Physical Characterization of Drug:Polymer Dispersion Behavior in Polyethylene Glycol 4000 Solid Dispersions using a Suite of Complementary Analytical Techniques

DIPY M. VASA, NAMITA DALAL, JEFFREY M. KATZ, RAHUL ROOPWANI, AKSHATA NEVREKAR, HARSHIL PATEL, IRA S. BUCKNER, PETER L. D. WILDFONG

Department of Pharmaceutical Sciences, Duquesne University, Pittsburgh, Pennsylvania 15282

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ABSTRACT: Fifteen model drugs were quenched from 3:1 (w/w) mixtures with polyethylene glycol 4000 (PEG4000). The resulting solids were characterized using powder X-ray diffraction (PXRD), analysis of pair distribution function-transformed PXRD data (where appropriate), hot-stage polarized light microscopy, and differential scanning calorimetry (DSC). Drug/polymer dispersion behavior was classified using the data from each technique, independent of the others, and limitations to single-method characterization of PEG-based systems are highlighted. The data from all characterization techniques were collectively used to classify dispersion behavior, which was compared with single-technique characterization. Of the 15 combinations, only six resulted in solids whose dispersion behavior was consistently described using each standalone technique. The other nine were misclassified using at least one standalone technique, mainly because the phase behavior was ambiguously interpreted when only the data from one technique were considered. The data indicated that a suite of complementary techniques provided better classifications of the phase behavior. Of all the quenched solids, only cimetidine was fully dispersed in PEG4000, suggesting that it solidified from a completely miscible mixture of molten drug and polymer that did not phase separate upon cooling. In contrast, ibuprofen and PEG4000 completely recrystallized during preparation, whereas the remaining 13 drugs were partially dispersed in PEG4000 at this composition. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:2911–2923, 2014

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INTRODUCTION

As poorly soluble new chemical entities enter drug development pipelines, different approaches for solubility enhancement may be attempted as they are considered for adoption as candidate molecules. Among these, preparation of solid amorphous dispersions has received considerable attention.[1–5] Solid dispersions are prepared by rapid co-solidification of an active pharmaceutical ingredient (API) and a carrier excipient (frequently a water soluble polymer), by one of several methods, including spray drying,[6] super-critical fluid processing,[7] lyophilization,[8] hot-melt extrusion,[9] and high-shear co-trituration.[10,11] Solid dispersions can increase the apparent solubility of a material by allowing the drug to persist as an amorphous solid.[12] Spontaneous recrystallization of the drug is inhibited by its physical intercalation within interstices formed by entanglement of the polymeric host.[5,13–15]

Since both formation and physical stability of solid dispersions rely on solidification from a mutually miscible API and polymer mixture, research in this area has focused on predicting how the interactions between API and carrier enable dispersability.[16–20] Despite predictive advances, dispersion formulation still relies on the analytical techniques to confirm that a true dispersion has been formed. Several different characterization approaches are reported throughout the literature, and include single-instrument,[14,21,22] two-instrument,[17,23] and multi-instrument methods,[24] each aimed at demonstrating that the physical properties and microstructure of the binary solid, established by intimate, mutual dispersion of the components, are distinct from the physical mixtures of the two solids. Moreover, as solid dispersions become viable formulation strategies for poorly soluble API, regulatory agencies will see an increased number of filings for these materials. At present, no standard guidance directs characterization of solid dispersions, leaving it to the literature to report best practices.

In this study, solid dispersions were attempted using a modest library of 15 model API in polyethylene glycol 4000 (PEG4000). PEG4000 is a hydrophilic, semicrystalline polymer potentially useful as a solid dispersion carrier,[1,2,25] which has been shown to increase the dissolution rate of poorly water-soluble drugs such as carbamezapine.[26] Despite historical use, the phase behavior of API in PEG remains challenging to characterize. Upon co-solidification, PEG4000 has been shown to disperse API as pure amorphous solid,[27] a combination of amorphous and crystalline phases,[28] only crystalline solid,[26] and form eutectic mixtures with API.[29,30] PEG4000 was, therefore, chosen for this study as illustrative of resulting in very complex solid mixtures with API, providing analytically challenging signals for interpretation using individual techniques commonly employed in solid dispersion characterization. In this work, API:PEG4000 combinations will be classified in one of three categories, (1) Fully dispersed: quenching of a completely miscible molten mixture results in a single amorphous phase; (2) partially dispersed: quenching results in a detectable

Correspondence to: Peter L. D. Wildfong (Telephone: +412-396-1543; Fax: +412-396-4660; E-mail: wildfongp@duq.edu)

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amorphous phase, and recrystallized drug and/or polymer; (3) fully phase separated: quenching results in complete recrystallization of the drug and polymer. A fourth potential outcome might be expected in some cases, where both components are in the amorphous state, but they are not dispersed in one another. This possibility is unlikely with the polymer used here, and was not observed, most likely because of the propensity of PEG4000 to rapidly crystallize.

The key objective of this work was to demonstrate that comprehensive characterization is needed for PEG-based dispersions in order to properly classify API:polymer behavior. Each sample in the library was characterized using a suite of techniques including powder X-ray diffraction (PXRD), pair distribution function (PDF) analysis,[17,23] hot-stage polarized-light microscopy (HSM), and differential scanning calorimetry (DSC). The dispersion behavior of each API in PEG4000 was inferred using this suite of techniques. In some instances, inferences drawn from single techniques resulted in inconsistent classifications, whereas complementary characterization allowed for better informed classification of the binary materials.

MATERIALS AND METHODS

Materials

Chlorpropamide, indomethacin, tolbutamide, cimetidine, and griseofulvin were all purchased from MP Biomedicals (Solon, Ohio). Ketoconazole and ibuprofen were purchased from Spectrum (Gardena, California). Quinidine and cloperastine·HCl were purchased from Sigma–Aldrich (St. Louis, Missouri). Terfenadine and sulfanilamide were purchased from Acros Organics (Geel, Belgium). Propranolol·HCl, nifedipine, and itraconazole were purchased from TCI Chemicals (Portland, Ohio). Melatonin and PEG4000 were purchased from Alfa-Aesar (Ward Hill, Massachusetts). The structures for all model drugs and PEG4000 are shown in Table 1.

Co-solidification of API:PEG4000 Mixtures

Physical mixtures of each API and PEG4000 were manually prepared in a 3:1 (w/w) API:polymer ratio, and equilibrated at 10% relative humidity for 24 h. Physical mixtures were transferred to a crucible immersed in silicone oil maintained at $T_{m,API}$ +10°C. The molten mixture was stirred for 20–30 min to ensure that all solid had disappeared. Mixing times were determined based durations at $T_{m,API}$ +10°C at which insignificant thermal degradation was observed. Each material was held isothermally in a thermogravimetric analyzer at $T_{m,API}$ +10°C, and <2% (w/w) weight loss was set as a criterion for thermal stability at this temperature. Additionally, each API was heated in a DSC to T_m +15°C, and held isothermally for 30 min. After the extended isothermal hold, samples were quenched in the DSC, before reheating. The T_g values all corresponded well with reported literature values, and the baseline heat flows following melting of these samples were steady, suggesting that each API was stable under the conditions used to make the dispersions. Additionally, the literature suggests that no significant chemical degradation should be expected at temperatures equal to or greater than those used in the present experiments for chlorpropamide,[31] griseofulvin,[32] indomethacin,[33] itraconazole,[34] ketoconazole,[35] nifedipine,[33] terfenedine,[36] and tolbutamide.[33]

Nitrogen gas was continuously streamed over the crucibles during preparation, to prevent moisture sorption. Molten mixtures were quenched by immersion of the crucible in liquid nitrogen. Pure component amorphous samples were prepared using the same method as the API:PEG4000 mixtures. All preparations were repeated in triplicate.

Differential Scanning Calorimetry

Glass transition temperatures (T_g), melting temperatures (T_m), and recrystallization temperatures (T_c) were measured in triplicate for all samples using a Model Q100 DSC (TA Instruments, New Castle, Delaware), operated under a three-point temperature/enthalpy calibration using o-terphenyl, indium, and tin standards, and a cell constant calibration using indium. All experiments were conducted using 50 mL/min nitrogen purge to the cell. Sample "chips" of cosolidified mixtures (4–8 mg) were hermetically sealed in aluminum pans, and initially cooled at 20°C/min to −80°C. Following *in situ* equilibration at −80°C, each sample was heated at either 2°C/min or 20°C/min to $T_{m,API}$ +10°C. All pure component drug and polymer samples (3–5 mg) were heated at 20°C/min from room temperature to T_m +10°C, held isothermally for 5 min, and then rapidly cooled to −80°C *in situ*. Quenched samples were then reheated at 20°C/min to T_m +10°C.

The expected T_g for drug:polymer mixtures (assuming intimate mixing of the two liquid phases) was calculated using the Couchman–Karasz equation:[37]

$$T_g = \frac{w_{API} T_{g,API} + K w_p T_{g,p}}{w_{API} + K w_p} \quad (1)$$

where w_{API} and w_p were the weight fractions of API and polymer, respectively, $T_{g,API}$ and $T_{g,p}$ are the glass transition temperatures of amorphous API and polymer, respectively, and $K = \Delta C_{p,p}/\Delta C_{p,API}$, where $\Delta C_{p,p}$ and $\Delta C_{p,API}$ are the changes in the heat capacity through the glass transitions of the polymer and API, respectively. Calculated T_g values were compared with observed T_g values for mixtures, interpolated from the DSC heat flow signal, measured as the midpoint of the step change in heat capacity. It is important to note that $T_{g,p}$ measured in these experiments was very low (−67.92°C),[38–40] and PEG4000 rapidly recrystallized at room temperature. As such, pure amorphous PEG4000 could not be prepared as a pure component reference for use with any of the other characterization experiments.

Optical Hot-Stage Microscopy

Small, intact chips of each co-solidified API:PEG4000 mixture were placed on a microscope slide and heated/cooled using an Instec HCS 302 Pelletier heating stage with an STC 200 temperature controller (Instec, Boulder, Colorado). Samples were heated at 10°C/min from ambient temperature to $T_{m,API}$ +10°C, held isothermally for 5 min, and then cooled back to ambient temperature at 10°C/min. Observations were made using an Olympus BX-51 optical microscope equipped with a polarizing filter, under 10× magnification. Photomicrographs were obtained throughout the heating/cooling profile to observe phase changes in the solids as a result of heating, or to distinguish between crystalline polymer and crystalline API.