Characterization of Solid Pharmaceutical Systems from Heats and Rates of Solution

Christin T. Choma
TA Instruments, 109 Lukens Drive, New Castle, DE 19720, USA

The preparation of a solid pharmaceutical formulation requires several processes before the final tablet or capsule is produced. These processes may include milling, wet granulation, drying and compression. 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, stable, final product.

When a promising new compound enters early drug development, studies are conducted to determine the properties of the compound under various chemical and physical conditions. This constitutes the first step in finding a formulation suitable for use in clinical trials. Generally a number of preferred formulation schemes are tried in the hope that a previously well-characterized set of excipients and processing steps can be used to rapidly arrive at a robust formulation.

Milling, often used to reduce the particle size of a drug in order to improve solubility, flow characteristics or compressibility, can 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 materials can impact both bioavailability and chemical stability of the drug (Buckton *et al*., 1995).

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. The goal of the entire process is to achieve a form that can easily be compressed into a convenient, stable and efficacious product.

INSTRUMENTATION AND EXAMPLE DATA

Figure 1 shows example results generated with a TAM solution calorimeter. A pharmaceutical compound was studied before milling, and after one and two milling cycles (milling was by glass beads in a vortex apparatus).

The y-axis is the total amount of heat absorbed (normalized to the mass of solid sample) during the dissolution process and indicates that all the heats of solution were endothermic. The unmilled material (blue trace) dissolved smoothly over time and is typical of the shape obtained for a simple salt such as KCl (commonly used as a reference standard). However, the red curve shows that 15 minutes of milling resulted in a significant drop in the heat of solution and that a fraction with a different rate of solution was generated. After 30 minutes of milling, both these effects were more pronounced.

The observed reduction in total heat of solution is consistent with formation of a higher energy material such as a metastable polymorphic crystalline form or amorphous material (Gu and Grant, 2001; Royall and Gaisford, 2005). The appearance of a fraction

dissolving at a different rate is also consistent with formation of an amorphous fraction or a crystalline fraction with smaller particle size, and hence of higher surface energy.

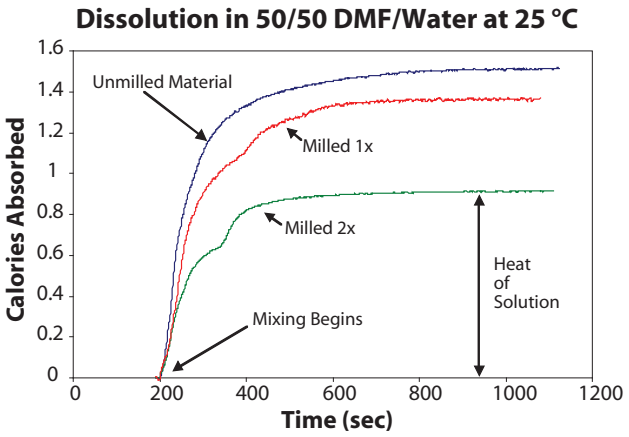

Figure 1. Example heats of solution data generated with a TAM solution calorimeter.

SUMMARY

Milling and other forms of pre-formulation processing of a drug substance can result in production of unwanted amorphous or crystalline polymorphic forms. Physical effects can also induce the formation of multiple particle size distributions if the milling process is not well controlled. The presence of these physical alterations can be quickly screened and quantified by solution microcalorimetry.

CITED REFERENCES

1. Buckton, G., P. Darcy and A. J. Mackellar. **(1995)** The use of isothermal microcalorimetry in the study of small degrees of amorphous content of powders. *Int. J. Pharm.* 117, 253-256.
2. Gu, C. H. and D. J. Grant. **(2001)** Estimating the relative stability of polymorphs and hydrates from heats of solution and solubility data *J. Pharm. Sci.* 90, 1277-1287.
3. Royall, P. G. and S. Gaisford. **(2005)** Application of solution calorimetry in pharmaceutical and biopharmaceutical research. *Curr. Pharm. Biotech.* 6, 215-222.

The technical and consultation services of Jeffery Rachford (ThermalCal International) are gratefully acknowledged.