Matrix-Assisted Cocrystallization (MAC) Simultaneous Production and Formulation of Pharmaceutical Cocrystals by Hot-Melt Extrusion

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Received 1 February 2014; accepted 25 March 2014

Published online 7 May 2014 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.23983

ABSTRACT: A novel method for the simultaneous production and formulation of pharmaceutical cocrystals, matrix-assisted cocrystallization (MAC), is presented. Hot-melt extrusion (HME) is used to create cocrystals by coprocessing the drug and coformer in the presence of a matrix material. Carbamazepine (CBZ), nicotinamide (NCT), and Soluplus® were used as a model drug, coformer, and matrix, respectively. The MAC product containing 80:20 (w/w) cocrystal:matrix was characterized by differential scanning calorimetry, Fourier transform infrared spectroscopy, and powder X-ray diffraction. A partial least squares (PLS) regression model was developed for quantifying the efficiency of cocrystal formation. The MAC product was estimated to be 78% (w/w) cocrystal (theoretical 80%), with approximately 0.3% mixture of free (unreacted) CBZ and NCT, and 21.6% Soluplus (theoretical 20%) with the PLS model. A physical mixture (PM) of a reference cocrystal (RCC), prepared by precipitation from solution, and Soluplus resulted in faster dissolution relative to the pure RCC. However, the MAC product with the exact same composition resulted in considerably faster dissolution and higher maximum concentration (∼five-fold) than those of the PM. The MAC product consists of high-quality cocrystals embedded in a matrix. The processing aspect of MAC plays a major role on the faster dissolution observed. The MAC approach offers a scalable process, suitable for the continuous manufacturing and formulation of pharmaceutical cocrystals. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:2904–2910, 2014

Keywords: cocrystals; matrix; formulation; extrusion; continuous manufacturing; dissolution; supersaturation; crystal engineering; polymers; crystallization; solid dispersions

INTRODUCTION

Among the different formulation strategies for addressing the low systemic exposure of poorly soluble compounds administered by the oral route, cocrystallization is a promising approach that remains relatively underexplored in terms of formulation improvement. Pharmaceutical cocrystals, defined as solid-state stoichiometric molecular complexes of a drug molecule and a complementary coformer molecule, have demonstrated the ability to improve the solubility and physical stability of drugs.[1–3] Nevertheless, their applicability in the pharmaceutical industry remains limited due in good measure to the lack of a suitable large-scale production method. Established cocrystal production methods rely on the generation of an intermediate phase with increased molecular mobility, such as the liquid or amorphous state, from which the components cocrystallize.[4–6] Such methods include cocrystallization from a eutectic melt of the cocrystal components, cocrystallization via neat or liquid-assisted grinding (where the liquid acts as a catalyst), and cocrystallization by precipitation from solution. While each of these methods is capable of generating cocrystals, each also poses some limitations. Thermal methods involving melting require elevated temperatures that can compromise the integrity of thermolabile compounds. Besides being energetically inefficient, mechanical energy input methods like grinding can induce amorphization and their effectiveness tends to be limited without the use of a catalytic solvent. Finally, in methods based on precipitation from solution, the location of the system in the phase diagram is critical to the cocrystallization process and to the attributes of the cocrystals produced,[7] requiring both dynamic and precise control of supersaturation levels of the concentration of the component concentrations as cocrystallization takes place. This type of coordinated control can be difficult to maintain.[6,8–10] A scalable production method for pharmaceutical cocrystals that draws on the advantages of existing methods, such as the control of stoichiometry offered by the thermal and energy input methods, along with the high crystal quality offered by the solution based methods, would be of significant valuable to pharmaceutical scientists during preformulation and formulation development. An equally important aspect for realizing the full potential of pharmaceutical cocrystals is the availability of a robust, scalable production method that effectively addresses the drawbacks (such as the potential chemical and physical stability issues mentioned above) associated with the cocrystal formation methods.

In response to the need for an improved process, matrix-assisted cocrystallization (MAC) is introduced here as a novel method of cocrystal production. Medina et al.[11] have shown that hot-melt extrusion (HME) can be used as an effective cogrinding process to create cocrystals. The MAC approach utilizes HME to produce cocrystals embedded in a formulation matrix. Briefly, equimolar quantities of drug and coformer are mixed with a matrix material in the solid state prior to feeding the mixture into a hot-melt extruder. The extruder is set at a temperature where only the matrix material is made fluid, either by softening or by actual melting. Cocrystallization occurs during the extrusion process, induced by the intimate mixing and grinding of the components in the softened (or liquefied) matrix.

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Journal of Pharmaceutical Sciences, Vol. 103, 2904–2910 (2014)

The cocrystal particles formed this way become embedded in the matrix material, which solidifies upon exiting the extruder. The end product of the MAC process, termed MAC product in this report, is a matrix-embedded cocrystal with the level of controlled stoichiometry offered by both thermal and mechanical cocrystal production methods. The MAC product is a formulated cocrystal where the matrix material plays a double role. During the HME process, the matrix plays role analogous to that of a catalytic solvent. In the final extrudate, the matrix is a functional component of the formulation. In MAC, the use of the melted/softened matrix phase promotes intimate mixing, while reducing excessive shear stresses produced when subjecting dry solid materials to extrusion. The reduced shear stress of MAC abates potential crystal damage. Producing cocrystal particles in functional matrices makes the physicochemical properties of the matrix as important as those of the cocrystal itself. Therefore, selection of the matrix material can be exploited to impart additional functionality into the formulated cocrystal, such as improved flowability, compaction, drug release kinetics, and so on. Thus, MAC serves as a method of simultaneous production and formulation of pharmaceutical cocrystals. In this report, we examine the ability of the MAC process to produce high-quality cocrystals. We also present the results of characterization studies comparing the physical attributes of the MAC product with those of a reference cocrystal (RCC) material, that is, the same cocrystal obtained by the careful implementation of the solution cocrystallization method. The study also includes a comparison of the *in vitro* dissolution performance between the MAC product and the RCC.

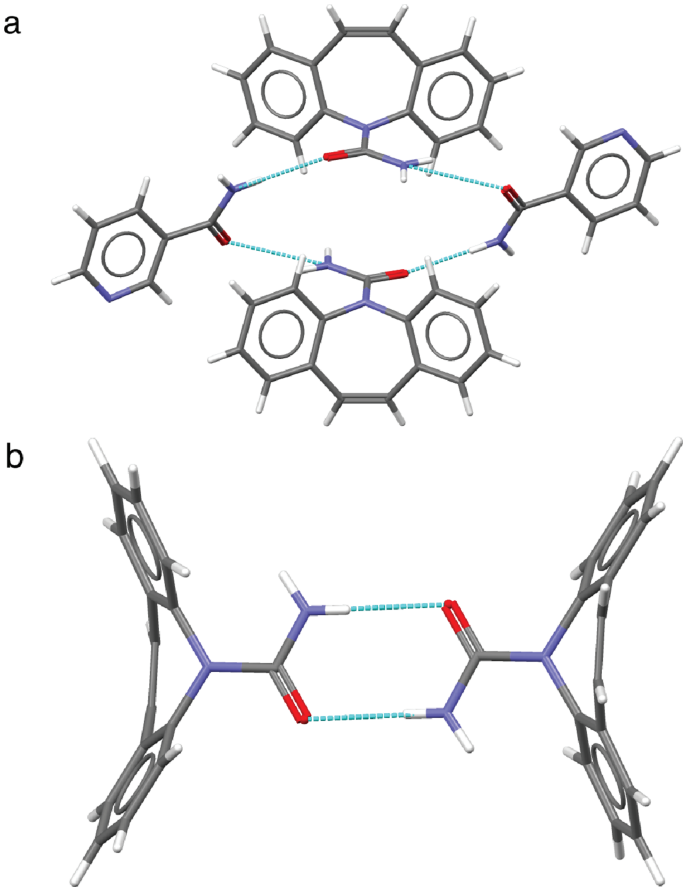

Figure 1. Hydrogen bonding synthons (indicated by dashed lines) for (a) the CBZ–NCT cocrystal, and (b) CBZ, polymorphic form III.

MATERIALS AND METHODS

Carbamazepine (CBZ) and nicotinamide (NCT) were used as the drug and coformer, respectively, for the model cocrystal system of this study. Figure 1 shows the structures of the CBZ–NCT cocrystal and that of crystalline CBZ. CBZ is a BCS class II compound, with dissolution rate-limited absorption. One important aspect is that the anhydrous form of crystalline CBZ rapidly transforms into the dihydrate form during dissolution in aqueous media. This poses a problem because the transformation to the dihydrate results in a physical form that is less soluble, with considerably slower dissolution than the original anhydrous form. NCT was used as coformer for this study because it has been reported to form a cocrystal with CBZ whose solubility is 152-fold greater than that of the CBZ dihydrate.[1] Soluplus® was utilized as the matrix agent for cocrystal formation because of its relatively low glass transition temperature (~72°C), allowing for a convenient processing window during extrusion. In addition, Soluplus has been shown to solubilize drugs and prevent their precipitation from supersaturated solutions.[12,13] CBZ (CAS #298–46–4, Fig. 1b) was purchased from Alfa Aesar (Ward Hill, MA); NCT (CAS #98–92–0) was purchased from Sigma–Aldrich (St. Louis, MO); and Soluplus (CAS #402932–23–4) was obtained from BASF (Florham Park, NJ). All materials were used as received.

In a typical MAC experiment, 3.2 g of a 1:1 molar ratio (66:34 mass ratio) CBZ–NCT mixture and 0.8 g Soluplus were blended using a spatula prior to addition of the 4 g mixture into a Thermo Scientific Haake™ Minilab Micro Compounder (Thermo Fisher Scientific, Waltham, Massachusetts). The Minilab unit is equipped with conical, corotating screws (screw diameter narrowing from 14 to 5 mm, with a length of 11 cm), and with a control valve for adjusting material residence time. Preliminary tests showed that for this model system, 20% (w/w) polymer load provided a sufficient level of the matrix material, suitable for processing with the extruder, which has a torque limit of 500 N cm. The matrix content of the MAC product plays an important role on processing conditions. The lower the matrix content, the higher the induced shear stress during processing and the higher the exerted torque in the extruder. Therefore, the minimum matrix content is controlled, to a good extent, by the highest acceptable torque for the extrusion unit. In this study, the operating conditions were chosen to enable processing with high mixing intensity (high but acceptable shear stress) of the solid drug and solid coformer, in order to promote cocrystallization. This situation involves the use of a processing temperature where the two cocrystal-forming components exist in the solid state, resulting in intimate mixing conditions similar to those produced by cogrinding. The liquid/softened matrix provides an intervening medium whose effect is analogous to that of a catalyzing solvent for cocrystal production by grinding. Under these conditions, the highest screw speed (shear forces) allowable is set by the torque limit of the extruder. Using these guidelines, MAC batches were processed at a barrel temperature of 115°C, with a screw speed of 75 rpm, and residence time of 20 min. It should be pointed out that the residence time in most extruders is controlled by barrel length, screw design, and either screw speed or feed rate, depending on the material feed type. As a result, feed materials experience