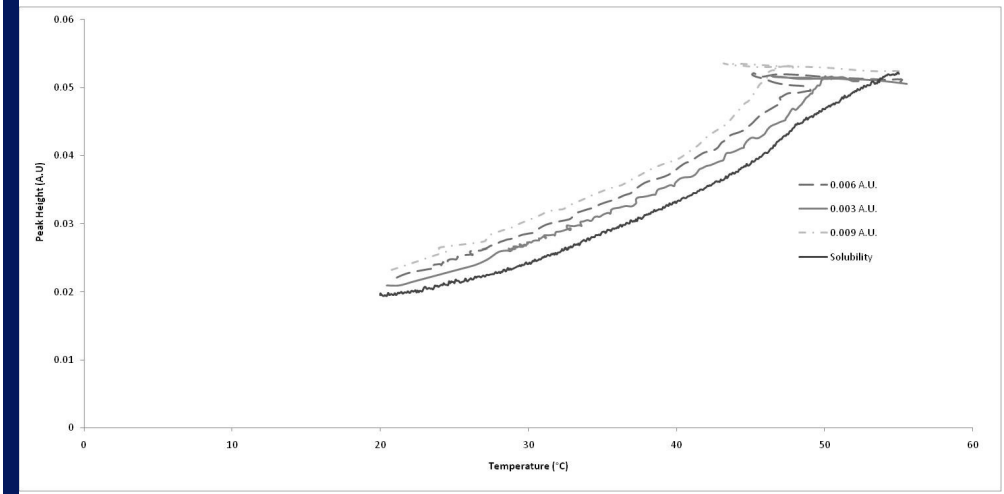
*Project:**10 Effect of Mixing Environment on Supersaturation Generation* Date: **21/08/10**	Author: **Damian Duffy** Strand: **Particle Engineering** Institute: University College Dublin

Title:

Novel Calibration Free strategies for Supersaturation Control in Crystallisation Processes

Principal Focus: To design and implement a feedback control strategy for crystallisation processes that does not rely on chemometrics to generate a calibration model. This methodology allows for control of crystal size and a reduction in common crystallisation problems such as agglomeration and secondary nucleation by using a single peak height in a spectral region to track the solute concentration in order to follow generated concentration profiles. In this way, desired supersaturation profiles can be obtained and in turn, optimal cooling profiles which can then be used upon scale-up to achieve the desired objective..



Control Experiments:

1. The solubility curve was constructed by applying a slow heating rate (0.1°C) to a 350g solution of Paracetamol and water (3g per 100g water)

2.MSZW information was then gathered to define the upper boundary.

2. With the upper (MSZW) and lower (solubility curve) boundaries defined, a series of concentration profiles were then implemented using the control software.

Figure 1: Solubility Curve along with three constant supersaturation profiles (0.003, 0.006 and 0.009 A.U.) resulting from the implementation of a feedback control strategy that used the decreasing peak height to cool the crystallisation to a pre-determined concentration profile.

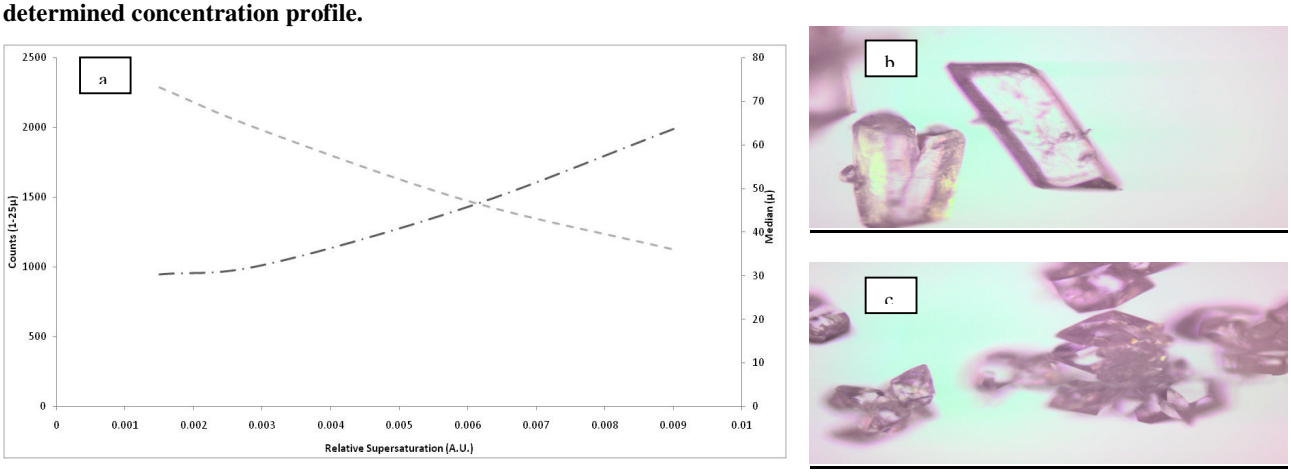


Figure 2: (a) Plot of FBRM fine counts against the constant relative supersaturation used for each control experiment, also included in this figure is the median (µm) plotted against the constant relative supersaturation. Shown on the right hand side (b and c) are two microscopic pictures of paracetamol crystals obtained from two control experiments, 0.003 (Top) and 0.009 (Bottom).

Discussion: The solution was cooled from 55°C and each control experiment was seeded with 0.1g of Paracetamol once the starting point of the concentration profile had been reached. This starting point varied depending on the level of supersaturation that was to be maintained. As one would expect, a higher level of supersaturation required a lower starting temperature as this increase in supersaturation naturally brings the solution further from the solubility curve. As was hoped, the higher levels of supersaturation brought about an increase in the fine counts as well as a decrease in the median size of the particles. As can be seen by the microscopic pictures, a controlled crystallisation operating between the upper and lower boundaries, relatively close to the solubility curve resulted in no agglomeration and regularly shaped crystals as opposed to the higher level of supersaturation (0.009A.U.) which despite being controlled gave a lot of agglomeration and small irregularly shaped particles.

Future Work: Work is currently being carried out to adopt this method to anti-solvent crystallisations as well as investigating the effect of mixing and level of impurities on the control profiles. There is work planned on integrating

FBRM into the control method and Dynochem software is being used to simulate the temperature profiles obtained to estimate the results of using the temperature profiles at plant scale.