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Commentary

The Measurement of Small Quantities of Amorphous Material—Should We Be Considering the Rigid Amorphous Fraction?

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There has been considerable interest in recent years concerning the measurement of small quantities of amorphous material within otherwise crystalline samples. This interest has arisen as a result of the suggestion that many observed phenomena such as anomalous water sorption behavior may be interpreted in terms of a surface layer of glassy material. While constituting only a small percentage of the entire mass of the sample, this layer could nevertheless constitute a significant proportion of the surface and hence have a profound effect on product performance (1). The emphasis to date in both academia and industry regarding this issue has been to attempt to quantify the proportion of amorphous material present with techniques such as microcalorimetry and vapour sorption measurements being, particularly, widely used (2). This approach does, however, carry the concomitant assumption that the amorphous fraction of these semi-crystalline systems is essentially comparable to wholly amorphous material prepared by spray- or freeze-drying. Indeed, this assumption is central not only to the concept of the "quantity" of amorphous material being a definable (and indeed useful) parameter but also to the methods by which the aforementioned techniques are calibrated. Clearly, in theory, an infinite number of amorphous states may be generated by supercooling a material below its melting temperature under different experimental conditions. However, for most pharmaceutical systems, there does appear to be general acceptance of the two-phase model of a semi-crystalline material containing discrete crystalline and amorphous regions of uniform behaviour equivalent to that of "perfect" crystals and "perfect" glasses.

Examination of the polymer science literature suggests that there may be alternative approaches to this issue. More specifically, it is now recognized that a proportion of amorphous material in semi-crystalline polymers may exist in a distinct state whereby molecular mobility is restrained to a greater extent than in the "perfect" glass. This material, known as the rigid amorphous fraction, is believed to be associated with the interface between the crystalline and mobile amorphous phases and has properties that are intermediate between the two (3–8). The formation of the rigid amorphous fraction is shown schematically in Fig. 1 for a polymer that forms a semi-crystalline solid on cooling from the melt. As the material is cooled through the crystallization temperature Tc, a proportion remains fully amorphous (the mobile amorphous fraction) while a further proportion forms a crystalline solid. However, associated with this crystalline solid is the rigid amorphous fraction that does not undergo a mobility change on subsequent cooling through the glass transition temperature. Consequently, this fraction does not contribute to the heat capacity change (ΔCp) at the glass transition (Tg). This leads to discrepancies between the degree of crystallinity calculated from ΔCp and the figure calculated from, for example, melting or crystallisation behavior or from data obtained using techniques such as X-ray diffraction, NMR, or Raman spectroscopy (6). The proportion of the material in this state may be expressed via (9)

$$f_{RAF} = 1 - \frac{\Delta C_p^{sc}}{\Delta C_p^{am}} - C_r \quad (1)$$

where f_{RAF} is the rigid amorphous fraction and C_r is the degree of crystallinity such that

$$f_{RAF} + f_{MAF} + C_r = 1 \quad (2)$$

with f_{MAF} being the mobile amorphous fraction, given by the ratio of the heat capacity change through the glass transition for the semicrystalline material (ΔC_p^{sc}) and the (mobile) amorphous material (ΔC_p^{am}). The magnitude of f_{RAF} may be considerable, with values of over 90% having been reported for some polymeric systems (10).

There are several important implications for the presence of such a fraction within the polymer sciences. These include the analysis of the miscibility of polymer blends (11,12), crystallization (10,13), aging (14) and melting behavior (8). The existence of such a fraction has not yet been directly demonstrated for low molecular weight pharmaceuticals. Indeed, such measurements are more difficult for these materials because even when "semi-crystalline" they contain

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ABBREVIATIONS: C_r, degree of crystallinity; ΔCp, heat capacity change (at the glass transition temperature in this context); ΔC_p^{sc}, heat capacity change through the glass transition for a semicrystalline material; ΔC_p^{am}, heat capacity change through the glass transition for a (mobile) amorphous material; f_{MAF}, mobile amorphous fraction; f_{RAF}, rigid amorphous fraction; Tc, crystallization temperature; Tg, glass transition temperature.

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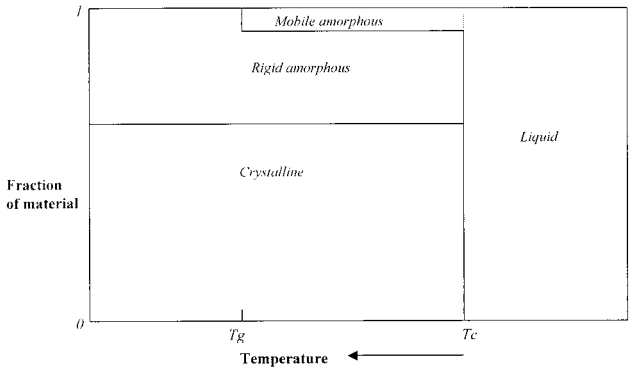

Fig. 1. Schematic representation of the formation of a mobile amorphous, rigid amorphous and crystalline fractions on cooling from the melt (adapted from (6)).

only small amounts of amorphous material compared to most polymeric systems, thereby rendering the measurement of anomalies in the heat capacity step change relatively subtle. However, we raise this as a possibility for two principle reasons. Firstly, the presence of a rigid amorphous fraction generated by, for example, grinding may result in that material behaving in a markedly different manner to that expected from studies on a wholly amorphous material, particularly in terms of recrystallization as this process is highly dependent on the molecular mobility of the amorphous phase. Secondly, the possibility of the existence of such a fraction suggests that care is required in the use of 100% amorphous spray- or freeze-dried materials as calibrants for the measurement of the degree of amorphous material in semi-crystalline systems, as the behavior of the former may not accurately reflect systems in which a proportion of the amorphous material is not "mobile" to the same extent. Indeed, it could be argued that the current emphasis on the "quantity" of amorphous material is potentially misleading, as the "nature," and more specifically the mobility, of that material may be of equal or greater relevance to product performance.

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