Characterizing Polymorphic Conversions

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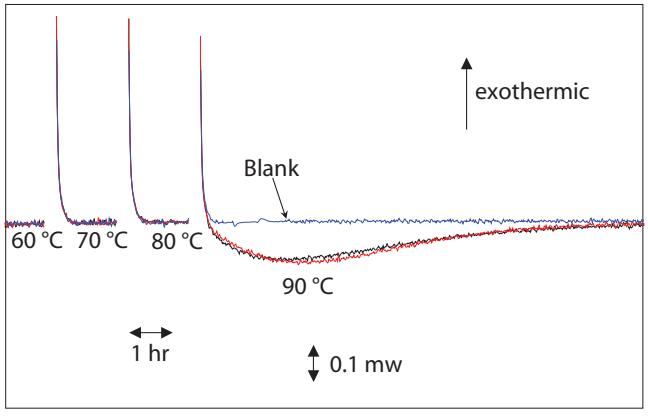
Many drugs are formulated as solids. Although convenient and compact, solid drug formulations can be problematic because the active pharmaceutical ingredient can exist in more than one thermodynamically or kinetically stable crystalline or amorphous form, and can interconvert between these forms during processing or storage. The ability of a compound to exist in different solid state forms (polymorphism) impacts the solubility, and thus the bioavailability, of the pharmaceutical. Interconversion from a more soluble to a less soluble form may occur during manufacture of the pure drug, during formulation processes, and after long-term storage, thereby changing the pharmaceutically-active properties of the final product.

Calorimetry provides a rapid and straightforward approach for monitoring polymorphic conversions in pharmaceutical compounds. Using a high sensitivity differential scanning calorimeter, a drug was exposed for 1.5 hours to successively higher temperatures (60, 70, 80 and 90 °C). The data in the figure clearly show that at 90 °C, an endothermic transition spontaneously occurs, with excellent agreement between duplicate runs. The curve shape suggests an autocatalytic mechanism of interconversion, consistent with nucleation and growth, which went to completion in about 10 hours. Independent experiments using a TAM solution calorimeter verified in a matter of minutes that the event at 90 °C was in fact interconversion between two polymorphic states, and not degradation of the compound.



Monitoring isothermal polymorph conversions on a MC-DSC.