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High-throughput screening and scale-up of cocrystals using resonant acoustic mixing

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ABSTRACT

This paper explores the effectiveness of resonant acoustic mixing RAM for screening and scale up of cocrystals. 16 cocrystal systems were selected as test cases based on previous literature precedent. A 96 well plate set up in conjunction with zirconia beads was used for cocrystal screening using RAM. A success rate of 80% was obtained in the screen for plates containing solvent or solvent plus Zirconia beads. A proof of concept production of hydrated and anhydrous cocrystals of 1:1 Theophylline Citric acid system at a 400 mg scale was demonstrated using solvent and bead assisted RAM. Finally the parameters affecting the scale up of 2:1 Theophylline Oxalic acid cocrystals was explored in a systematic fashion using a Design of Experiments DOE approach. The RAM parameters of acceleration and mixing time were optimized using the DOE approach. A quantitative XRPD method was developed to determine the extent of conversion to the cocrystal when using RAM Mixing time of 2 h and an acceleration of 60 G were determined to be optimal. The optimized parameters were used to demonstrate scale up of 2:1 Theophylline Oxalic acid cocrystals at an 80 gram scale with a net yield of 94%. RAM is thus established as an environmentally friendly mechanochemical technique for both high throughput screening and scaled up production of cocrystals.

1. Introduction

Poorly soluble crystalline small molecules pose a challenge during drug development as they may have limited oral bioavailability (Lipinski et al., 2012). Increased number of such poorly soluble compounds in development has forced pharmaceutical scientists to look for ways to improve oral bioavailability. Cocrystals have emerged as one of the strategies to overcome low bioavailability (Bak et al., 2008; McNamara et al., 2006; Stavropoulos et al., 2015; Variankaval et al., 2006; Wang et al., 2016). In addition cocrystallization has also been shown to improve physical stability (Trask et al., 2005; Trask et al., 2006) and mechanical properties (Karki et al., 2009; Sun and Hou, 2008) of the active molecule thereby making them more amenable to traditional solid dosage form development.

Cocrystals have been defined as solids that are comprised of two or more components in the unit cell of the crystalline structure which are solids at room temperature are held together by non-covalent forces (Bond, 2007; Desiraju, 2003; Duggirala et al., 2016; Dunitz, 2003). This definition distinguishes cocrystals from solvates. These components in the cocrystal are typically held together by hydrogen bonding as opposed to salts in which proton transfer takes place between the constituents. In the last decade or so there has been intense activity in the field of cocrystals in the pharmaceutical industry and several papers have been published about identifying and making cocrystals. However there are still challenges associated with screening methodologies and manufacturing of cocrystals.

Traditionally cocrystals have been prepared using solution or slurry crystallization. The use of solution crystallization poses a challenge as the components of the cocrystal may have different solubilities in the solvent used for crystallization thereby making it complicated to ensure the production of the right form of the cocrystal (Chiarella et al., 2007). At small scale mechanochemical methods such as dry grinding and liquid assisted grinding using ball mills have been demonstrated as efficient methods to generate cocrystals and have been shown to circumvent the issues seen with solution crystallization (Friščić et al., 2006). However, the ball milling process is difficult to scale up. Recently scale up of cocrystallization by mechanochemical means was demonstrated using Twin Screw Extrusion (TSE) (Daurio et al., 2011; Daurio et al., 2014; Dhumal et al., 2010; Kulkarni et al., 2015; Li et al., 2016) and Resonant Acoustic Mixing (RAM) (am Ende et al., 2014; Anderson et al., 2014) technologies, both of which are conducive to

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making cocrystals at large scales. In contrast to ball milling and TSE, RAM is a low shear approach where low frequency high intensity acoustic energy is used to agitate samples. The energy is uniformly distributed across the sample and the mixing elements do not come into contact with the sample.

Screening of cocrystals using traditional solution-based high throughput techniques (Morissette et al., 2004) suffers from problems similar to that outlined for manufacturing of cocrystals from solution and have low success rates. In order to improve the success of screening methods, slurry and mechanochemical based high throughput screening have been reported (Bysouth et al., 2011; Kojima et al., 2010; Luu et al., 2013). Luu et al. (2013) have reported high throughput screening using a combination of sonication, vortexing and centrifugation while Kojima et al. (2010) have reported slurry based high throughput screening. On a different note Leung et al. (2014) have demonstrated a high throughput screening procedure for nanosuspension formulations using a 96-well plate in the RAM apparatus. They achieved nanosizing using small zirconia beads in the 96-well plate. The use of RAM for low throughput screening of cocrystals was already demonstrated by am Ende et al. (2014) in the same paper where they demonstrated scale up of cocrystals.

In this paper we have combined the methodology of Leung et al. and am Ende et al. and demonstrate for the first time high throughput 96-well plate cocrystal screening using RAM. For the screening Caffeine, Carbamazepine, and Theophylline were used as model cocrystal formers as they have been shown in literature to form cocrystals with a variety of acids (Childs et al., 2008; Trask et al., 2005, 2006). Following screening we describe the scale up of both hydrated and anhydrous form of Theophylline-citric acid cocrystal system using RAM. Finally we have also systematically studied the parameters that affect the scale up of Theophylline-oxalic acid cocrystal system produced by RAM by using a design of experiments approach.

2. Materials and methods

Caffeine, Theophylline and Carbamazepine were used in the screening and scale up studies. All three APIs (Active Pharmaceutical ingredients) were sourced from Sigma–Aldrich Co (St. Louis, MO) and were used as received. The following cocrystal formers were used in the screening: oxalic acid, glutaric acid, malic acid, maleic acid, succinic acid, malonic acid, benzoic acid, adipic acid, and citric acid. All cocrystal formers and solvents used in the study were sourced from Sigma–Aldrich Co (St. Louis, MO) and were used as received. All sourced APIs and cocrystal formers had >98% purity.

2.1. Procedure for high throughput screening of cocrystals using RAM

All reagents and Zirconium beads were dosed to an aluminum vial block designed to hold 96-individually sealed wells (Unchained Labs, Part# S141937) (Fig. 1) using a solids dosing system (SV powder dispense system, Unchained labs *freeslate* robotic platform). APIs were dispensed at a target of 6 mg per well and the coformers at 1:1 equivalents to the corresponding API unless noted (Fig. 2). The 0.5 mm Zirconium beads (Glenmills, Clifton, NJ) were dispensed at a target of 6 mg weight per well. If the well condition required water or ethanol, it was dispensed at a 6 μL level using a manual pipette. Total concentration in each well where solvent was used was kept at 1000 mg/mL. The plate design used is shown in Fig. 2. The composition of each well is represented as a colored pie chart based on both mole and weight fraction of components added. For example well A1 contains Caffeine (red) and Oxalic acid (green)

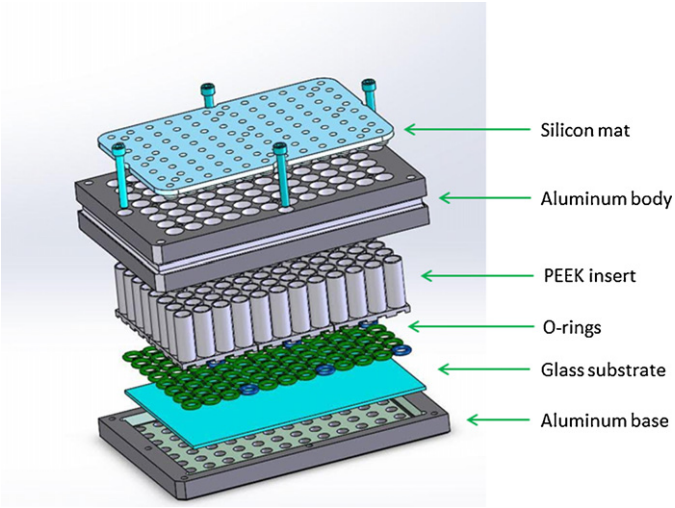

Fig. 1. 96-well high throughput assembly.

at a mole ratio of 2:1. The actual composition of the components by weight in each well is provided in the Supplementary information section.

After all the dispensing was completed the aluminum block was covered with a silicon sealing mat and placed into the RAM (LabRAM II, Resodyn Inc., Butte, Montana). A mixing program with four consecutive 35 min intervals was used. In each 35-min interval, 30 min of acoustic mixing was performed at an acceleration set point of 60 g with 5-min stop time at the end of the mixing period. After the mixing program was completed, the plate was unsealed and allowed to rest overnight. XRD was performed on all the samples using a Bruker D8 X-Ray diffraction system set in reflection mode.

2.2. Procedure for making cocrystals using RAM

Proof-of-concept scale up experiments at a 400 mg scale using RAM was conducted with Theophylline-citric acid cocrystal system. Theophylline and citric acid (at a 1:1 mole ratio) were weighed in 20 mL plastic vials. Five different conditions were tested: (i) solids with no beads, (ii) solids with water, (iii) solids with beads and water, (iv) solids with ethanol, (v) solids with beads and ethanol. 50 μL of solvent and 3 mm stainless steel beads were used. The five vials were placed in a sample holder and subjected to Acoustic mixing at an acceleration of 60 g. The mixer was stopped for 10 min after a mixing time of 30 min for a total mixing time of 2 h.

A design of experiments (DOE) approach was used to study the parameters that affected the scale up of Theophylline-Oxalic acid cocrystal system in the RAM. Two designs were conducted to assess the effect of acceleration and mixing time on cocrystal conversion. The main difference between the designs was in the range for the levels of the two factors investigated. For Design 1, 200 μL of water was used with a total of 400 mg of solids (2:1 molar ratio) and 3-mm steel beads (1× of solids loading) were used. For Design 1, the solid reactants were individually weighed into the vials for each experimental condition. At the end of the experiment the samples were dried for 3 h under vacuum at 60 °C. Parameters investigated in Design 1 are presented in Table 1. For Design 2, 600 μL of water was used with a total of 1.2 g of solids and 3-mm Zirconia beads (1× of solids loading) was used. For Design 2, 30 g blend of Theophylline and Oxalic acid was prepared at 2:1 mole ratio using Turbula blender (Glenmills, Clifton, NJ) operated for 10 min. This blend was then subdivided into 1.2 gram samples for the different experiments. At the end of the experiment the samples