Crystallization Tendency of Active Pharmaceutical Ingredients Following Rapid Solvent Evaporation—Classification and Comparison with Crystallization Tendency from Undercooled Melts

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ABSTRACT: In this study, the crystallization behavior of a variety of compounds was studied following rapid solvent evaporation using spin coating. Initial screening to determine model compound suitability was performed using a structurally diverse set of 51 compounds in three different solvent systems [dichloromethane (DCM), a 1:1 (w/w) dichloromethane/ethanol mixture (MIX), and ethanol (EtOH)]. Of this starting set of 153 drug–solvent combinations, 93 (40 compounds) were selected for further evaluation based on solubility, chemical solution stability, and processability criteria. These systems were spin coated and their crystallization was monitored using polarized light microscopy (7 days, dry conditions). The crystallization behavior of the samples could be classified as rapid (Class I: 39 cases), intermediate (Class II: 23 cases), or slow (Class III: 31 cases). The solvent system employed influenced the classification outcome for only four of the compounds. The various compounds showed very diverse crystallization behavior. Upon comparison of classification results with those of a previous study, where cooling from the melt was used as a preparation technique[1], a good similarity was found whereby 68% of the cases were identically classified. Multivariate analysis was performed using a set of relevant physicochemical compound characteristics. It was found that a number of these parameters tended to differ between the different classes. These could be further interpreted in terms of the nature of the crystallization process. Additional multivariate analysis on the separate classes of compounds indicated some potential in predicting the crystallization tendency of a given compound.
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INTRODUCTION

The current drug discovery process is characterized by an increase in new chemical entities which can be classified as Class II and Class IV compounds, according to the Biopharmaceutical Classification System[2] (BCS). Hence, bioavailability of these compounds is limited due to a low aqueous solubility and, in some cases, also permeability. To enhance bioavailability, a number of formulation platforms have been introduced, such as particle size reduction,[3] complexation,[4] the use of cosolvents,[5] chemical derivatization using prodrug strategies,[6] and rendering the drug amorphous, often through the formation of a solid dispersion.[7] The interest in the latter strategy originates from the higher (apparent) solubility of the amorphous form compared to the crystalline counterpart(s). Calculations based on thermodynamic parameters suggest relative increases in solubility up to 1600-fold, although the extent of the theoretical enhancement is highly compound specific.[8] Furthermore, crystallization often drastically reduces any potential solubility advantage; crystallization can occur both during storage of the solid[9–11] and upon dissolution of the amorphous solid.[12–14]

Crystallization during storage of amorphous pharmaceuticals has recently been reviewed.[15] The authors highlighted that crystallization from the amorphous state is a complex phenomenon, making an overall understanding of the crystallization behavior of

Supporting Information may be found in the online version of this article.

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amorphous drugs an ambitious goal. As crystallization is the combined result of nucleation and crystal growth, all factors affecting one or both processes can be expected to have an effect on the overall crystallization behavior. Factors known to have an effect on crystallization from the amorphous state are thermodynamic [e.g., the free energy difference between the crystalline and amorphous states (ΔG_v)], kinetic [e.g., molecular mobility, for which the glass transition temperature (T_g) is often used as an indicator], or molecular [e.g., hydrogen bonding interactions] in nature. Furthermore, factors such as moisture content and the method employed for generation of the amorphous form have also been reported to influence crystallization behavior[15] (and references therein).

Possible routes for the generation of amorphous materials are cooling from the melt, condensation from the vapor state, mechanical disruption of the crystal lattice, precipitation from solution and solvent evaporation.[15,16] From the perspective of industrial production, however, it is pertinent to mention that amorphous drugs and formulations are conventionally prepared either by cooling from the melt (e.g., melt extrusion) or by solvent evaporation/sublimation (e.g., spray drying or freeze-drying).[17]

There are numerous examples in the literature describing the stability and/or stabilization of amorphous pharmaceuticals.[18–20] Typically, the crystallization behavior of only one or a few compounds is reported in such studies. The crystallization behavior of a larger data set of compounds is seldom evaluated although this approach would potentially yield a more general understanding of the crystallization of pharmaceuticals, in particular if the crystallization conditions are standardized. A recent example of this approach is provided in the study by Greaser et al.,[21] where the authors attempted to correlate the amorphous stability of 12 active pharmaceutical ingredients (APIs) with a number of kinetic and thermodynamic parameters. Samples were prepared *in situ* in a differential scanning calorimeter (DSC) by cooling from the melt in DSC pans. Although a reasonable correlation could be observed between the physical stability above the glass transition temperature (T_g) and the configurational entropy, the authors concluded that: "*. . . when dealing with the amorphous state, complex kinetic and thermodynamic processes have to be considered and no simple straightforward attempt will suffice to characterize physical stability . . .*" Furthermore, multivariate analysis was suggested to be a potentially better approach, given the complexity of crystallization. In a recent study, the glass forming ability and glass stability of a set of 51 structurally diverse compounds was investigated and classified.[1] In common with the Greaser study, samples were prepared by cooling from the melt in DSC pans. Multivariate analysis was utilized to probe important compound properties that correlated with the crystallization tendency.

Although solvent evaporation techniques are commonly used to produce amorphous materials, there are fewer studies evaluating the crystallization tendency of APIs produced using this method. Furthermore, it is of interest to evaluate if there are similarities between the crystallization tendency from the melt and following solvent evaporation, in other words, how much does the method of preparation affect the crystallization tendency versus the inherent properties of the compound? The aim of the current study was thus to investigate the crystallization behavior of a large group of compounds following rapid solvent evaporation and to compare the results to the melt crystallization behavior. Fifty-one model compounds, for which the melt crystallization behavior has been determined, were evaluated. Three different solvent systems having different polarities were selected [dichloromethane (DCM), a 1:1 (w/w) dichloromethane/ethanol mixture (MIX), and ethanol (EtOH)] and rapid solvent evaporation was performed by spin coating, enabling the formation of thin films using milligram quantities of drug. The short-term physical stability of the resultant films was monitored using polarized light microscopy. The observed crystallization behavior following spin coating was then classified into three classes: "Class I": rapid crystallization; "Class II": intermediate crystallization; "Class III": slow crystallization and compared to the melt crystallization behavior, Principal component analysis (PCA) was performed using a set of physicochemical compound characteristics in order to provide insight into the origin of the differences in crystallization behavior.

MATERIALS AND METHODS

Materials

Atenolol, benzocaine, dibucaine, lidocaine, miconazole, procaine, and tolbutamide were obtained commercially from Spectrum Chemical (Gardena, CA). Aceclofenac, clarithromycin, and loratadine were obtained commercially from Attix Pharmachem (Toronto, ON, Canada). 4-biphenylcarboxylic acid, 4-biphenylmethanol, 4-biphenylcarboxaldehyde, 4-phenylphenol, acetaminophen, anthranilic acid, antipyrin, benzamide, bifonazole, anhydrous caffeine, chlorpropamide, chlorzoxazone, cinnarizine, clofoctol, clotrimazole, droperidol, felbinac (4-biphenylacetic acid), fenofibrate, flufenamic acid, flurbiprofen, haloperidol, indomethacin, indoprofen, ketoprofen, niclosamide, nilutamide, nimesulide, PABA (4-aminobenzoic acid), phenacetin (*p*-acetophenetidide), pimozide, probucol, D-(−)-salicin, tolazamide, and