

# On-line monitoring of Solvent Mediated Polymorphic Conversion by Isothermal Microcalorimetry

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Isothermal microcalorimetry is a technique by which the heat flow generated by an arbitrary chemical, physical or biological process is continuously monitored while the sample is kept at constant temperature. The heat flow is directly related to the rate of heat produced or consumed by an arbitrary sample placed in the calorimeter. In most cases, the sample is contained in a removable insertion vessel positioned in an ampoule holder inside the microcalorimeter during measurement.

Essentially two routes are available for the conversion of one crystal structure to another of a lower free energy. The metastable solid can undergo internal rearrangement of molecules such that the complete conversion occurs in the solid state. This is in many cases a very slow process at ambient conditions. The second route is conversion via a solvent phase with which the metastable particles are in contact in slurry. The metastable particles are thus allowed to dissolve while a more stable form nucleate and crystallise from solution.

Only few reports on the kinetics of solvent mediated polymorphic conversion has been published in the past. The rate measurements were conducted either by measuring the solute in the solution by UV-Vis Spectrophotometry or the solid phase composition by PXRD with time. To my knowledge, no work on solvent mediated polymorphic conversions measured by isothermal microcalorimetry has been published although this appears to be an ideal tool to follow such processes on-line.

The first attempt to rationalize solvent mediated conversions in terms of kinetic equations were made by *Cardew and Davey* (1985) [1]. The model developed realised that the overall conversion rate depends on the dissolution rate of the metastable form as well as the crystallisation rate of the stable form. It was further assumed that the dissolution and crystallisation rates were surface limited and could be described by first order kinetics with respect to particle size.

In this presentation, the results of measurements of slurries with metastable drug in a stirred microcalorimetric vessel will be presented. In this respect Sulfamerazine was used as a test substance. This substance has been characterised recently by its conversion of the metastable form to the stable phase in slurries of a number of different solvents, *Gu et al* (2001) [2]. The microcalorimetric data was rationalised in terms of a Cardew and Davey type model, which had been developed to fit with heat flow measurements.

## References

- [1] P.T. Cardew and R.J. David, Proc. R. Soc. London. A 398, 415-428 (1985).
- [2] C. Gu, V. Young JR., D. J.W. Grant. J. Pharm. Sci. 90 (11) 1878-1890 (2001).