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Research Paper

The discovery and investigation of a crystalline solid solution of an active pharmaceutical ingredient

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ABSTRACT

Understanding the phase behavior of crystal forms is essential in drug formulation development, as physical stability of the active pharmaceutical ingredient (API) is critical to achieving the desired bioavailability. Solvents greatly impact the physical stability of crystalline solids, resulting in a variety of well-known phase transitions, such as hydrate/solvate formation. However, solvent incorporation may also result in the formation of a less-known crystalline solid solutions (CSSs). The identification and characterization of CSSs and their effect on API physicochemical properties have not been investigated. This is the first reported instance of a CSS for an API. An exhaustive study of the phase behavior of the enantiotropically related polymorphs, I and II, of Benzocaine in water and ethanol revealed that Form I formed a CSS with water below 294.5 K. Construction of the phase diagrams of Forms I and II in water and ethanol revealed that CSS formation significantly decreased the phase transition temperature between Forms I and II in water. This change resulted from the increased disorder in the lattice of Form I due to the presence of water. This work demonstrates the importance of understanding the formation of CSSs on the thermodynamic behavior of crystalline pharmaceutical solids.

1. Introduction

In the pharmaceutical industry, the majority of active pharmaceutical ingredients (APIs) or intermediates are present as a crystalline phase during manufacturing. Therefore, understanding the physicochemical properties of these crystalline materials are of utmost importance for the production of robust formulations with desired efficacy (Karashima et al., 2014; Nagy and Braatz, 2012). Selection of the correct crystalline solid not only influences properties important to manufacturing, such as flowability and compressibility, but also those that impact bioavailability, including solubility and dissolution (Blagden et al., 2007; Chen et al., 2011; Variankaval et al., 2008). As solvents are frequently used for the manufacturing and/or processing of API, it is of utmost importance to understand the possible phase transformation which can originate due to incorporation of solvent in to the API crystals. Solvent in these processes could be simply the water or some other organic solvent. Both water and solvents could be responsible for phase transition such as formation of hydrate or solvate, respectively. Phase transformation from anhydrous form to a hydrate or a solvate is known to influence the physicochemical properties of the API. For instance, formation of a hydrate form of piroxicam have shown to lower the dissolution rate and the bioavailability of the API (Lust et al., 2013). Similarly, formation of a solvate of olanzapinium salt have also shown to alter the physicochemical properties of the API (Thakuria and Nangia, 2013). Therefore, it is vital to understand solid forms of the API with solvent incorporation as it can affect the physicochemical properties of the API. For a given API, screening for the possible hydrate and solvate is very commonly done. However, there are few other types of phase changes which are difficult to detect and not much investigated. These are the phase changes where the solvent incorporation in the solid forms does not change the parent crystal structure. These phase changes include the formation of non-stoichiometric solvate, solvent inclusion, or crystalline solid solution (CSS).

Non-stoichiometric solvates are compounds where the solvent tends to interact with the parent crystal without any repeating stoichiometry (Feth et al., 2011; Griesser, 2006; Kiang et al., 2014). These non-stoichiometric solvates can also impact the properties of the API crystals. For example, a partially non-stoichiometric channel-hydrate formation for an API have shown to increase tendency of crystal agglomeration upon isolation and drying (Feth et al., 2011). Macroscopic solvent inclusion are another types of crystals where solvent becomes a part of the crystals. In this case, the solvent is trapped inside a crystals in the form of vacuoles during the growth of the crystal (Braun et al., 2015; Cabeza et al., 2007; Waldschmidt et al., 2011). Ciclopirox showed to

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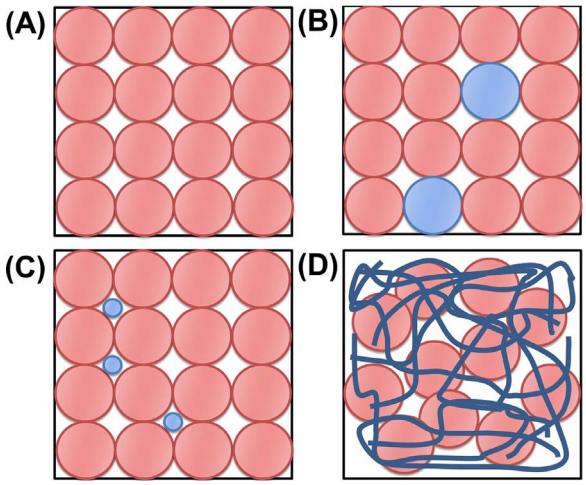

Fig. 1. Schematic representation of various solid solutions. (A) Pure crystalline phase, (B) Crystalline solid solution formed substitutionally, (C) Crystalline solid solution formed interstitially, and (D) Glass solid solution or Amorphous solid solution with polymer matrix.
Adapted and modified from (Partlow, 2012).

trap the mother liquor (ethanol) inside the crystals to form macroscopic solvent inclusion (Waldschmidt et al., 2011).

Solvent incorporation can also lead to formation of CSS which is a type of solid solution where the crystalline solid phase act as a "solvent" and solvent molecule incorporated in the crystalline phase act as the "solute" (Khachaturyan, 1978). In CSS, solvent molecules occupy previously unoccupied sites in the crystal lattice interstitially or replaces host crystal molecules in its lattice substitutionally (Callister and Rethwisch, 2007; Partlow, 2012). A schematic representation of these types of crystalline solid solution is depicted in Fig. 1A–C. The formation of CSS are well studied with respect to the field of inorganic materials sciences and have been shown to change the physicochemical properties of some inorganic crystals (Kobayashi et al., 2003). For instance, electrical and ferromagnetic properties of an inorganic layer oxide crystal were changed because of formation of the CSS (Kobayashi et al., 2003). However, CSS is not much studied with respect to APIs and in the field of pharmaceutical solids. CSS should not be confused with glassy solid solution or amorphous solid solution (ASS) in which amorphous API is dispersed in polymer matrix (Fig. 1D) to enhance the aqueous solubility (Leuner and Dressman, 2000; Tackenberg et al., 2015). As the formation of CSS can change the physicochemical properties of the crystalline compound, it is important to study the CSS formation and effect of solvent incorporation on API.

Herein, a first instance of formation of a CSS for an API was discovered. A meticulously designed experiments to study the interaction of solvent with the API crystal led to the discovery of the CSS. Benzocaine (BZC) was used as a model API to understand the role of solvent incorporation on phase behavior of enantiotropically related polymorphs Form I and II. BZC is a local anesthetic drug used in many formulations such as solid lozenges (Cepacol® and Chloraseptic®), gels (Orajel®) or liquid solutions (Anbesol®). In manufacturing of BZC formulations, water and ethanol are commonly used solvents. For instance, for the manufacture of lozenges, crystalline BZC and water were used for wet granulation (Jones, 2010). In addition, for preparation of bioadhesive films containing BZC, it was first dissolved in ethanol followed by precipitation in the film by evaporation (Tapolsky and Osborne, 1998). Therefore, in the present study both water and ethanol were selected to study the effect of solvent incorporation on phase behavior of BZC. Having confirmed that BZC Forms I and II are enantiotropically related, BZC was then screened for any possible formation of hydrate or ethanolate of BZC. Further, a series of analytical experiments were performed and it was identified that Form I forms CSS with water. Finally, it was shown that due to formation of CSS, there was a change in the enthalpy of melting as well as an apparent change in the T_t. This was due to the water present in Form I as CSS, which led to changes in the free energy of the system.

2. Material and methods

2.1. Materials

BZC, purity > 99%, was purchased from Sigma-Aldrich (Saint Louis, MO). Absolute ethanol, purity > 99.5%, was purchased from Fisher Scientific Inc. (Pittsburgh, PA). Ultrapure water was obtained using a Millipore ultrapure water system (Billerica, MA).

2.2. Preparation of single crystals of Form I

An ethanolic solution of BZC (C = 225 mg/g) was prepared at 303.15 K. The solution was then cooled and maintained at 293.15 K (C_{sat} = 146 mg/g; supersaturation, $\sigma = (C - C_{sat})/C_{sat} = 0.54$) without stirring. In addition, single crystals of Form I were obtained from water. An aqueous solution of BZC (C = 1.30 mg/g) was prepared at 303.15 K. The solution was then cooled and maintained at 293.15 K (C_{sat} = 0.96 mg/g; supersaturation, $\sigma = (C - C_{sat})/C_{sat} = 0.35$) without stirring. Absolute ethanol was used for the crystallization experiments. In addition, the experiments were performed utilizing newly open ethanol bottle in a sealed environment

2.3. Preparation of single crystals of Form II

An ethanolic solution of BZC (C = 292 mg/g) was prepared at 315.65 K. The solution was then cooled and maintained at 305.65 K (C_{sat} = 234 mg/g; supersaturation, $\sigma = (C - C_{sat})/C_{sat} = 0.25$) without stirring. In addition, single crystals of Form II were obtained from water. An aqueous solution of BZC (C = 2.0 mg/g) was prepared at 315.65 K. The solution was then cooled and maintained at 305.65 K (C_{sat} = 1.4 mg/g; supersaturation, $\sigma = (C - C_{sat})/C_{sat} = 0.43$) without stirring. Absolute ethanol was used for the crystallization experiments. In addition, the experiments were performed utilizing newly open ethanol bottle in a sealed environment.

2.4. Preparation of Forms I and II by slurrying

Form I was prepared by stirring BZC (50 g) in ethanol (100 ml) at 293.15 K for 18 h. Form II was prepared by stirring BZC (25 g) in water (100 ml) at 306.15 K for 18 h. The resulting crystals were filtered, and dried at room temperature.

2.5. X-ray powder diffraction (XRPD)

Diffraction patterns were collected using a Rigaku SmartLab (XRD 6000) diffractometer (The Woodlands, TX) with Bragg–Brentano mode as described previously (Kavuru et al., 2016). A target material made of copper was used in the X-ray tube which emits Kα radiation (λ = 0.15405 nm). Samples (~40 mg) were placed onto a glass sample holder. Diffraction data were recorded at room temperature between 5 and 40° 2θ (step size – 0.02°).

2.6. Polarized light microscopy (PLM) and single crystal to single crystal transformation

A small quantity of crystals were placed onto a clean microscope slide, which was then mounted onto the heating stage of an AxioCam imager optical microscope (Carl Zeiss Microscopy, LLC, Thornwood, NY) equipped with a polarizer in transmittance mode. The images were collected in polarized mode. For single crystal to single crystal transformation, the crystal of Form I was heated from 298.15 to 363.15 K at