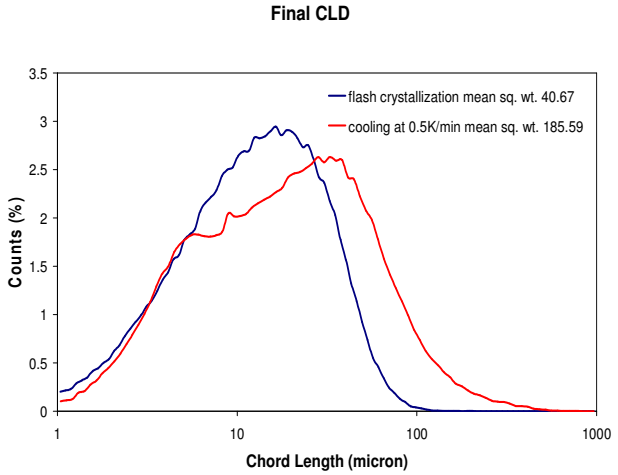
Project 12: Study of the Role of Agglomeration in Process Optimization Date: **19/08/10**	Author: **Barbara Wood** Strand: **Process Crystallization** Institute: University College Dublin

Title:

Investigating Alternative Crystallization Processes for Production of Fine Crystalline Material

Principal Focus: The objective of this project is to investigate alternative crystallization processes, with an overall aim to produce fine crystals. Fine crystals are normally produced by micronization after the crystallization step. The aim is to eliminate the micronization step by producing a narrow size distribution of crystals from the crystallization step. Agglomeration is a key factor to be considered in the production of fine crystalline material. Flash crystallization is a method in which a pressure change is utilized to drive crystallization. Another side to this project will be to characterize cooling crystallization using PAT – FBRM, PVM and FTIR. Results from flash crystallization will be compared with more traditional methods such as cooling crystallization. Ultimately the aim is to cut down the process time and cost and increase efficiency.

Flash crystallization and Cooling:



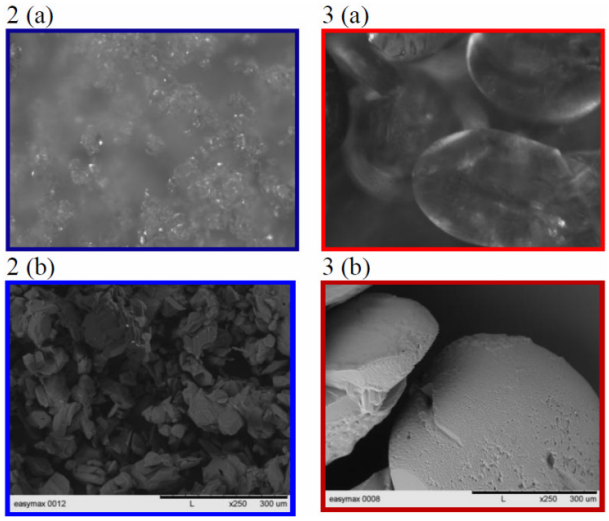
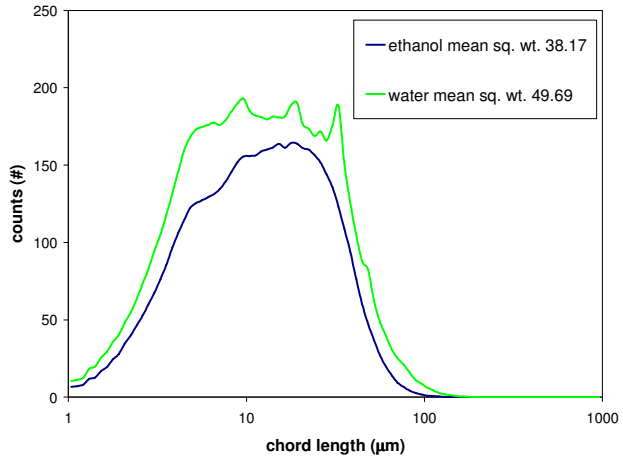


Figure 1,2,3: FBRM (figure 1), PVM and SEM analysis show that the particles obtained via flash crystallization (figure 2 (a, b)) and cooling crystallization (figure 3 (a, b)).



Adipic acid was used as a model system for the development of these differing crystallization techniques. 1 L cooling experiments, from 85˚C to 20˚C, were carried out in a LabMax and variable cooling rates and profiles assessed for their impact on the systems' metastable zone width and particle dimension. These were compared with crystals obtained from 200mL flash crystallization.

2L flash crystallizer has now been developed. Solvent selection is being investigated as a factor for minimizing crystal size. Solvents were selected initially on the basis of solubility data and then from flash simulations using PRO II. The effect of temperature, pressure and flow rate as well as nozzle configuration on the final CLD are also being investigated.

Figure 4: Final CLD using adipic acid and water and adipic acid and ethanol in 2L flash crystallization process

Discussion FBRM, PVM and SEM analysis show that the particles obtained via flash crystallization (figure 2 (a, b)) are much smaller in size, with a decrease in the FBRM mean square weight from 185 µm to 40 µm evident, when compared with the developed cooling crystallization (figure 3 (a, b)). Additionally, the obtained CLDs are more unimodal in shape when compared to the slightly bimodal cooling CLD (figure 2). The SEM and PVM analysis of crystals obtained from flash crystallization indicate that agglomeration is a key factor to be addressed with the possibility of further reducing the CLD by reducing agglomeration. Figure 4 indicates that a narrow CLD results from using ethanol as a solvent. There is a reduction of 17% in the mean square wt as well as a reduction in fine counts.

Future Work: Further characterization of the 2L flash crystallizer is ongoing. This includes the incorporation of a pressure control system so as to maintain / change the pressure driven force throughout the flash crystallization technique. There is potential for further growth from cooling instead of isolating the crystals immediately. There is also a possibility to use the slurry output for seeding of a batch crystallization. As flash crystallization is not well defined within the literature the combination of *in situ* PAT, like FBRM, Raman, ATR-FTIR and PVM, to heighten process understanding, is key.