**Project: Controlling Particle Size and Particle Distribution in Crystalization Operations**

Crystallization is a widely used technology for solid-liquid separation in the process industry. It is extensively used in the production of pharmaceuticals to separate the drug from the solvent mixture as well as to ensure that the drug crystal product conforms to size and morphology specifications. The crystal size in crystallization processes is one of the most important variables since it influences factors such as filtration rate, de-watering rate, dissolution rate and bioavailability, amongst others.

The driving force in crystal formation is supersaturation. The trend of supersaturation generation during the process has a direct and substantial role on crystal characteristics such as size, morphology and purity. There is a number of ways to control supersaturation and these include temperature and evaporation. In the last decade the salting-out method has drawn more attention. In this method which is also known as solventing-out, drowning-out and quenching, a substance known as antisolvent or precipitant is added to the solution which reduces the solubility of the solute in the original solvent and consequently generating supersaturation. This technique is regarded as an energy-saving alternative to evaporative crystallization, provided that antisolvent can be separated at low (energy) costs. Also in cases where solute is highly soluble or its solubility does not change much with temperature, antisolvent crystallization is an advantageous method. The initial focus in this research will be on the antisolvent crystallization processes; however, further studies to extend the results to joint cooling antisolvent crystallization are envisaged. This project builds upon the synergy among the research teams at LSU and at the University of Cagliari.
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Data

This page contains links to non-isothermal antisolvent crystallization data for a ternary system consisting of sodium chloride-water-ethanol. In this system 95% ethanol is used as the antisolvent. Included in the data are nine training experimental runs, one validation experimental run, and two optimal experimental runs. Each link contains an Microsoft Excel html file that contains the crystal size data for each experimental sampling time, experimental conditions, and the date of the experiment.

<table>
<thead>
<tr>
<th>Crystallization Data</th>
<th>Training Experimental Data</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Temperature at Antisolvent Flowrate</td>
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<tr>
<td></td>
<td>10 °C</td>
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<tr>
<td></td>
<td>0.8 mL/min</td>
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<tr>
<td></td>
<td>1.5 mL/min</td>
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<td></td>
<td>3.0 mL/min</td>
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<table>
<thead>
<tr>
<th>Validation Experimental Data</th>
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| Objective: 145 µm mean size |

| Objective: 165 µm mean size |
Support

NSF: Award No. CBET-1132324

Visiting Professor

Regione Sardegna, University of Cagliari

Project Personnel

Supervisors

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Description

The development of effective mathematical models describing the crystal growth dynamics is a crucial issue towards finding the optimal process performance and to control the crystal size and distribution. The main approach so far exploited is by developing population balance models taking into account the evolution of crystal particles across temporal and spatial domains. An alternative and novel approach to deal with particulate systems characterized by mean crystal size (MCS) and crystal size distribution (CSD) is the Fokker-Planck Equation (FPE). In this approach, rather than understanding the complex interactions at the microscopic level along the crystallization process, one seeks to explain the observed macroscopic behavior. In this regard, crystallization can be visualized as a self-organizing and complex process which is subjected to apparently disordered and erratic phenomena such as turbulence at micro-scale mixing, temperature fluctuations, etc. These fluctuations affect the crystal growth habits and its morphology. Thus, in an effort to explain the observed macroscopic behavior of crystal growth in an anti-solved aided crystallization, we will incorporate the Fokker–Planck equation (FPE) as the centerpiece of our approach. The Fokker–Planck equation has been used in atmospheric sciences, financial market dynamics, and polymerization among others. However, this approach has not been attempted so far to predict particle size distribution in crystallization operations. Within this context, the use of FPE represents a new direction in developing a population balance model, taking into account the natural fluctuations present in the crystallization process, and allowing a novel description, in a compact form, of the PSD in time.

The proposed project aims at the formulation and implementation of a novel stochastic approach to describe the crystal growth for the prediction of MCS and CSD in antisolvent mediated crystallization processes. The crystal growth will be modeled as a stochastic process ruled by a classic logistic equation of common use in theoretical ecology coupled with a stochastic component. The resulting model is a continuity equation (Fokker-Planck Equation, FPE) for the probability density function of the crystal size distribution. Model-based dynamic optimization studies will then be performed using the proposed stochastic formulation to develop optimal operational policies and will be validated using experimental investigations.

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Experimental Facilities

For our experimental work, a number of facilities both at the pilot and bench scale are available to carry out our experimental investigations at LSU. LSU has recently commissioned a new 5 liter crystallization pilot plant interfaced to the Honeywell's Experion® industrial control system providing a complete environment for the advanced monitoring and control. This state-of-the-art crystallization apparatus has been designed with certain unique features that will immensely facilitate the validation of the crystallization research proposed in this project.

In the case of our bench scale experimental unit, the experimental rig is made up of one liter glass, cylindrical jacked crystallizer. The temperature in the reactor is measured using an RTD probe which is wired up to a slave temperature control system capable of heating and cooling. In similar fashion, the anti-solvent addition is carried out by a slave peristaltic pump. The master control is performed by a computer control system which is wired up to the slave temperature and flow-rate controllers respectively. The desired set-points are calculated at the master controller. All relevant process variables are recorded using a computer data acquisition and control system. The crystal size distribution is determined by visual inspection of images taken using a digital camera mounted in a stereo-microscope at 25x magnification. The captured images, for each sampling point during batch run, are then processed by means of the sizing computer software (Amscope®) to obtain the particle size distribution (histograms).
In our approach the crystal size samples are further processed in order to infer the related probability density function needed for the parameter estimation problem as well as model and optimization validations. To this end, non-parametric methods will be used and the experimental probability density distribution can be eventually estimated as a linear combination of kernel basis functions. An example of the distribution estimation obtained from a typical run in our laboratory is reported in the Figures.
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Publications

Journals:


Proceedings:

- "Optimal control of particle size in antisolvent crystallization operations", M. Nowee, A. Abbas, J.A. Romagnoli, DYCOPS 07, Cancun, Mexico (2007)


"Evaluation of the Effect of the Solubility Model on Antisolvent Crystallization Predicted Volume Mean Size", D. J. Widenski, A. Abbas, J. A. Romagnoli, ICheap-09, Rome, Italy (2009)


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