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Letter to the Editor

Polyamorphism: a pharmaceutical science perspective

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The occurrence of polymorphic forms of crystalline drugs and excipients is well known to pharmaceutical scientists (Byrn et al 1999), and at several recent scientific meetings the possible occurrence of polymorphic forms of amorphous pharmaceutical materials has been proposed. "Polyamorphism" is an intriguing concept from both a scientific and commercial perspective, and worthy of further comment in the pages of this journal. This is especially so because of the significant impact amorphous character can have upon the performance of pharmaceutical materials (Hancock & Parks 2000), and the potential opportunities that might arise to exploit (and maybe patent) new and improved forms of existing pharmaceutical materials.

Polyamorphism, that is, the possible existence of two distinct amorphous states of the same material separated by a clear phase transition, has been discussed for over twenty years (Angell & Sare 1970). In the most well known example it has been noted, based on a thermodynamic analysis of the heat capacity of water and ice, that there are differences in the properties of amorphous ice samples formed by vapor-deposition and by quench-cooling from the liquid state. By this definition, polyamorphs are similar to crystalline polymorphs in that they represent different and discrete phases from a thermodynamic perspective.

Several other examples of such polyamorphic materials which exhibit clear phase transitions between amorphous phases of the same chemical composition have been reported (Grimsditch 1984; Mishima et al 1984; Aasland & McMillan 1994). For the most part these materials are inorganic substances (Shalaev & Zografi 2002), and the use of the term polyamorphism has been restricted to describe only those systems where multiple super-cooled thermodynamic liquid states have been shown to exist[1].

The occurrence of true polyamorphs thus appears to be quite rare for typical pharmaceutical materials, so why all the interest in such systems by pharmaceutical scientists?

Over the past decade there have been several anecdotal reports of apparently different forms of amorphous pharmaceutical materials with readily discernible physical and chemical characteristics, and some marked differences in their pharmaceutical performance. Examples include an antibiotic prepared by lyophilization (Pikal et al 1978) and glasses of an anti-inflammatory agent produced by fast cooling of the molten material (Yoshioka et al 1994). For these particular materials, even though the amorphous samples had significantly different physical properties, there was no direct evidence of polyamorphism according to the strict thermodynamic definition provided above.

Close inspection of the relevant literature reveals that most apparently polyamorphic amorphous pharmaceutical materials have been isolated and/or stored below their calorimetric glass transition temperatures. Such "glassy" amorphous materials are by definition not at energetic equilibrium with their surroundings and their properties reflect the conditions under which they were isolated and subsequently stored. As a result of their departure from equilibrium and the very long time that it takes glasses to spontaneously relax back to the equilibrium super-cooled liquid state, it appears that it is possible to isolate amorphous materials with distinct physical and chemical properties which are not true polyamorphs.

[1]Different terminology has been used to describe other amorphous states, such as the "rigid amorphous fraction" in polymers (see Craig et al, 2001).

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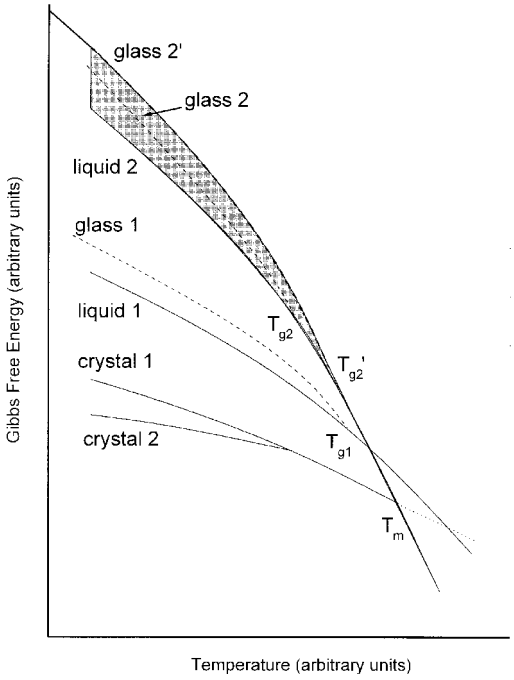

Figure 1 Schematic Gibbs free energy curves for a hypothetical single-component system that exhibits both liquid/liquid phase transition and polymorphism. Crystal 1 and crystal 2 lines correspond to two crystalline polymorphs. Liquid 1 and liquid 2 describe two liquids that exhibit a first-order phase transition (true polyamorphism). Glass 2 and glass 2′ represent pseudo-polyamorphism due to different processing and/or storage histories. The difference between curves "liquid" and "glass" is exaggerated for clarity.

No simple phrase has yet been coined to describe glassy amorphous materials that have different energetic states as a result of their different conditions of production and storage. The term "pseudo-polyamorph" may be most appropriate, by analogy to the term pseudo-polymorph which is used to describe different crystalline forms which do not fit the strict thermodynamic definition for crystalline polymorphs. Since such pseudo-polyamorphs can exist for significant periods of time (certainly longer than the shelf life of pharmaceutical products) they can present very real and significant challenges for practicing pharmaceutical scientists. These systems still need to be carefully characterized and understood if they are to be incorporated in pharmaceutical dosage forms, and to this end techniques need to be developed to monitor and distinguish their characteristics, and to track their very slowly evolving physical and chemical properties (e.g., heat capacity, true density).

The difference between true polyamorphs and pseudo-polyamorphs with different processing histories can be illustrated using a schematic Gibbs free energy diagram (Figure 1) (Shalaev & Zografi 2002). This figure highlights the difference between a behaviour based on kinetic properties (described by curves "glass 2" and "glass 2′") and true polyamorphic behaviour where a first-order phase transition occurs between two amorphous phases in the supercooled or equilibrium liquid state (depicted by curves "liquid 1" and "liquid 2"). In addition, this depiction shows the similarity between crystalline polymorphic behaviour (curves "crystal 1" and "crystal 2") and true polyamorphic behaviour.

In conclusion, we can state that there is such a phenomenon as polyamorphism which pharmaceutical scientists should be aware of. Based on current reports in the literature the number of instances of true polyamorphism with pharmaceutical materials appears likely to be very small. However, there are many possible relaxational states of most glassy amorphous pharmaceuticals (those produced and stored below their glass transition temperatures) and these might possibly be described as "pseudo-polyamorphs". These different amorphous forms are sufficiently long lived that a formulation scientist may seriously consider incorporating them into pharmaceutical dosage forms to take advantage of their distinct pharmaceutical properties. Significant challenges still remain so that the attributes of such materials can be fully understood and techniques developed for their complete and meaningful characterization. This is especially so because they do not represent distinct thermodynamic phases, but rather a continuum of kinetic states differentiated primarily by their extent of energetic departure from the equilibrium supercooled liquid condition. Finally, it should be noted that there are several other states of matter intermediate to the fully ordered (crystalline) and fully disordered (amorphous) states, and for the reader who is interested in learning more about these materials they are described in detail in a recent article (Shalaev & Zografi 2002).

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