

# Enhanced Physical Stability of Amorphous Drug Formulations via Dry Polymer Coating

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*Received 29 December 2014; revised 17 March 2015; accepted 24 March 2015**Published online in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.24451*

**ABSTRACT:** Although amorphous solid drug formulations may be advantageous for enhancing the bioavailability of poorly soluble active pharmaceutical ingredients, they exhibit poor physical stability and undergo recrystallization. To address this limitation, this study investigates stability issues associated with amorphous solids through analysis of the crystallization behavior for acetaminophen (APAP), known as a fast crystallizer, using a modified form of the Avrami equation that kinetically models both surface and bulk crystallization. It is found that surface-enhanced crystallization, occurring faster at the free surface than in the bulk, is the major impediment to the stability of amorphous APAP. It is hypothesized that a novel use of a dry-polymer-coating process referred to as mechanical-dry-polymer-coating may be used to inhibit surface crystallization and enhance stability. The proposed process, which is examined, simultaneously mills and coats amorphous solids with polymer, while avoiding solvents or solutions, which may otherwise cause stability or crystallization issues during coating. It is shown that solid dispersions of APAP (64% loading) with a small particle size (28  $\mu\text{m}$ ) could be prepared and coated with the polymer, carnauba wax, in a vibratory ball mill. The resulting amorphous solid was found to have excellent stability as a result of inhibition of surface crystallization. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association *J Pharm Sci*

**Keywords:** Amorphous; surface-enhanced crystallization; dry polymer coating; physical stability; amorphization; crystallization; coating; formulation

## INTRODUCTION

Amorphous solids are garnering an increased amount of attention in pharmaceutical drug formulation development owed to their potential to improve the bioavailability of active pharmaceutical ingredients (APIs).<sup>1,2</sup> Because of the higher aqueous solubility of amorphous solids compared with the corresponding crystalline solid, amorphous solids may be a particularly simple solution for the delivery of BCS Class II, low solubility, APIs. Aside from the advantage of high solubility, amorphous solids are also characterized by poor physical stability and readily undergo solid-state transformation otherwise known as recrystallization.<sup>2</sup> Poor physical stability is obviously a major obstacle for formulation scientists who must ensure adequate product shelf-life and product performance that may be altered because of recrystallization.

The physical stability of an amorphous solid depends on a thermodynamic driving force that is determined by the difference in free energy between the amorphous solid and the crystalline solid as well as kinetic factors that may include temperature and humidity. A number of studies have also found that amorphous solids exhibit unusual crystallization behavior, among which is the observation of surface-enhanced crystallization.<sup>3–8</sup> Because of the higher mobility of molecules on the free surface of an amorphous solid, crystallization rates can be 10–100 times higher than that in the bulk solid.<sup>9,10</sup> A common method to improve the stability of amorphous solids is

through the preparation of solid dispersions that typically consists of a API–polymer mixture in which the role of the polymer is to inhibit or slow nucleation and crystallization.<sup>1,11</sup>

Solid dispersions offer a convenient route for stabilization; however, studies have shown that the bulk can be effectively stabilized, whereas crystallization associated with the free surface is less influenced by the stabilizing polymer.<sup>3,12</sup> The difficulty associated with surface-enhanced crystallization can be further exacerbated if milling or micronization must be performed in downstream processing.<sup>4,6,13</sup> For example, Wu and Yu<sup>6</sup> found that decreasing the particle size (increasing the surface/volume ratio) of the amorphous API, indomethacin, led to greater instability because of crystallization occurring at the particle's surface. Despite this fact, high surface area amorphous solids or solid dispersions may be desired because of their faster dissolution rates.<sup>4</sup> Consequently, poor physical stability attributed to surface-enhanced crystallization seems to be one of the main impediments in achieving a stable amorphous solid or solid dispersion drug formulation.

In order to inhibit surface-enhanced crystallization, several coating processes utilizing vacuum deposition,<sup>7</sup> sputter coating,<sup>8</sup> plasma vapor deposition,<sup>14</sup> polyelectrolyte film coating,<sup>15</sup> or solvent-based film coating<sup>16–18</sup> have been investigated with varying success. Coating the surface of an amorphous solid or solid dispersion can mitigate the high surface molecular mobility, effectively reducing the crystallization rate of the surface to that of the bulk. Therefore, a surface-coated amorphous solid or solid dispersion will remain stable as long as the bulk is properly stabilized. Despite these developments in stabilization, the above-mentioned coating processes may not be amenable to industrial scale processes and have various disadvantages. Amorphous solids and solid dispersions are

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*Journal of Pharmaceutical Sciences*

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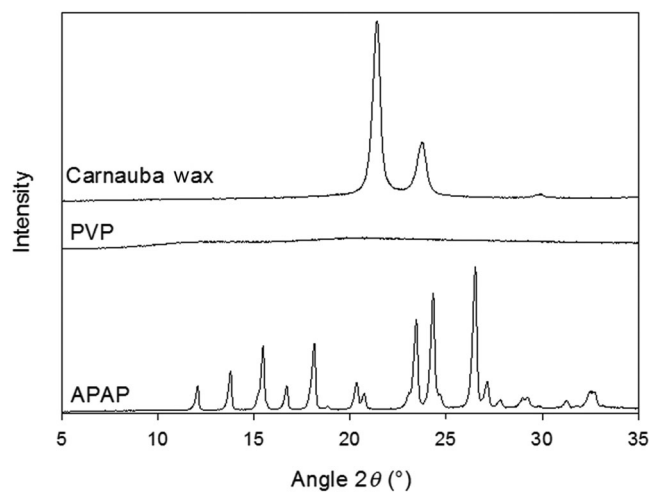
sensitive to moisture and coating processes utilizing liquids or solvents may negatively impact stability and may cause outright crystallization.<sup>16,17</sup> Furthermore, the above-mentioned coating processes can only be performed on the final product size of the amorphous solid or solid dispersion whether they are fine or coarse. If the amorphous solid or solid dispersion surface is particularly unstable, crystallization may occur during particle size reduction (i.e., milling) and before the coating can be applied.

This study investigates stability issues, particularly surface-enhanced crystallization, associated with amorphous solids through analysis of the crystallization behavior for the API acetaminophen (APAP). Although APAP is not poorly soluble, it was chosen because of its poor physical stability and tendency to crystallize at room temperature. Milling was utilized to prepare the amorphous solid of APAP, a method known as activated milling or amorphization, but it was found that surface-enhanced crystallization prevented full conversion. APAP was also milled with polyvinylpyrrolidone (PVP), a polymer used to prevent crystallization, to form a solid dispersion. Although solid dispersions of APAP and PVP could be prepared by milling, high PVP contents were required to prevent surface crystallization, whereas bulk crystallization could be prevented by relatively low polymer contents. Such critical insight was determined by scrutinizing stability data with a modified form of the Avrami equation that kinetically models both surface and bulk crystallization. Accordingly, surface-enhanced crystallization was identified as a major obstacle in preparing a stable amorphous solid of APAP. As a major novelty, a dry-polymer-coating process referred to as mechanical-dry-polymer-coating was used to inhibit surface crystallization. The coating processes simultaneously mills and coats amorphous solids with dry polymer without the use of solvents, solutions, or liquids of any kind. As shown in this study, a solid dispersion with a small median particle size (28  $\mu\text{m}$ ) could be prepared and coated with the polymer carnauba wax in a vibratory ball mill. The resulting solid dispersion with an API loading as high as 64% was found to have excellent stability as a result of inhibition of surface crystallization because of the coating process. Overall, this study emphasizes processing and stability issues associated with amorphous solids while also presenting a simple coating method to prevent surface crystallization that may improve formulation strategies for amorphous drugs.

## MATERIALS AND METHODS

### Materials

The crystalline API, APAP, was purchased from AnMar International Ltd. (Bridgeport, CT, USA). APAP has a melting point of 170°C and a glass transition temperature of 24°C.<sup>19</sup> PVP with an average molecular weight of 10,000 g/mol was purchased from Sigma-Aldrich Company (St. Louis, MO, USA). PVP is an amorphous polymer with a glass transition temperature of 89°C.<sup>20</sup> PVP was used to form solid dispersions with APAP. Carnauba wax powder with median size 6  $\mu\text{m}$  was purchased from Micro Powders, Inc. (Tarrytown, NY, USA) under the name Microclear418 and was used as a coating polymer. X-ray diffraction patterns of the as-received materials are shown in Figure 1.



**Figure 1.** X-ray powder diffraction patterns for as-received materials.

### Methods

#### Amorphization (Activated Milling)

A vibratory ball mill was used for the solid-state transformation of APAP from a crystalline to an amorphous solid. This process is otherwise known as activated milling or amorphization in which milling energy disrupts the crystalline structure and causes molecular disorder of the API. Five gram of APAP was placed into a cylindrical steel vessel (5 cm height, 4.5 cm ID) with six 9/16 inch steel balls. The vessel was subjected to vertical vibration with a frequency of 60 Hz and a predetermined acceleration (described as milling intensity hereafter) using the mechanical driver of the LabRAM manufactured by Resodyn Acoustic Mixers, Inc. (Butte, MT, USA). Solid dispersions of APAP and PVP were also prepared by the same milling method by adding both components in the milling vessel in 5 g batches. PVP loading is defined as the weight percent of PVP with respect to the total mass of API and PVP. Because heat is generated during processing, the outer wall of the milling vessel was cooled. The temperature of the powder in the vessel remained  $29 \pm 1^\circ\text{C}$  and the relative humidity varied between 20% and 30% for all experiments.

#### Melt Quenching

Amorphous solids and solid dispersions were also prepared using the melt-quench method. Ten gram of APAP or 10 g of APAP and PVP (for solid dispersions) was placed into an aluminum pan (9 cm diameter) and heated to 200°C and mixed for 5 min. The aluminum pan was then dipped in an ethylene glycol and water mixture (50:50) at  $-20^\circ\text{C}$  for 2 min, thereby quenching the melted material that solidified into a disk in the shape of the aluminum pan (the sample itself did not come into contact with the glycol and water mixture). Five gram of the resulting solid was milled according to the procedure detailed in the section *Amorphization (Activated Milling)*.

#### Mechanical-Dry-Polymer-Coating

Melt-quenched samples were dry polymer coated by milling with carnauba wax in the milling method as described in section *Amorphization (Activated Milling)*. Melt-quenched samples and carnauba wax were placed into the milling vessel in 5 g

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