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Anti-solvent co-crystallization of carbamazepine and saccharin

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ABSTRACT

The co-crystal approach has been investigated extensively over the past decade as one of the most promising methods to enhance the dissolution properties of insoluble drug substances. Co-crystal powders are typically produced by mechanical grinding (neat or wet) or a solution method (evaporation or cooling). In this study, high-purity carbamazepine-saccharin (CBZ–SAC) co-crystals were manufactured by a novel method, anti-solvent addition.

Among various solvents, methanol was found to perform well with water as the anti-solvent for the co-crystallization of CBZ and SAC. When water was added to the methanol solution of CBZ and SAC at room temperature under agitation, nucleation of CBZ–SAC co-crystals occurred within 2–3 min. Co-crystallization was complete after 30 min, giving a solid yield as high as 84.5% on a CBZ basis. The effects of initial concentrations, focusing on the SAC/CBZ ratio, were examined to establish optimal conditions.

The whole anti-solvent co-crystallization process was monitored at-line via ATR-FTIR analysis of regularly sampled solutions. The nucleation and crystal growth of CBZ–SAC co-crystals were detected by a significant increase in absorption in the range of 2400–2260 cm^{-1}, associated with the formation of hydrogen bonds between the carbonyl group in CBZ and the N–H of SAC. When CBZ hydrates were formed as impurities during anti-solvent co-crystallization, the hydrogen bonding between methanol and water was reduced greatly, primarily due to the incorporation of water molecules into the CBZ crystal lattice.

In conclusion, an anti-solvent approach can be used to produce highly pure CBZ–SAC co-crystal powders with a high solid yield.

1. Introduction

It has been reported that the co-crystal approach has the potential to improve key pharmaceutical properties, such as dissolution and stability, especially for poorly soluble drug substances (McNamara et al., 2006; Hickey et al., 2007). New co-crystal entities can also be protected by intellectual property, based on their novelty, utility, and non-obviousness (Trask, 2007; Bhatt et al., 2009). Recently, the US FDA published a guidance for industry on pharmaceutical co-crystal issues (FDA, 2011). Several overviews and reviews can be found in the literature (Aakeroy et al., 2007; Sekhon, 2009; Qiao et al., 2011; Babu and Nanjia, 2011).

Pharmaceutical co-crystals have been prepared primarily by solution routes (evaporation and cooling) and solid-state grinding (neat and wet) methods (Weyna et al., 2009; Wishkerman et al., 2009). The latter approach has been recognized for its co-crystal screening capability and environmental merits (Friscic et al., 2006). Among other reported co-crystallization methods are the supercritical fluid method (Padrela et al., 2009), solvent-mediated phase transformation (SMPT) (ter Horst and Cains, 2008), and ultrasound-assisted processing (Dhumal et al., 2009). A spray drying approach gave pure co-crystal powders, even under non-congruently saturating conditions, whereas solvent evaporation produced a mixture of co-crystal and individual components (Alhalaweh and Velaga, 2010). It was suggested that the formation of co-crystals was kinetically controlled and mediated by the glassy state of materials during spray drying. Survey data regarding co-crystallization methods found in the literature have been reported (Sheikh et al., 2009).

A screening method based on thermodynamic saturation temperature differences for carbamazepine (CBZ)-containing co-crystals was reported (ter Horst et al., 2009). As a consequence, several novel co-crystals of CBZ have been synthesized. A cocktail grinding method was established as a potential screening tool for pharmaceutical co-crystals (Yamamoto et al., 2012), and

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several novel co-crystals of CBZ were produced with a higher efficiency compared to a conventional one-at-a-time approach. Unusual co-crystals or co-crystal polymorphs were produced by a fast evaporation approach (Bag et al., 2011). The rapid evaporation of solvent controls the crystallization kinetics, improving the chances of creating further metastable crystalline forms. For example, the form II polymorph of CBZ–saccharin (SAC) co-crystal has not been synthesized before this study, except by a polymer-assisted hetero-nucleation approach (Porter et al., 2008).

It has been reported that solvent mixtures can drive CBZ-containing co-crystallization selectively by suppressing solvate formation in ultrasound-assisted solution reactions (Rager and Hilfiker, 2010). The chances of success using this approach increase with the number of solvents in the mixture. In a study of caffeine–maleic acid co-crystals, the use of ultrasound in the solution altered the supersaturation conditions of the co-crystallizing components (Aher et al., 2010). A membrane-based crystallization technology has been proposed to produce CBZ–SAC co-crystals directly from a water/ethanol solvent mixture (Profio et al., 2011; Caridi et al., 2012). The solvent, ethanol, was evaporated through 0.2-μm filter pores to render a supersaturated state for the component solution. By adjusting the initial composition appropriately, the selective production of CBZ and SAC crystals, as well as CBZ–SAC co-crystals, was achieved. A process design study for a scalable solution cooling route using CBZ–nicotinamide (NCT) has been reported (Sheikh et al., 2009). The methodology consisted of three key elements: solvent selection rationale, thermodynamic stability domains in a solid–liquid phase equilibrium diagram, and understanding the kinetic processes for controlled de-saturation.

A system combining differential scanning calorimetry (DSC) and Fourier transform infrared (FTIR) spectroscopy in one step was used to perform screening of co-crystal formation, including CBZ, in the form of KBr pellets (Wu et al., 2011). The effect of water on CBZ–SAC co-crystals was examined by co-grinding with hydrated forms of the reactants (Jayasankar et al., 2006). Water played a crucial role as plasticizer in controlling process-induced co-crystallization. In another study of co-milling of CBZ and NCT (Chieng et al., 2009), water molecules increased the co-crystal formation rate and its stability significantly. No apparent transient amorphous phase was detected in the process of co-crystallization. CBZ–NCT co-crystal was prepared by SMPT when CBZ and NCT crystalline powders were suspended in ethanol (ter Horst and Cains, 2008). Needle-like form II co-crystals were created initially, which then transformed into plate-like form I co-crystals. The SMPT process was monitored using in situ attenuated total reflectance (ATR)-FTIR, based on the solute concentrations of CBZ and NCT (Gagniere et al., 2009, 2011). The consumption of CBZ by the formation of CBZ–NCT co-crystals was balanced by the dissolution of CBZ crystals during SMPT.

A solubility model of a binary co-crystal with non-ionizable components was developed and applied to CBZ–NCT co-crystals in three organic solvents (Nehm et al., 2006). It is well-known that the true solubility of co-crystals is not easily measured, especially for highly soluble ones, primarily due to transformation in solution. A method to estimate the solubility of co-crystals, including CBZ, has been proposed based on solubility product equations (Good and Rodriguez-Hornedo, 2009). Various analytical tools have been used to measure the characteristics of CBZ-containing co-crystals. Rapid-heating differential scanning calorimetry (RHDSC) was used to isolate and characterize the metastable CBZ–NCT form II by fast heating of a CBZ–NCT glass at 400–500 °C/min (Buanz et al., 2011). Different polymorphs of CBZ-containing co-crystals resulted, depending on the type of milling (Limwikrant et al., 2012). A vibrational rod mill provided higher mechanical forces and thermal activation than regular ball milling, resulting in unusual co-crystal polymorph formation. CBZ–SAC co-crystals prepared via solution cooling were compared with the marketed form of CBZ in terms of key attributes (Hickey et al., 2007). The co-crystal showed advantages, such as a favorable dissolution profile and suspension stability, compared to commercial immediate-release products.

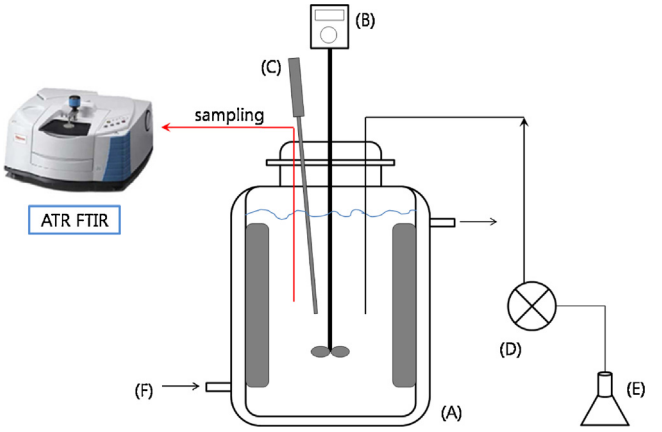

Fig. 1. Experimental set-up for anti-solvent co-crystallization. (A) crystallizer reactor, (B) high-speed stirrer, (C) thermometer, (D) peristaltic pump, (E) anti-solvent (water), (F) circulator.

The objectives of this study were to assess the feasibility of an anti-solvent route for CBZ–SAC co-crystal preparation and to propose a valid mechanism of co-crystal formation. Because methanol was the only solvent that resulted in pure co-crystal powders, in combination with water as an anti-solvent, the co-crystallization mechanism was examined in methanol–water mixed solvent at various initial CBZ and SAC compositions.

2. Materials and methods

2.1. Materials

CBZ (5H-dibenzo[b,f]azepine-5-carboxamide) and SAC (2-benzothiazol-1,1,3-trione) powders were purchased from Sigma–Aldrich (St. Louis, MO, USA). Several organic solvents were used as the solvent for CBZ and/or SAC: methanol, ethanol, acetone, methyl acetate, and ethyl acetate. They were all supplied as "reagent grade" by Merck & Co. (Whitehouse Station, NJ, USA) and were used without further purification. Water was purified using a deionizer (Human Corp., Seoul, Korea) prior to use as the anti-solvent.

2.2. Preparation of CBZ–SAC co-crystal powders

In this work, CBZ–SAC co-crystal powders were prepared under various conditions via an anti-solvent method and characterized as part of a comprehensive mechanistic study. CBZ–SAC co-crystals were also produced by a natural evaporation method for comparison, based on a previous study (Scott and Fleischman, 2003).

For evaporation co-crystallization, equal molar amounts of CBZ and SAC were dissolved in 100 mL of methanol to make an unsaturated solution (0.06 M) and aged for hours under mild agitation at 25 °C. Each fully solvated solution was filtered using a syringe filter (Whatman, 0.45-μm grade) to remove residual particles prior to natural evaporation in a beaker. It typically took 10 h to form to a slurry state. During evaporation, 20 μL of solution was sampled for at-line ATR-FTIR analysis at each time interval. Sampling was stopped at 8 h when the solution was too viscous for sampling with a syringe. The final slurry product was dried further overnight under vacuum at 25 °C, followed by DSC and X-ray diffraction (XRD) characterization.