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Moisture-Induced Amorphous Phase Separation of Amorphous Solid Dispersions: Molecular Mechanism, Microstructure, and Its Impact on Dissolution Performance

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ABSTRACT

Amorphous phase separation (APS) is commonly observed in amorphous solid dispersions (ASD) when exposed to moisture. The objective of this study was to investigate: (1) the phase behavior of amorphous solid dispersions composed of a poorly water-soluble drug with extremely low crystallization propensity, BMS-817399, and PVP, following exposure to different relative humidity (RH), and (2) the impact of phase separation on the intrinsic dissolution rate of amorphous solid dispersion. Drug-polymer interaction was confirmed in ASDs at different drug loading using infrared (IR) spectroscopy and water vapor sorption analysis. It was found that the drug-polymer interaction could persist at low RH ($\leq$75% RH) but was disrupted after exposure to high RH, with the advent of phase separation. Surface morphology and composition of 40/60 ASD at micro-/nano-scale before and after exposure to 95% RH were also compared. It was found that hydrophobic drug enriched on the surface of ASD after APS. However, for the 40/60 ASD system, the intrinsic dissolution rate of amorphous drug was hardly affected by the phase behavior of ASD, which may be partially attributed to the low crystallization tendency of amorphous BMS-817399 and enriched drug amount on the surface of ASD. Intrinsic dissolution rate of PVP decreased resulting from APS, leading to a lower concentration in the dissolution medium, but supersaturation maintenance was not anticipated to be altered after phase separation due to the limited ability of PVP to inhibit drug precipitation and prolong the supersaturation of drug in solution. This study indicated that for compounds with low crystallization propensity and high hydrophobicity, the risk of moisture-induced APS is high but such phase separation may not have profound impact on the drug dissolution performance of ASDs. Therefore, application of ASD technology on slow crystallizers could incur low risks not only in physical stability but also in dissolution performance.

Introduction

Advances in combinatorial chemistry and high-throughput screening have given rise to increasing amount of poorly water-soluble drugs in drug discovery.[1] The appearance of amorphous solid dispersions (ASDs) has provided a promising formulation strategy to increase the dissolution rate and solubility of poorly water-soluble compounds thus to improve the oral bioavailability.[2-6] As high energy and metastable binary systems where drug molecules disperse in polymer matrix above crystalline drug solubility,[7] one of the major physical stability concerns of ASDs is amorphous drug recrystallization into a thermodynamically more stable crystalline form, thus diminishing the solubility advantage of amorphization. At the same time, ASDs could also undergo amorphous phase separation (APS), either due to suboptimized processing conditions

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or aging during storage,[8-10] to produce drug-rich and polymer-rich domains, wherein drug still remains amorphous. For poorly water-soluble drugs that crystallize relatively slow, the risk of APS could be dominant, especially considering most of these drugs are highly lipophilic (i.e., high risk of phase separation from hydrophilic carriers but without crystallization), whereas the presence of moisture serves as an unavoidable APS catalyst.

Moisture-induced APS was reported in many ASD systems prepared by drugs and polymers with various physicochemical properties, including nifedipine-PVP, droperidol-PVP, and pimozide-PVP, felodipine-PVPVA, pimozide-PVPVA, and pimozide-HPMCAS and so forth.[9-13] When sorbed water penetrates into ASDs, water molecules could overtake the drug molecules to form new hydrogen bonding with polymers, destroy the original drug-polymer interaction and render it thermodynamically immiscible.[9,13] At the same time, water also acts as a strong plasticizer to significantly decrease the glass transition temperature (T_g) and increase the molecular mobility of ASDs.[14-16] These 2 mechanisms could be driving the moisture-induced APS indistinguishably and synergistically.

It is generally assumed that in a miscible ASD system, amorphous drug disperses in the polymer matrix at molecular level, and polymer stabilizes the amorphous drug by decreasing the molecular mobility through specific or nonspecific drug-polymer interactions.[7,17,18] Meanwhile, the drug-polymer interaction was also believed to be a key mechanism behind the improved drug supersaturation in solution with the presence of polymers.[19,20] In addition, hydrophilic polymer carrier could also increase the wettability and dispersability of the hydrophobic amorphous drug during dissolution by surrounding and interacting with it intimately.[21] Therefore, the potential impacts of the disruption of drug-polymer interactions and APS on the physical stability and dissolution performance of ASD could be catastrophic, and the risk of APS is certainly worth attention during ASD formulation development.

Previous studies on APS have been focusing on the factors affecting the apparent tendency and kinetics of APS on exposure to moisture.[10-13,22] For instance, it was concluded that weaker drug-polymer interactions, high ASD hygroscopicity, and more hydrophobic APIs, were reasons behind ASDs susceptible to moisture-induced APS.[10] It was also reported that the rate of ASD phase separation depended on the initial drug content and drug-polymer interactions.[13] APS was also reported to be related with accelerated crystallization kinetics of amorphous drugs in a number of systems,[11] wherein much earlier onset of drug crystallization was observed in pimozide-PVP, and 2 other systems exhibiting phase separation when compared to indomethacin/PVP system that remained homogenously mixed.[11]

Although moisture-induced phase separation kinetics and phase behaviors of ASDs have been extensively studied, knowledge about its molecular mechanism, microstructure, and the explicit consequence on the intrinsic dissolution rate of ASDs is still lacking. While it is generally considered that crystallization will inevitably negate the solubility advantage of amorphous drugs, the impact of APS on the dissolution rate of ASDs and subsequent supersaturation maintenance has not been clearly studied so far. Previously, we compared the intrinsic dissolution performance of ASDs with good uniformity, and physical mixtures with the same overall drug content but mixed by ASDs with high and low drug loading (i.e., artificially prepared ASD systems with APS), and the results suggested that changes in the mixing state of ASDs could affect the dissolution behavior of ASDs to different extents, largely depending on the strength of drug-polymer interactions.[23] The artificially prepared ASDs with APS could certainly be very different in their microstructure and dissolution performance, compared with ASDs with moisture-induced APS, which are real-life scenarios. Therefore, in this study, we aim to (1) investigate the effect of moisture on the drug-polymer interaction and microstructure of a model ASD system based on BMS-817399, a lipophilic slow crystallizer, and PVP, a commonly used hydrophilic polymer; (2) to study the impact of APS on the intrinsic dissolution rate of both the drug and polymer from ASDs.

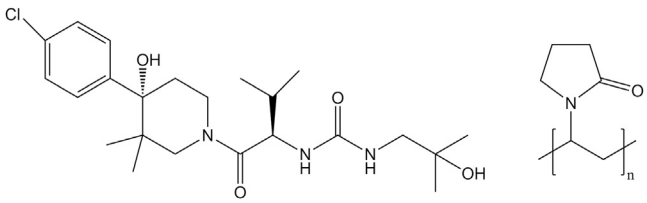

Figure 1. Chemical structures of model compound and polymer.

Materials and Methods

Materials

BMS-817399 was obtained from BMS (Bristol-Myers Squibb). BMS-817399 is a poorly water-soluble, nonionizable (pH 2-11) drug with a melting point of 210°C, a glass transition temperature of 116°C, water solubility of 40 μg/mL, and Log D (pH 6.5) = 3.26. PVP K30 (Kollidon) was provided by BASF Chemical Company Ltd. (Ludwigshafen, Germany). PVP was used as a model polymer here because PVP is widely used in ASDs, and it also forms specific interactions with BMS-817399 (shown below). Moreover, PVP was selected due to its high hygroscopicity, which facilitated the investigation on moisture-induced APS in ASDs. The chemical structures of BMS-817399 and PVP were shown in Figure 1. All buffer salts used for dissolution medium, as well as methanol (high-performance liquid chromatography [HPLC] grade) were obtained from Beijing Chemical Works (Beijing, China).

Preparation of BMS-817399/PVP Amorphous Solid Dispersions Using Spray Drying

The amorphous solid dispersions were prepared by spray drying (B-90; Büchi Labortechnik AG, Postfach, Switzerland). Pure BMS-817399 and drug-polymer blends with 20, 40, 60, and 80 wt % drug were dissolved in methanol with a total concentration of 5 wt %, and then the solution was spray-dried using the following conditions: inlet temperature 80°C, outlet temperature 50°C-53°C, N_2 flow rate of 100 L/min. After spray drying, materials were collected and vacuum-dried for 24 h, and then stored at 4°C for further use. The solid dispersions were confirmed to be amorphous by powder X-ray diffraction (PXRD) and polarized microscope (data not shown). Physical mixture (PM) with 20, 40, 60 and 80 wt % drug loading were prepared by PVPK30 and pure amorphous BMS-817399 prepared by spray drying. Another physical mixture with a total 40% drug loading was also prepared by mixing 2 spray dried ASDs with 20% and 60% drug loading, respectively.

Powder X-Ray Diffraction

PXRD patterns of the samples from 5° to 45° (2θ) were collected by a PANalytical X' pert Powder X-ray Diffractometer (copper X-ray tube, 40 kV × 40 mA; PANalytical, Almedo, The Netherlands), at a speed of 8°/min, with automatic divergence slit graphite monochromator, 0.2 mm receiving slit.