

Research Plan / Model

Faculty of Technology / Chemical Technology

Monitoring of crystallization processes using IR-spectroscopy

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Background:

Batch cooling crystallization is a widely used unit operation especially in the pharmaceutical industry. The crystalline product quality is characterized as the crystal shape, mean crystal size and the width of the crystal size distribution (CSD). In pharmaceutical industry, it is also important that a specified polymorph is obtained. Supersaturation, i.e., the concentration difference between the solute during the crystallization and solubility of the solute at specific temperature, is the driving force of the batch cooling crystallization process and, therefore, the most important process parameter that affect strongly the product quality. An effective in-line concentration measurement method is essential for determining the optimal cooling conditions for a batch cooling crystallization process. Attenuated total reflection Fourier transformation infrared spectroscopy (ATR-FTIR) together with chemometric calibration is a promising technique for in-situ monitoring of concentration during the batch cooling crystallization process. ATR-FTIR concentration measurement based closed loop control for cooling policy of batch cooling crystallization process could, in practice, improve the repeatability and controllability of the cooling crystallization process. However, close attention should be paid to appropriate calibration in order to gain fast and reliable concentration predictions for control purposes.

Objective:

ATR-FTIR spectroscopy combined with chemometrics will be used to study the degree of supersaturation during the batch crystallization process. Based on the measurements, the process conditions leading to the formation of different polymorphs and effects on product size and shape will be studied.

Tasks and schedule:

- Task 1.** Calibration model: PLS model building (cases Sulfathiazole and KDP). *Completed May 2011.*
- Task 2.** Comparison of traditional regression methods and PLS models. *To be completed May 2011.*
- Task 3.** Building the calibration model: Spectral preprocessing (cases Sulfathiazole and IFT). *To be completed September 2011.*
- Task 4.** Unseeded batch cooling crystallizations using different batch times and cooling profiles. *To be completed September 2011.*
- Task 5.** Study of polymorphism of obtained crystalline product (case Sulfathiazole): Combined DRIFT and XRPD techniques. *To be completed December 2011.*
- Task 6.** Improvement the calibration models to be suitable for control purposes. *To be completed June 2012.*
- Task 7.** Unseeded batch cooling crystallizations using theoretically determined optimal cooling profile *To be completed December 2012.*
- Task 8.** Development of method to predict primary nucleation from in-situ ATR-FTIR data and to evaluate the upcoming polymorph from in-situ ATR-FTIR data for crystallization control purposes. *To be completed June 2013.*
- Task 9.** Combining developed tools for controlled crystallization *To be completed December 2013*
- Task 10.** Writing an introductory part to doctoral thesis and putting the thesis together. *To be completed June 2014.*
- Task 11.** Expected graduation *September 2014.*