Feasibility Assessment for Studying Crystallization Onset in Amorphous Pharmaceutical Preparations

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Introduction

The long-term stability of pharmaceutical products formulated with amorphous solids is of significant concern owing to the inherent instability of the amorphous state and the potential for transformation, or relaxation, to a more stable, crystalline form [1]. Initiation of this change will ultimately lead to the spontaneous and often catastrophic decrease of critical product performance attributes, including solubility and bioavailability.

Previous work has clearly demonstrated the importance of thermodynamic and structural contributions to the relaxation process [2]. It is hypothesized that as amorphous solids "age" under isothermal conditions, they become more energetically relaxed, and the probability that crystallization will ultimately occur increases. At present, there is no method that assesses the "effective age" of an amorphous raw material relative to its initially unrelaxed state. A method that uses enthalpic-relaxation master curves to determine the effective age of an amorphous material having known excursions during storage has been developed [3]. Given the constraint that the system is to remain below its glass transition temperature and within the region of the enthalpy–temperature diagram defined by the equilibrium supercooled liquid and the glassy state, experimental results from using indomethacin and salicin as model compounds show that master curves can be used to predict aging behavior under nonisothermal conditions, with temperature excursions as large as 10°C. The model also supports the assertion that the amorphous solid is indeed composed of a distribution of thermodynamically relaxed subpopulations in which only the most relaxed segments of the amorphous population crystallize.

To complement the study of the energy contribution, an investigation of molecular conformational changes occurring in amorphous preparations was initiated in order to understand the fundamental events that represent the crystallization precursors. In other words, as an amorphous solid initially relaxes to a more stable crystalline form, characteristic distances in the x-ray diffraction pattern should become apparent as the material becomes more ordered as determined by simple inspection or mathematical treatment of the data.

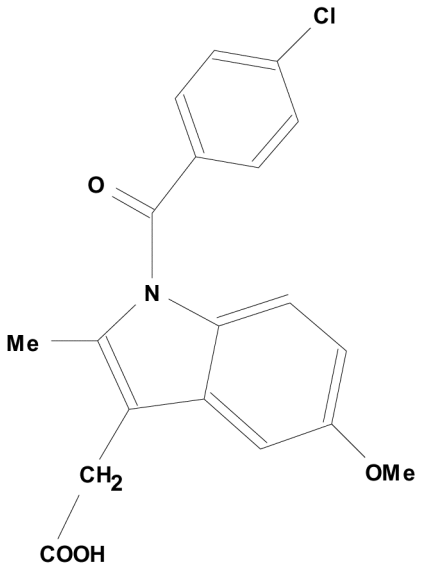

FIG. 1. Indomethacin ($C_{19}H_{16}ClNO_4$; 1-(p-chloro-benzoyl)-5-methoxy-2-methyllindole-3-acetic acid).

Methods and Materials

Samples of crystalline and ground, quench-cooled, amorphous indomethacin (Fig. 1) were prepared as compacts (1-mm thick, 25-mm diameter), whereas glassy samples were obtained by slower cooling of the melt in a mold of equivalent dimensions. For the amorphous or glassy samples, isothermal aging was performed for as long as 4 days (off-line) at temperatures that were less than the glass transition temperature. It has been reported that only the γ-form of indomethacin has been observed to recrystallize from amorphous preparations below the glass transition temperature [4, 5]; it crystallizes in space group $P\bar{1}$ (triclinic) having cell constants a = 9.295 Å, b = 10.969 Å, c = 9.742 Å, α = 69.38°, β = 110.79°, and γ = 92.78°. Initial experiments performed by using a laboratory Cu-$K\alpha$ source (λ = 1.54178 Å) proved to be less suitable for generating diffraction data at a resolution sufficient to identify subtle structural changes occurring during isothermal aging. High-energy diffraction experiments were performed at MR-CAT beamline 10-ID at the APS by using synchrotron radiation (25 keV, λ = 0.4962 Å) optimized for resolution of the data. Samples were mounted perpendicular to the incident beam on an

x,*y*-positioning platform to facilitate analysis of different regions of the sample during data collection.

Results

The diffraction pattern for crystalline indomethacin between 0.4 and 13.5 Å is presented as Fig. 2. These data were collected to provide baseline information on patterns at small *d*-spacings that might exist as molecules begin to rearrange and form regions of local order in the amorphous state. It is hypothesized that the region of smaller *d*-space may provide information related to the conformational changes of molecules that can be monitored during the aging of amorphous materials; the study of small *d*-spacings in amorphous or glassy samples during aging is planned as future work. A second approach, that of probing longer-range distances, was also completed for the samples prepared as amorphous or glassy samples. For these noncrystalline samples, the range between 2.0 and 10.0 Å, or where evidence of the characteristic diffraction peaks was first discernable without the use of more computationally intensive tools, was probed. Figure 3 shows the data from one such experiment where an initially amorphous sample was aged *in situ* for 9 hours at 30°C and monitored at different locations of the sample using the *x*,*y* stage. As expected, peaks characteristic of the γ-form of indomethacin developed in the diffraction pattern, providing evidence of increased crystallinity with increasing aging time. Additional studies of longer-range distances in initially amorphous materials are planned for the future.

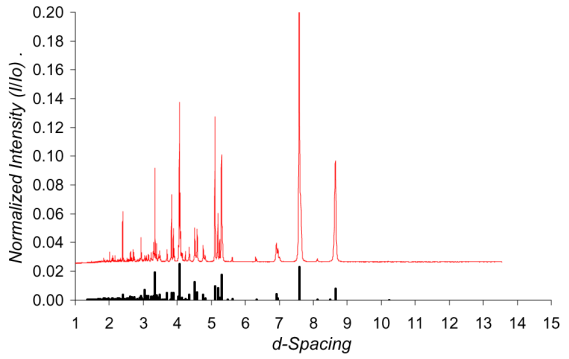

FIG. 2. Diffraction pattern of crystalline indomethacin. The bars plotted below the data represent the characteristic reflections for the γ-form.

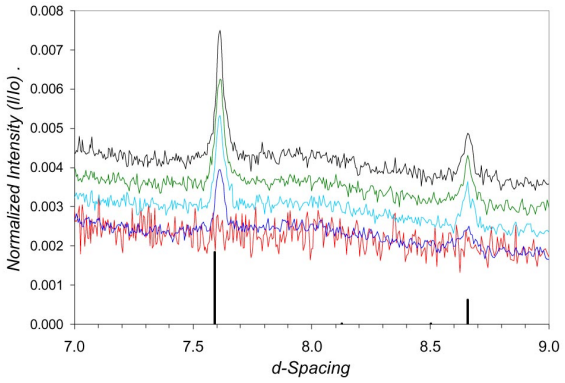

FIG. 3. Isothermal aging (30°C) of an initially amorphous indomethacin compact for up to 9 hours of total aging time. The bars plotted below the data represent two characteristic reflections for the γ-form between 7 and 9 Å in d-space.

Discussion

This preliminary research served to define the experimental parameters and provide the data from which to develop the necessary structural analysis techniques, such as pair-distribution functions, that will be used as tools to guide our future research at the APS.

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