Characterization of Pseudo-polymorphic Drugs

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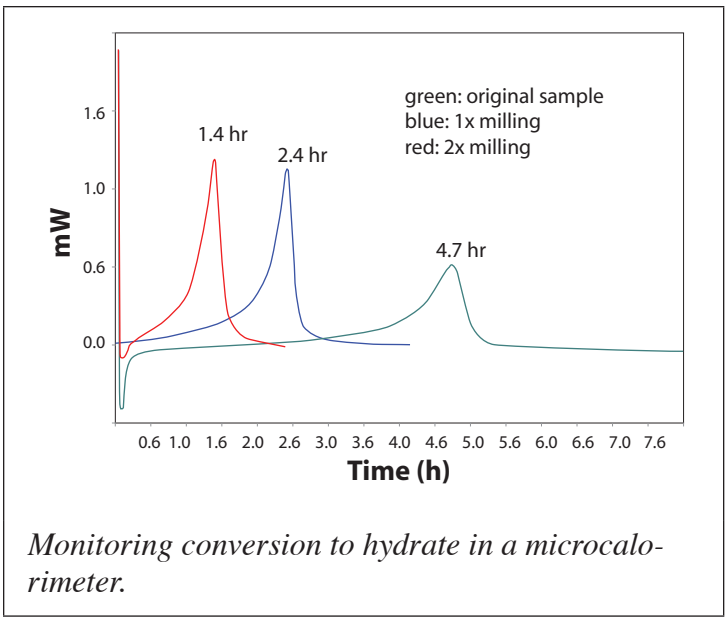
A large percentage of pharmaceutical products are formulated as solids due to their ease of manufacture and packaging, and for the convenience of the patient. However, pharmaceutical compounds can often exist in more than one solid state form, including polymorphs and hydrates (pseudo-polymorphs). Since the solid state structure has potentially significant impact on the stability and bioavailability of the final product, it is essential that the solid state energetics of the compound be characterized and understood.

Solvated systems can be studied by techniques such as moisture sorption, thermogravimetric analysis (TGA), differential scanning calorimetry (DSC) and isothermal calorimetry. Although in theory any one of these techniques can provide adequate data on the energy changes associated with solvation or desolvation, in practice isothermal microcalorimetry often provides superior data on pseudo-polymorphs, especially when only small (milligram) samples are available, or when unexpected results are obtained from other thermal techniques. For example, TGA was unable to detect formation of a drug hydrate in the presence of lactose monohydrate since there was no net change in mass associated with exchange of water between the drug substance and the lactose excipient. However, as shown in the figure, the conversion was easily detected by isothermal microcalorimetry since it is an enthalpy-based measurement. The technique could also differentiate different particle sizes on the basis of the time required for the formation of the hydrated drug, with smaller (milled) particles converting faster than larger particles. In addition, since the area under each curve is the same, isothermal microcalorimetry proved that hydrate formation was occurring uniformly throughout each particle, and was not just a surface reaction.



Monitoring conversion to hydrate in a microcalorimeter.