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# Solid state drug-polymer miscibility studies using the model drug ABT-102

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ABSTRACT

Amorphous solid dispersions typically suffer storage stability issues due to: their amorphous nature, high drug loading, uneven drug:stabilizer ratio and plasticization effects as a result of hygroscopic excipients. An extensive solid state miscibility study was conducted to aid in understanding the mechanisms involved in drug/stabilizer interactions. ABT-102 (model drug) and nine different polymers with different molecular weights and viscosities were selected to investigate drug/polymer miscibility. Three different polymer:drug ratios (1:3, 1:1 and 3:1, w/w) were analyzed using: DSC, FTIR and PXRD. Three different techniques were used to prepare the amorphous solid dispersions: serial dilution, solvent evaporation and spray drying. Spray drying was the best method to obtain amorphous solid dispersions. However, under certain conditions amorphous formulations could be obtained using solvent evaporation. Melting point depression was used to calculate interaction parameters and free energy of mixing for the various drug polymer mixtures. The spray dried solid dispersions yielded a negative free energy of mixing which indicated strong drug-polymer miscibility compared to the solvent evaporation and serial dilution method. Soluplus was the best stabilizer compared to PVP and HPMC, which is probably a consequence of strong hydrogen bonding between the two C=O moieties of soluplus and the drug N—H moieities.


## 1. Introduction

Drug dissolution and gastrointestinal permeability are the important factors controlling the rate and extent of drug absorption. This forms the basis of the biopharmaceutics drug classification scheme (BCS class I, II, III and IV), which correlates *in vitro* drug product dissolution and *in vivo* bioavailability (Amidon et al., 1995). Dissolution is the rate-limiting step for gastrointestinal absorption for most BCS class II drugs (Cook et al., 2008). There are different approaches (solid dispersion, solid lipid nanoparticles, crystalline nanoparticles, liposomes, cyclodextrin complexes, *etc.*) in the pharmaceutical world to enhance the dissolution rate and increase the oral bioavailability of these poorly soluble drugs. Solid dispersion technology is a well-established method to prepare the most stable solid formulations (Lindenberg et al., 2004; Hauss, 2007).

Solid dispersion incorporate one or more crystalline or amorphous active ingredient in a solid matrix provided by an inert carrier (Bajaj et al., 2011). These formulations increase the dissolution rate and oral bioavailability of poorly soluble drugs, with an added advantage of high drug loading (Chaves et al., 2014). Commercially, three different methods are used to prepare solid dispersions (*i.e.* spray drying, hot melt extrusion and co-precipitation) (Shah et al., 2013a; Paudel et al., 2013; Shah et al., 2013b). Additionally, solid dispersions can be prepared using solvent evaporation and fusion techniques (Leuner and Dressman, 2000; Weuts et al., 2005). Generally, all these methods result in the production of amorphous solid dispersions (ASDs), which significantly enhance the solubility and bioavailability compared to the crystalline form of the drug (Lee et al., 2014). Additionally, these methods might also result in formation of semi-crystalline or crystalline systems. The amorphous form of drug has drawn considerable attention, as theoretically it represents the most energetic solid state, and may provide the advantages in terms of solubility and bioavailability (Hancock and Parks, 2000). Recently, amorphous solid dispersions have been successfully developed to thermodynamically or kinetically stabilize the amorphous form of

*Abbreviations:* API, active pharmaceutical ingredient; ASD, amorphous solid dispersion; BCS, biopharmaceutical classification system; DSC, differential scanning calorimetry; FTIR, fourier transform infrared spectroscopy; PXRD, powder x-ray diffraction; SD, spray drying.

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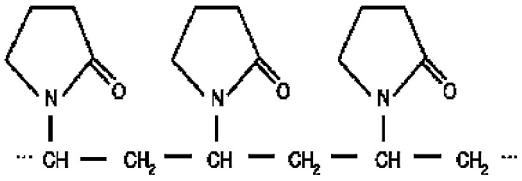
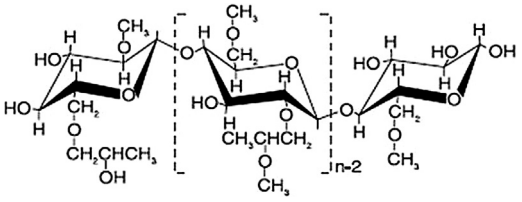
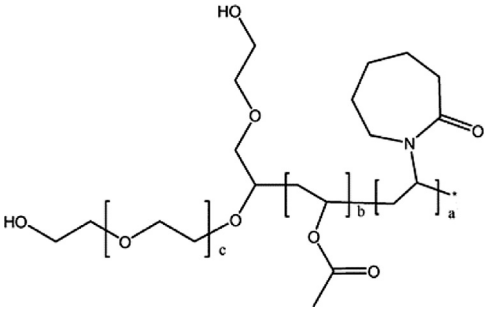
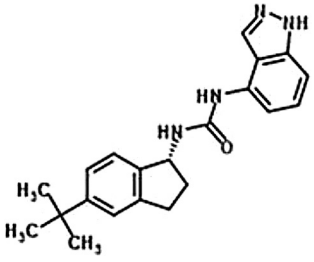
drugs and yield drug products with enhanced bioavailability (Baghel et al., 2016; Jackson et al., 2015; Savjani et al., 2012). Among the various techniques for preparing solid dispersions, hot-melt extrusion (HME) has stood out with obvious advantages due to its single-step, simple and organic solvent-free preparation process, and gained increasing popularity (Chaves et al., 2014; Wu et al., 2009). However, the elevated processing temperature has certainly limited the application of HME for heat-sensitive drugs, and so far only a few number of studies focused on this problem (Tres et al., 2015; Li et al., 2014; Wilson et al., 2012). Furthermore, amorphous solid dispersions have associated physical and chemical instability issues which become particularly apparent on scale up (Karanth et al., 2006). Selection of the best excipient at the formulation development stage may prevent the risk associated with these instabilities. Hence, it is very important to study drug stabilizer interactions (strong/weak) at the molecular level to predict the stability/miscibility of the drug in a given polymer matrix. Such understanding would allow a significant improvement over the conventional trial and error strategies for stabilizer selection.

Interactions between different stabilizers and poorly soluble drugs, has been reported in the literature for amorphous solid dispersions. Different solid state analytical tools such as DSC, FTIR and PXRD have been used to characterize both strong and weak interactions (Guo et al., 2014; Surwase et al., 2015; Dian et al., 2014; Homayouni et al., 2014; Wlodarski et al., 2015; Liu et al., 2015). In the present study the effect of the molecular weight of three different polymers (PVP, HPMC and soluplus) on interaction with the drug – ABT-102 (BCS class II) were investigated. Nine different polymers (PVP K-17, PVP K-25, PVP K-30, PVP K-90, HPMC E3, HPMC E5, HPMC E15, HPMC E50 and soluplus) with different molecular weights and viscosities were selected to investigate drug-polymer miscibility. Three different ratios of drug:polymer (1:3, 1:1 and 3:1, w/w) were studied using solid state characterization tools (DSC, FTIR and PXRD).

## 2. Materials

Poly (1-vinyl-2-pyrrolidone) (PVP) – K17 and K90 were gifted by Sigma Chemicals. Poly (1-vinyl-2-pyrrolidone) (PVP) – K25, K30 (USP, JP, EP) and soluplus (polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer) were gifted by BASF. Hydroxy propyl methyl cellulose (Methocel premium LV) – E3, E5, E15 and E50 were donated by the Dow Chemical Company. The

**Table 1**
Chemical structures of the active and excipients (DOW, 2002; BASF, 2013; Flory, 1953).

| | |
|---|---|
| Polyvinyl pyrrolidone K17, K25, K30 and K90 (**Kollidon**) |  |
| Hydroxypropyl methyl cellulose E3, E5, E15 and E50 **(Methocel)** |  |
| Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer **(Soluplus)** |  |
| ABT-102 **(drug)** |  |