Characterization of Heats of Solution of Solid Drugs

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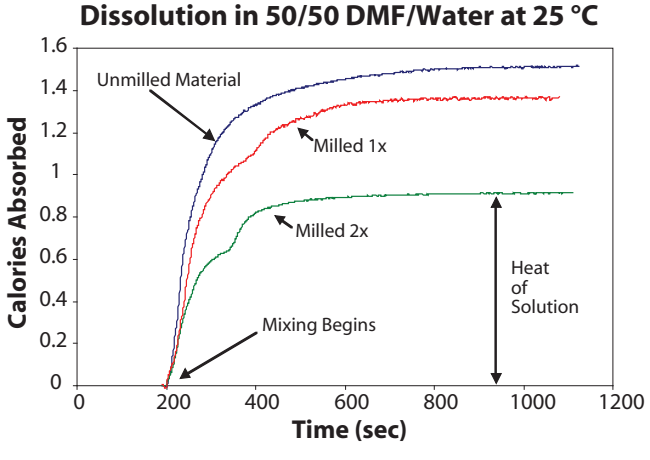
Solid pharmaceuticals are often milled, dried, compressed or otherwise manipulated during production of the final tablet or capsule format. Since any of these steps can change the solid state properties of the drug, each step must be carefully characterized and understood in order to ensure that the overall formulation process is robust and generates a reproducible and stable final product. For example, milling is often used to reduce the particle size of a drug in order to improve solubility, flow characteristics or compressibility. However, milling can also affect critical physical properties such as formation of an amorphous fraction, metastable crystalline polymorphs, or an unwanted hydrate fraction. The formation of any of these phases can impact both bioavailability and chemical stability of the drug.

The phase purity of drugs can be monitored by measuring the heat of solution. When these measurements are conducted in a fast response microcalorimeter, it is also often possible to monitor relative changes in the rate of solution as various mechanical steps (including milling) are applied.

A pharmaceutical compound was studied using a TAM solution calorimeter before it was milled, after milling for 15 minutes, and after a second round of milling. Each sample was solubilized in the calorimeter using a specially-designed ampoule and the heat of solution was measured. As the figure shows, just 15 minutes of milling resulted in both a significant drop in the heat of solution and the appearance of a second phase with a different rate of solution. Both effects were more pronounced after 30 minutes of milling. These results clearly indicate that microcalorimetry can quickly and unequivocally monitor phase changes occurring in solid pharmaceuticals caused by physical processing of the drug.



Example heats of solution data generated with a TAM solution calorimeter.