Milling-Induced Disorder of Pharmaceuticals: One-Phase or Two-Phase System?

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ABSTRACT: During milling, components are subjected to shear and tensile stresses, which can result in physical phase transformations. The purpose of the work described in this report is to understand the pathway by which two test compounds, D-salicin and γ-indomethacin, undergo a crystalline to amorphous transformation during cryomilling. The results show that the transformation cannot be described by a standard one-phase or two-phase disordering mechanism. In the one-phase model, a continuous set of states exist, linking perfect crystalline with completely amorphous material, whereas the two-phase model of disorder depicts the material as a binary mixture of crystalline and amorphous fractions. Instead, a model is proposed where two one-phase regions, defected crystalline and amorphous regions, are separated by a distinct transition. © 2011 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 101:1475–1485, 2012
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INTRODUCTION

Organic solids can exist in a variety of solid physical forms consisting of crystalline polymorphs, defected structures, and amorphous states that have distinguishing energies and densities.[1] This in turn can have important implications for physical properties and subsequent performance.[1–4] Polymorphs represent different solid-state packing arrangements of the same chemical composition and are described by unique crystal structures with characteristic free energies.[4,5] Converting from one polymorph to another requires passing through a phase transformation and involves a discontinuous change in the free energy.[5] The introduction of lattice defects into a given polymorph results in an increase in energy of the material relative to the perfect, defect-free crystal structure. Disruption of the crystal lattice by defect formation and the creation of amorphous content have been shown to occur for a variety of pharmaceuticals and excipients through processing operations such as milling.[6–10]

Analogous to polymorphism, the presence of a first-order phase transition that separates different solid amorphous states indicates the presence of polyamorphism.[11,12] Although the identification of true polyamorphism for organic glasses in the pharmaceutical sciences is still a matter of debate, in a recent article published by Winkel et al.[13] on solid carbonic acid, a phase transition separating two glassy states was inferred from computational and structural X-ray powder diffraction (XRPD) and infrared work.[12,13] Polyamorphous, high-density and low-density glasses are known to exist within the broader materials science community and have been demonstrated for several classes of substances including inorganic glasses, semiconductors, and ice.[14–17] Because glasses are heterogeneous at the molecular level, so it is possible to envision cases wherein differences in local order gives rise to amorphous structures that are not necessarily separated by a phase transition.[11,12] Such amorphous structures would have unique energy and density values but interconversion between them would be a matter of local molecular rearrangements without a first-order phase transition.

Figure 1 shows a volume temperature diagram for a glass-forming and crystal-forming species from the liquid melt. Tf1 and Tf2 denote the respective fictive
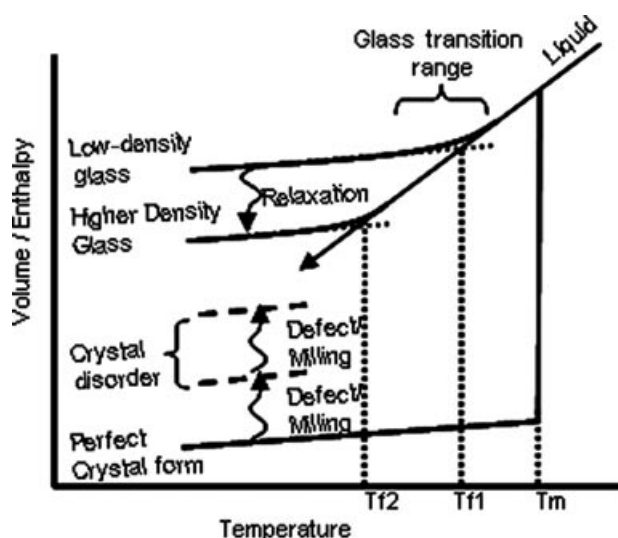
Figure 1. Volume–temperature diagram of a glass-forming and crystal-forming species from the liquid melt. Tf1 and Tf2 denote the respective fictive temperature in the T_g region associated with forming a higher or lower density glass based upon cooling rate. T_m is the melting point associated with a given crystalline polymorph. Overlaid on the diagram are disordered crystal states that can arise as a consequence of processing a particular polymorphic form.

temperatures in the glass transition temperature (T_g) region associated with forming a lower or higher density glass based upon cooling rate. In the idealized case, the fictive temperature is defined as the temperature at which the liquid structure is "frozen in" to the solid state. It is also the equivalent temperature at which a glass would attain thermal equilibrium upon heating. A higher density, lower energy glass is formed at slower cooling rates or following relaxation of higher energy structures. If the cooling rate is slow enough then crystallization to a particular polymorph is induced at the melting point (T_m). The perfect, defect-free, stable polymorph lies at the energetically lowest state in the diagram. As defects are progressively introduced into a crystal, the system increases in energy. An unanswered question is whether amorphous content arrived at through processing crystalline forms equates to the same amorphous structure arrived at through melt quenching or, indeed, any other processing technique such as spray drying, lyophilization, solvent evaporation, or vapor deposition. A second question involves the nature of the transitions involved from increasing or decreasing levels of crystallinity in a sample. From a practical perspective, the answers to both questions will dictate the way disorder could be characterized qualitatively or quantitatively by analytical techniques.

In a two-phase model of disorder, the material is depicted as a binary mixture of two unique states comprising amorphous and crystalline fractions.[9] This model asserts that a decreasing percentage of crystallinity corresponds to a decreasing crystalline fraction in an increasingly large portion of amorphous matrix. The one-phase model of disorder, in contrast, maintains a continuous set of states exists between perfectly crystalline and completely amorphous material.[9] Decreasing crystallinity in the one-phase model means a reduction of symmetry operators and an increase in defects, leading to disordered states lying somewhere, energetically, between perfectly crystalline and totally random and amorphous. A goal of the work described herein is to describe the characteristics of milling-induced disorder for two test compounds.

Crystallite size reduction, altering molecular mobility, and an increase in defect density are all potential changes brought about by milling that can result in modifying the Gibbs energy of a system.[10,18,19] An investigation of the possible pathways of defect formation that can occur during milling or processing of crystalline material can be aided by an analysis of their crystal structures. A previous publication by Wildfong et al.[10] attempted to develop a thermodynamic-structure model for predicting complete mechanically induced disorder in organic small molecule crystals from a knowledge of the crystal structure and physical properties.[10] Their attempt adapted a dislocation defect mechanism that has been applied in mineralogy to organics.[10,20] Dislocations are one-dimensional line defects that are assumed to be induced in a crystal subjected to the shear stresses involved during milling. Complete mechanical disordering is defined as the point that the free energy change associated with defect formation (ΔG_d) equals the free energy change associated with transitioning from the solid to the liquid state (ΔG_{am}) from Eqs. 1 and 2.[20]

$$\Delta G_d \approx \rho_d M_v \frac{b^2 \mu_s}{4\pi} \ln\left[\frac{2}{b\sqrt{\rho_d}}\right] \qquad (1)$$

$$\Delta G_{am} \approx \left(\frac{\Delta H_f}{T_m}\right)(T_m - T_{expt}) \qquad (2)$$

From Eq. 1, the material properties affecting ΔG_d are the shear modulus (μ_s); the molar volume (M_V); the Burgers vector (b); and ρ_d, which is the dislocation density.[20] The Burgers vector describes the direction and unit displacement of a line defect in a lattice. The shear modulus expresses a structure's resistance to strain from a perpendicular stress. In Eq. 2, ΔH_f is the heat of fusion, T_m is the melting temperature, and T_{exp} is the experimental temperature so that the free energy change calculated for a crystalline to amorphous transition relies on the assumption that the amorphous solid is structurally and energetically similar to the liquid phase.[10,20] In the model, the