fonseca Antunes et al., 2013). A growing method to improve solubility of poorly water soluble drugs includes the preparation of crystalline SD where the particle size of the drug has been reduced (Michael, 2007; Sinko, 2011) to increase its dissolution rate.

Several methods have been used to prepare SDs (both amorphous and crystalline) such as spray drying (Taylor et al., 2010), freeze-drying (Naik and Mokale, 2014), hot melt extrusion (Djuris et al., 2014; Pina et al., 2014), pressurised gyration (Raimi-Abraham et al., 2015) and solvent casting method (commonly used to prepare pharmaceutical thin films). Solvent casting method is an easy and manageable technique in which the API can either be suspended or dissolved in a polymer solution and with or without stabilizers. This method is ideal for heat-sensitive APIs as it can be conducted at room temperature (Qi et al., 2013).

Pharmaceutical films offer several advantages for oral drug delivery over other dosage forms. Upon direct contact with saliva (in the oral cavity), they instantly dissolve allowing the release of the API. Drug-loaded polymeric thin films (with a few micrometres thickness) have attracted attention for a variety of applications including oromucosal drug delivery, bio-adhesive formulations, skin delivery, and wound management (Qi et al., 2013). Pharmaceutical films are known to improve patient compliance especially in those who have difficulty or aversion to swallowing conventional oral dosage forms (Kianfar et al., 2011). These advantages make pharmaceutical thin films one of the most portable and convenient oral dosage forms of any available today (Ghodake et al., 2013; Koland et al., 2010).

This study highlights the use of solid microcrystalline dispersion (SMD) films as an alternative strategy to improve the dissolution rate (and in turn oral bioavailability) of poorly water soluble drugs. SMD films were prepared where the drug firstly undergoes gentle micronization resulting in uniform microcrystalline drug particles. Films were then generated using the solvent cast method from an aqueous polymeric base.

The aims of the work detailed here were two-fold. Firstly, to prepare poly(*N*-vinylpyrrolidone) (PVP, Kollidon 90F) based SMD films (using OLZ as a model API) offering enhanced dissolution rate compared to the API alone. Secondly, to explore the use of poloxamers (poloxamer 188 (P188), poloxamer 407 (P407)) and solubilizing agents (Soluplus® (SLP)) commonly used in the generation of amorphous SDs in melt methods (such as HME) to further improve the dissolution rate of OLZ.

2. Materials and methods

2.1. Materials

OLZ [molecular weight (Mw) = 312.43 g/mol] was purchased from Myjoy Ltd (Hangzhou, China). P188 [Mw = 7680 – 9510 g/mol], P407 [Mw = 9840 – 14600 g/mol]; PVP [Mw = 1000000 – 1500000 g/mol] and SLP [Mw = 90000 – 140000 g/mol] were kindly donated by BASF® (Ludwigshafen, Germany). Methanol, potassium dihydrogen phosphate, dipotassium phosphate and sodium chloride were obtained from Sigma-Aldrich (Dorset; UK). Fig. 1 shows the chemical structures of OLZ, SLP, PVP, P188 and P407.

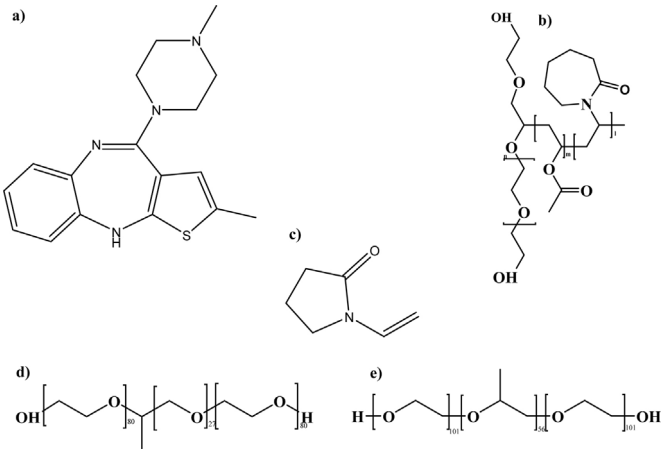

Fig. 1. Chemical structure of the different materials used in this study: a) OLZ; b) SLP; c) PVP; d) P188; e) P407.

2.2. Solid microcrystalline dispersions preparation

SMD films containing OLZ as microcrystalline structures were prepared using the solvent casting method from an aqueous polymeric base. To ensure a homogeneous particle size distribution of OLZ, prior to film preparation, OLZ was gently milled using a Ball Mill (Ballmill M/C number 2; Christison Ltd.; Gateshead) for 10 min (repeated three times with a cool-down period time of 15 min in between milling) at 150 rpm. The obtained powder was passed through a 63 μm sieve. PVP powders were dissolved in distilled water (in house system) and the poloxamers and solubilizing agents (i.e. P188, P407 and SLP) and OLZ were then added under stirring according to the formulation requirements as summarized in Table 1. Formulations were dried in a fume cupboard for 24 h to ensure evaporation of the solvent and allow film formation.

2.3. Film morphology and particle size analysis

Scanning electron microscopy (SEM) (JSM 4900LV; JEOL Ltd., Japan) images were collected on freshly prepared films to investigate SMD film morphology and particle size analysis. To improve conductivity prior to examination, samples were coated with 20 nm of gold under vacuum using a PolaronSC7640 sputter gold coater (Quorum Technologies, UK). The average diameter of the drug was determined from the mean value of 100 measurements using ImageJ (USA, version 1.46 v).

The particle size of formulated OLZ in SMD films was measured. Prior to the analysis a weighed amount of film was dissolved in

Table 1
Composition of OLZ, PVP, P188, P407 and SLP used to prepare SMD pharmaceutical films.

Formulation	Ingredient (% w/w)				
	OLZ	PVP	P188	P407	SLP
F1	10%	90%	–	–	–
F2	10%	85%	5%	–	–
F3	10%	85%	–	5%	–
F4	10%	85%	–	–	5%