Automated Cooling Crystallization of Paracetamol Using the 'Calibration-Free' Direct Supersaturation Control Method

Jon Goode and Ian Haley
Mettler-Toledo Ltd, 64 Boston Road, Beaumont Leys, Leicester, LE4 1AW, UK
*Email:Jon.Goode@mt.com

METTLER TOLEDO

www.mt.com/crystallization

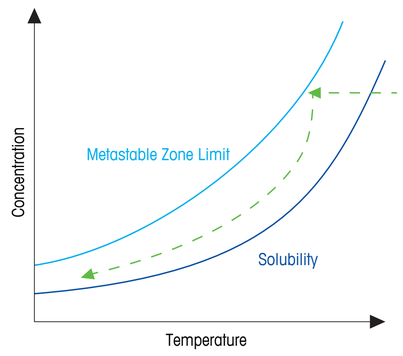
Many pharmaceutical and fine chemical compounds are manufactured via cooling crystallization from a solvent. Obtaining the optimum crystal size is essential to achieve consistent product quality and desired product performance. During a cooling crystallization the crystal size is governed by the relative rates of nucleation and growth. These in turn are driven thermodynamically by the level of supersaturation. At high supersaturation levels, nucleation tends to dominate, giving rise to a preponderance of smaller crystals. At low supersaturation levels, growth tends to dominate, resulting in fewer but larger crystals.

Typically, a cooling crystallization will proceed by cooling at a constant pre-determined rate over a pre-determined temperature range. While this is quite straightforward from a process control perspective, it often means that supersaturation levels – and thus the relative rates of nucleation and growth – can vary during cooling. This can lead to batch-to-batch inconsistency and an undesired crystal size.

This poster describes the use of a 'calibration-free'[1,2] method where the temperature during a cooling crystallization is controlled automatically in a water/IPA solvent in order to maintain a constant level of supersaturation. In this work, a seeded solution of Paracetamol in water/IPA was cooled automatically using two levels of supersaturation. The cooling was carried out in a OptiMax 1 litre synthesis workstation together multiple real-time monitoring probes. A Mid IR-ATR (ReactIR 15) system was used to directly measure the level of Paracetamol in solution - which acted as an input to the reactor temperature set-point control during cooling. PaticleTrack G400 provided real time measurement of crystal size and crystal population and a PVM V819 *in situ* imaging probe provided additional insight into particle shape and particle structure.

How Does the 'Calibration-Free' Method Work?

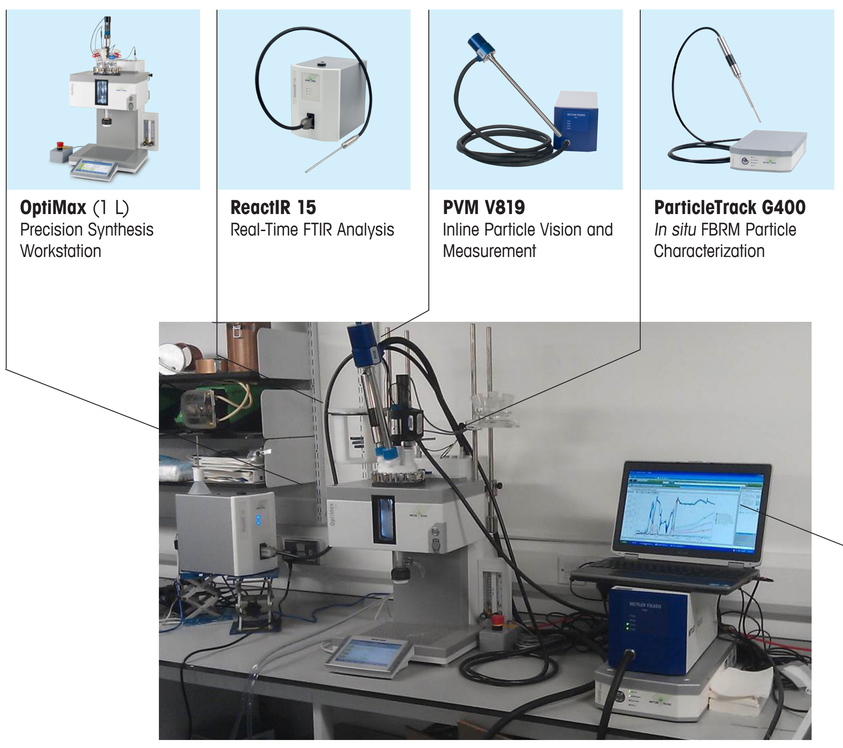
1. A saturated slurry of product is very slowly heated from low temperature at a rate of 0.05K/minute until complete dissolution is obtained
2. The IR absorbance spectrum is continually measured by ReactIR during this heating and the IR peak height (of a suitable solute absorbance band) plotted as a function of temperature
3. A second or third order polynomial is then fitted to this data – which expresses IR peak height as a function of temperature. It is this polynomial function (in effect the solubility curve) which can then be used to calculate a dynamic temperature set-point for controlled cooling.
4. To carry out a controlled cooling experiment, first a saturated seed bed at elevated temperature is obtained (typically by rapid cooling to just beyond the point of spontaneous nucleation followed by partial reheating to a hold temperature)
5. Next, the chosen IR peak height is measured by ReactIR, and the polynomial function used to determine the equilibrium temperature. The reactor is then set to cool, with the set-point defined as an offset (temperature difference) above the equilibrium temperature just derived.



Solubility curve and MSZW (Metastable Zone Width)

6. This process then carries on continually.
   - The higher the offset value, the faster the cooling rate – hence the greater the level of supersaturation
   - In effect, the temperature offset value equates to a relative supersaturation level
7. ParticleTrack with FBRM technology is used to quantify the effect different offset values have on:
   - Rate of nucleation
   - Rate of growth
   - Final chord length distribution
8. The cooling process continues until some pre-defined termination condition is achieved, typically when the reactor contents have reached a specific temperature.

Experimental Setup



Experimental Procedure

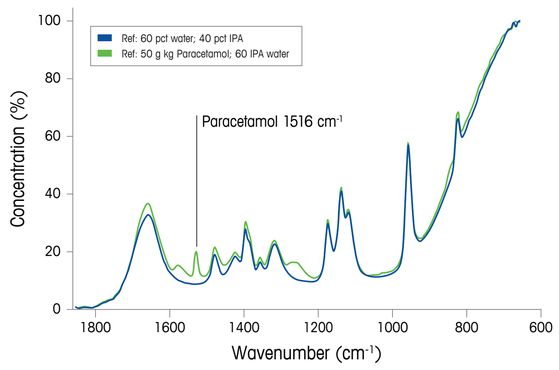
Developing the Solubility Curve
Paracetamol, at a concentration of 277.5 g/Kg of solvent, was dispersed in a 60:40 mix of Water:Isopropanol in the OptiMax reactor, and contents stirred at 10 °C for 60 minutes.

1. Contents heated to 50 °C at 0.05K/min

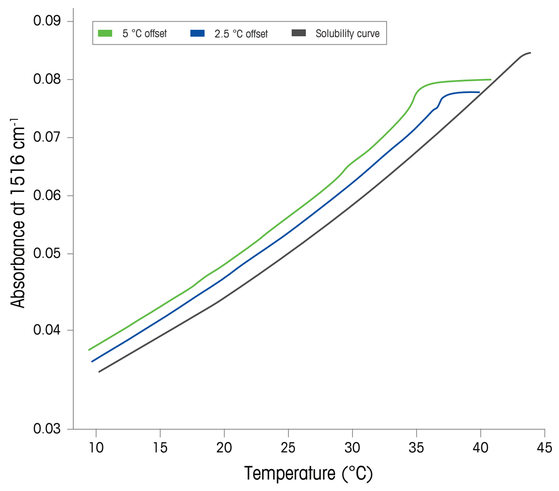
Performing an Automated Cooling Crystallization
Paracetamol, at 277.5 g/kg of solvent, was dispersed in a 60:40 mix of Water:IPA in the OptiMax reactor and contents heated rapidly to 50 °C to ensure complete dissolution

1. Contents cooled quickly to 25 °C to allow some spontaneous nucleation
2. Contents partially reheated to 40 °C and held there to ensure a stable, saturated suspension.
3. Contents cooled using automated temperature set-point control, based on real-time IR data:
   - Run 1 Offset = 5.0 °C
   - Run 2 Offset = 2.5 °C.

Results



This graph shows comparative Mid-IR spectra of the 60:40 Water:IPA solvent mixture, and the solvent plus Paracetamol at a concentration of 50 g/kg solvent. The absorbance band at 1516 cm^{-1} was chosen for this study.



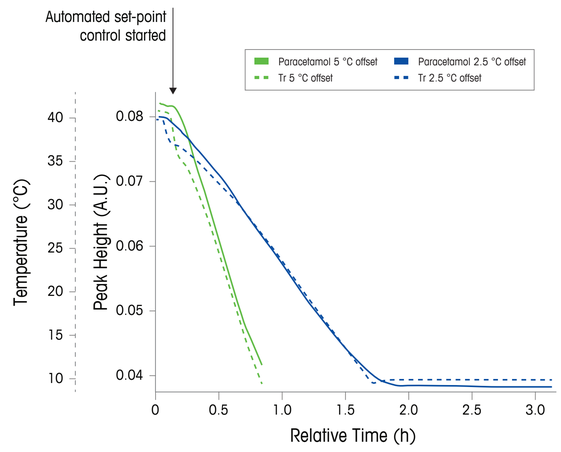
Temperature vs peak height (at 1516 cm^{-1}) for the following:

- Black line – very slow heating of the slurry of Paracetamol in Water:IPA, used to generate the relative solubility curve
- Green line – controlled cooling, offset of 5.0 °C
- Blue line – controlled cooling, offset of 2.5 °C

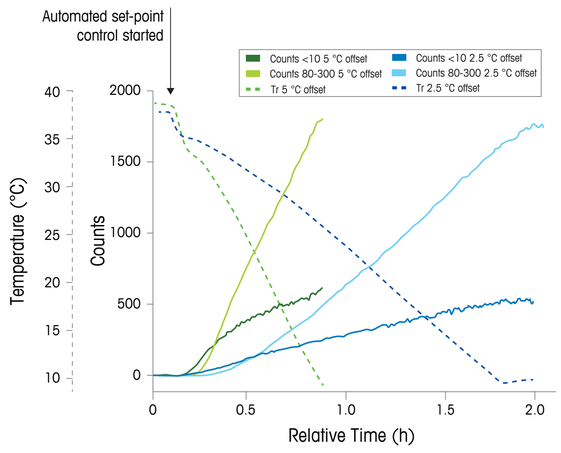
The black line was used to derive the following expression to control the set-point of the OptiMax reactor during controlled cooling:

$T_{SET} = -4392.1A^2 + 1238.2A - 30.485 - T_{OFFSET}$

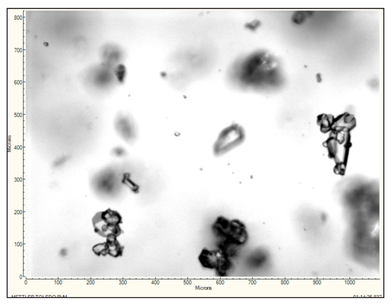
- Where A = absorbance at 1516 cm^{-1}



Comparative ReactIR data for the two supersaturation-controlled cooling runs. The absorbance at 1516 cm^{-1} is plotted, along with the OptiMax reactor temperature for the two runs.



Comparative ParticleTrack data for the two supersaturation-controlled cooling runs. The population of small particles, (<10 microns), and the population of larger particles (80-300 microns) is shown, along with the cooling profiles generated by the automated set-point control. At the higher set-point (greater level of supersaturation) the rate of increase of both small particles and large particles is greater than at the lower set-point. This data tells us that the relative rates of both nucleation and growth have increased as a function of increasing the supersaturation level.



PVM image obtained during the 2.5 °C offset run – and shows a mixture of very small individual crystals plus a number of larger aggregates. PVM images add insight into the shape of crystals and the nature of agglomeration.

Conclusions

Through this method a better understanding, and possibly a shorter process development time, can be realized by quickly isolating the ideal cooling profile and targeted particle size.

- The thermodynamic and kinetic process map derived by this method can be applied to minimize cycle times
- ParticleTrack and PVM facilitates a detailed understanding of nucleation and growth rate consistency through tech transfers and scale-up
- ReactIR enables automated supersaturation control via single peak height assessment
- Using the 'calibration-free' method enables scientists to derive optimal cooling / anti-solvent profiles and ensures product quality is maintained on scale

References

1. Du, D., Barrett, M., & Glennon, B. (2013). Novel, Calibration-Free Strategies for Supersaturation Control in Antisolvent Crystallization Processes Published as part of a Crystal Growth and Design virtual special issue of selected papers.
2. Barrett, M., McNamara, M., Hao, H. X. H., Barrett, P., & Glennon, B. (2010). Supersaturation Tracking for the Development, Optimization and Control of Crystallization Processes. Chemical Engineering Research and Design, 2010, 88 (8), pp 1108-1119

Acknowledgements

We would like to sincerely thank Professor Alastair Florence and the staff and students at CMAC for their assistance in carrying out the experimental work described in this poster.