**An *In Silico* Tool for a Pharmaceutical Crystallization Process Development: Comprehensive Sensitivity Analysis for Process Risk Assessment**

Merve Öner1, Stuart M. Stocks2, Jens Abildskov1, Gürkan Sin1\*

*1 Process and Systems Engineering Center (PROSYS), Department of Chemical and Biochemical Engineering, Technical University of Denmark, DK-2800 Kgs. Lyngby, Denmark;*

*2 LEO Pharma A/S, Industriparken 55, DK-2750 Ballerup, Denmark*

*\*Corresponding author: gsi@kt.dtu.dk*

**Highlights**

* An *in silico* tool was developed for a pharmaceutical crystallization process.
* Developed tool was used for process risk assessment.
* A comprehensive uncertainty and sensitivity analyses were performed to explore operation design space.

**1. Introduction**

Crystallization is still predominant separation and purification method during the recovery of solids from solutions especially in pharmaceutical industries [1]. The operating condition of a crystallization process is of critical importance because properties of a crystal product such as purity, size, shape distribution and polymorphic form depend strongly on the condition under which the crystallizer is operated [2, 3]. Moreover, these product properties affect the performance of the following downstream operations such as filtration and drying, and eventually efficacy of the product formulation. Traditionally, crystallization processes have been operated recipe-based in the pharmaceutical manufacture and the quality of the product has been determined by testing at the end of the process. Quality-by-testing (QbT) has often resulted in failed batches, which in return led to loss of profit, while the pressure of producing faster, cheaper and more efficiently has been increasing day by day [2, 4]. Process systems engineering methods and tools possess significant advantages over traditional methods; improving process understanding, speeding up process development and providing better control over process variables. Additionally, the FDA has promoted the usage of quality-by-design (QbD) approaches, integration of process analytical technology (PAT) tools into the process design and manufacturing as well as identification of uncertainties and quantification of process risk assessment [5, 6]. Therefore, the objective of this work is to develop an *in silico* tool for a pharmaceutical crystallization process to support design, optimization, control and uncertainty/sensitivity analysis for process risk assessment. The developed tool was used to explore an operational design space in order to guide the design using comprehensive sensitivity and uncertainty analysis. Additionally, we performed experiments to verify predicted results.

**2. Methods**

An *in silico* tool was developed for a batch cooling crystallization system. Crystallization of paracetamol from ethanol was chosen as a case study. The solubility and crystallization kinetic data of the mentioned solute-solvent system were taken from the literature [7, 8]. Related mass, energy and population balance equations are implemented and solved in MATLAB/Simulink environment. Several sources of uncertainties in process are identified and the effect of uncertain process parameters on the process output variability are quantified through uncertainty analysis. Sensitivity analysis is performed to investigate the design space of initial concentration, seed specification (mass, mean, sigma), cooling time and cooling profile. Additionally, experimental data are used to verify model predictions in terms of solute concentration and final crystal size distribution.

**3. Results and discussion**

A risk based approach requires understanding of how process factors affect the quality and performance of the product/process, which process variabilities have critical importance to achieve consistent product within desired quality requirements and therefore to quantify the risk of producing poor quality product. To this end, several uncertainties in the crystallization design space were identified. Using the developed tool, a study on the quantification of process risks was performed. The effect of the initial concentration, seed specification, cooling time and cooling profile on the process output in terms of process yield and nucleation was investigated though sensitivity analysis. Simulation results showed that cooling time, seed mass and cooling rate were the most significant factors that affected strongly the product yield and nucleation. Therefore, more effort should be given to optimize these parameters to get higher yield and avoid nucleation. Additionally, after performing experiments to compare simulation outcomes, we observed that model predictions were in good agreement with the experimental data.

**4. Conclusions**

In this study, we presented an *in silico* tool for a pharmaceutical crystallization process. We used uncertainty and sensitivity analysis to identify process variables and to quantify their effect on the process outcome for process risk assessment. As a case study, an application on the exploration of the operational design space was shown. We compared also experimental data with model predictions. In conclusion, *in silico* tools provide an effective and cost-efficient platform to develop processes, investigate design spaces, to explore feasibility of different operation and control strategies and to quantify the process risks. Pharmaceutical industries can benefit from model based approaches through reduction of process failures, consistent batch-to-batch products and gaining acceleration to compete with challenging market driving forces.

**References**

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