Application of mechanistic models for the online control of crystallization processes

N. A. Mitchell[1], presenting author, Y. Salman[2], C. Y. Ma[2], J. Mack[3], T. Mahmud[2], and K. J. Roberts[2]

[1]Process Systems Enterprise (PSE) Ltd., London, UK

[2]School of Chemical and Process Engineering, University of Leeds, Leeds, UK

[3]Perceptive Engineering Ltd, Daresbury, UK

Introduction

Mechanistic models are becoming more commonly applied for Research and Development in the pharmaceutical sector. Traditionally, the output from this activity, namely a validated mechanistic model, which is capable of quantitatively predicting the behaviour of the various Critical Quality Attributes (CQA) for the crystallization process for a wide range of Critical Process Parameters (CPP). However, these tools are almost exclusively employed in an offline manner currently, primarily aimed at assessing process robustness and variability, with very little subsequent online application of the model for control or soft sensing purposes.

Model Predictive Control (MPC) is an established industrial technology which has only recently been applied in the Pharmaceutical industry. Existing applications in batch and continuous crystallization processes provide tight control of supersaturation and final particle properties at various scales. Optimized supersaturation control has also been demonstrated to improve batch yield and deliver consistent product. The MPC applications to date have characterized the crystallization process using statistical models and data-driven techniques. The data generated during these experiments are used to develop dynamic process models, calibration models and establish Meta-Stable Zone (MSZ) boundaries. The MSZ boundary information is combined with the concentration prediction and MPC to provide closed loop control of super-saturation.

The drawback of this approach is the time and material costs associated with executing the experimental tests. For batch systems, the product generated during these tests is typically discarded. Furthermore, a subset of the tests must be repeated during scale up as the MSZ is both product and process dependent. The

experimental testing time during initial development and scale-up could be reduced by combining information from validated mechanistic models into the Model Predictive Control system. The system Meta-Stable Zone boundaries and growth characteristics could be used to update the system during the plant tests and control system commissioning.

Methodology and Results

In this work, as the first stage of development of a MPC approach, we outline the application of an advanced process modelling tool, namely gCRYSTAL (PSE), to build a model for the seeded batch cooling crystallization process of L-glutamic acid from aqueous solutions. The process model with the crystallization kinetic parameters obtained from references [1, 2] was validated using process data gathered from the laboratory based experiments carried out in 0.5 L and 20 L agitated crystallizers at Leeds [2]. The laboratory based crystallization process model was subsequently employed to predict the behaviour of a pilot-scale industrial crystallizer. In order to make the mechanistic model more predictive of the process behaviour observed at the larger scale, some refinement of the kinetic parameters for secondary nucleation was required using minimal experimental data from the typical plant runs.

The validated mechanistic model of the crystallizer will be integrated with a PharmaMV (Perceptive Engineering) Advanced Process Control system. PharmaMV provides the multivariate control and monitoring platform for the online laboratory and pilot-scale crystallization processes. With this approach the validated mechanistic model will be utilized to drive the successive control steps to achieve a target product crystal size distributions, defined by the D_{10}, D_{50} and D_{90} of the final product CSDs.

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