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Unexpected solvent impact in the crystallinity of praziquantel/poly (vinylpyrrolidone) formulations. A solubility, DSC and solid-state NMR study

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ABSTRACT

The saturation solubility of PVP:PZQ physical mixtures (PMs) and solid dispersions (SDs) prepared from ethanol (E/E) or ethanol/water (E/W) by the solvent evaporation method at 1:1, 2:1 and 3:1 ratio (w/w) was determined. The presence of PVP improves the solubility of PZQ (0.31 ± 0.01 mg/mL). A maximum of 1.29 ± 0.03 mg/mL of PZQ in solution was achieved for the 3:1 SD (E/E). The amount of PZQ in solution depends on the amount of polymer and on the preparation method. Solid-state NMR (ssNMR) and DSC were used to understand this behavior. Results show that PMs are a mixture of crystalline PZQ with the polymer, while SDs show different degrees of drug amorphization depending on the solvent used. For E/W SDs, PZQ exists in amorphous and crystalline states, with no clear correlation between the amount of crystalline PZQ and the amount of PVP. For E/E SDs, formulations with a higher percentage of PZQ are amorphous with the components miscible in domains larger than 3 nm (^{1}H ssNMR relaxation measurements). Albeit its higher saturation solubility, the 3:1 E/E PVP:PZQ sample has a significant crystalline content, probably due to the water introduced by the polymer. High PVP content and small crystal size account for this result.

1. Introduction

Schistosomiasis is an acute and chronical parasitic disease caused by trematode worms of the genus *Schistosoma*. The infection exists in tropical and sub-tropical areas, affecting mainly poor communities with no access to potable water and sanitation. According to the World Health Organization (WHO), there are close to 240 million people in the world infected, several million of which suffer from severe morbidity, in an area where around 700 million people live (WHO, 2016a). The disease has been fought successfully with anthelminthic drugs, with Praziquantel (PZQ), 2-(cyclohexylcarbonyl)-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-*a*] isoquinolin-4-one, as the recommended treatment against all forms of schistosomiasis (Fig. 1).

PZQ exists commercially as a racemic compound, with two isomers (*R* and *S* enantiomers). Studies have revealed that only the enantiomer *R* has therapeutic value, with the *S* enantiomer being only responsible for the bad taste associated with the drug (Meyer et al., 2009). Although the WHO and the Center for Disease Control (CDC) consider PZQ an effective, safe and low-cost drug (CDC, 2012; WHO, 2016b), this is far from being a perfect drug, mainly because of its low solubility in water (only 0.04 g/100 mL) (de la Torre et al., 1999; El-Arini et al., 1998) and a first pass effect (Lindenberg et al., 2004) that compromises its bioavailability. In fact, PZQ is classified in the Biopharmaceutical Classification System (BCS) as a type II drug (poorly soluble, highly permeable) (Lindenberg et al., 2004).

Abbreviations: PZQ, praziquantel; PVP, poly(vinylpyrrolidone); NMR, nuclear magnetic resonance; DSC, differential scanning calorimetry; SEM, scanning electron microscopy; PMs, physical mixtures; SDs, solid dispersions.

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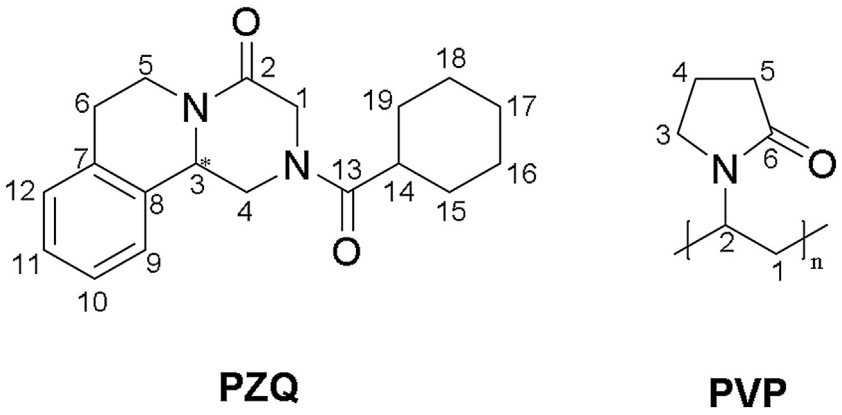

Fig 1. Molecular formulas of PZQ and PVP, with the numbering scheme adopted. The * in C3 of PZQ denotes the chiral center.

Attaining a better bioavailability can be economically achieved by the appropriate pharmaceutical formulations that help dissolve PZQ in water, improving its effectiveness. Several strategies have been reported in the literature, such as the encapsulation in cyclodextrin derivatives (Arrúa et al., 2015; Chaves et al., 2010), the use of water soluble polymers such as PVP (Baghel et al., 2016; de la Torre et al., 1999; Trastullo et al., 2015) and poly(ethyleneglycol) (Bagade et al., 2015; Passerini et al., 2006), inclusion in poly(methyl metacrylate) nanoparticles, (Fonseca et al., 2013; Malhado et al., 2016) liposome encapsulation (Frezza et al., 2013) and even complexation to metal centers (Patra et al., 2013).

PVP:PZQ formulations have attracted the attention of several research groups. PVP has been extensively used as an excipient in several pharmaceutical formulations mostly as a tablet binder and bioavailability enhancer and is considered safe (Haaf et al., 1985). Given the molecular structures of both PVP and PZQ (Fig. 1), one expects that the interactions between the two molecules to be mostly van der Waals forces that should be strong enough to promote drug dissolution but weak enough to allow its release. And indeed it has been demonstrated that an increase in the amount of PVP increases PZQ solubility and that physical mixtures and solid dispersions behave differently in terms of solubility and dissolution rates (El-Arini et al., 1998). Furthermore, amorphous PZQ inclusion in the PVP matrix has been demonstrated by scanning electron microscopy (SEM) and X-ray powder diffraction (DRX) (de la Torre et al., 1999).

The development of amorphous solid dispersions is of great interest, so it is crucial to find suitable techniques to characterize them in terms of drug degradation, crystallinity of the active principle, drug-carrier miscibility and intermolecular interactions. Common techniques include thermal analysis and X-ray diffraction (Baird and Taylor, 2012; LaFountaine et al., 2016), but these can have some limitations in differentiating between amorphous and crystalline phases and in obtaining further information if specific thermal events are not well resolved, when for instance the drug and the polymer mixture having similar *Tg* values (Newman et al., 2008; Tatton et al., 2013). Solid-state Nuclear Magnetic Resonance (ssNMR) spectroscopy has emerged as an important nondestructive technique since it allows us to look at the formulation without the interference of solvent molecules and thus probe the initial stage of the dissolution process, while giving information on short range interactions (Ito et al., 2010; Tres et al., 2015; Yuan et al., 2015). In this context, the aim of the present work is to promote a deeper knowledge on PVP:PZQ formulations by using solid-state Nuclear Magnetic Resonance (NMR) and Differential Scanning Calorimetry (DSC) to demonstrate, for the first time, that solvent choice in the preparation of solid dispersions plays a crucial role in the physicochemical properties of the resulting formulations, as it can promote or inhibit PZQ crystallization.

2. Materials and methods

2.1. Materials

Racemic Praziquantel ($C_{19}H_{24}N_2O_2$, purity >99.4%) was purchased from Romikin (Buenos Aires, Argentina). Poly(vinylpyrrolidone) powder (K30, average MW 40,000) was purchased from BASF SE (Ludwigshafen, Germany). All the reagents and chemicals used for analytical purpose were of chromatography grade.

2.2. Preparation of amorphous praziquantel

The PZQ sample was melted inside a stainless steel container in a vacuum oven for 3 h at 150 °C. The melted sample was then rapidly cooled with liquid nitrogen to form an amorphous glass of PZQ that was kept at −10 °C (*circa* 50 °C bellow the glass transition temperature, T_g). It should be noted that under these conditions no decomposition of the sample was observed, either by DSC or NMR. This is in line with literature reports (El-Subbagh and Al-Badr, 1998) and was confirmed by LC–MS (96.8% *vs* 98.9% for the initial crystalline sample—see Appendix for more details).

2.3. Preparation of physical mixtures

Physical mixtures (PMs) of PVP and PZQ (150 mg), in 1:1, 2:1, and 3:1 weight ratios were prepared by physically mixing the components thoroughly for 10 min in a mortar until a homogeneous mixture was obtained. The powder was then passed through 100 mesh sieve and stored in a desiccator.

2.4. Preparation of solid dispersions

I) Solid dispersions (SDs) of PVP:PZQ at 1:1, 2:1, and 3:1 (w/w) were prepared by the solvent evaporation method. PZQ (150 mg) was dissolved in 10 mL of ethanol, and the polymer was dissolved in 10 mL of water. The solutions were mixed under magnetic stirring for 30 min. The solvents were then evaporated under reduced pressure, dried at 40 °C (48 h), passed through 100 mesh sieve and stored in a desiccator. II) Solid dispersions of PVP:PZQ at 1:1, 2:1 and 3:1 (w/w) were also prepared dissolving both components exclusively in ethanol using the same procedure as described in I).