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*Publication date:*  
2012

*Document Version*  
Publisher's PDF, also known as Version of record

[Link back to DTU Orbit](#)

*Citation (APA):*  
Meisler, K. T., Abdul Samad, N. A. F. B., von Solms, N., Gernaey, K., & Gernaey, K. (2012). *Crystallization Kinetics Identification within a Generic Modeling Framework*. Abstract from 2012 AIChE Annual Meeting, Pittsburgh, PA, United States. <https://aiche.confex.com/aiche/2012/webprogram/Paper287223.html>

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## Crystallization Kinetics Identification within a Generic Modeling Framework

**Tuesday, October 30, 2012: 12:55 PM**

Crawford West (Westin )

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Crystallization kinetics identification within a generic modeling framework

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Crystallization serves as an efficient separation process for compounds, which are solid in their pure form at the given separation conditions. Crystallization is an essential step in the production of many pharmaceutical products as the active pharmaceutical ingredients (APIs) are often separated efficiently through this operation. The monitoring and analysis of crystallization operations has recently received increased attention due to the growing need to control the final crystal size distribution (CSD) in a relatively narrow range as well as to measure and monitor the final product characteristics. CITATION EAa10 \ 1030 (1). This monitoring and analysis requires models that describe the multiple phenomena and their interplay encountered in crystallization operations in order to have the ability to design effective control strategies and the possibility of planning crystallization operations. To this end, models of the phenomena (kinetics, solubility, etc.) are needed within a generic framework that allows the generation of the needed models to achieve a more complete description of specific crystallization operations. For example, certain size distributions can be desired in order to obtain specific properties for the product such as rate of dissolution. Growth of the crystals occurs in multiple dimensions and the growth rates of the facets determine the shape of the crystals. The size distribution is obtained because of different competing phenomena such as nucleation and growth, each with different kinetics. A full representation of a crystallizer requires models for all these kinetic phenomena and saturation descriptions (constitutive equations) coupled with descriptions of the equipment and an operational policy. Such a description is possible within a generic framework where the models can be combined, reused and identified. This framework has been established CITATION Noo11 \ 1030 (2) and tested for simulation of selected crystallization processes.

The objective of this work is to provide the ability to establish the kinetics of a crystallization operation systematically and efficiently. Initially an operational scenario is defined for which the specific balance equations are set up. The constitutive models are chosen based on the system description and the objectives of the model. Once the model is ready, that is, all model parameters are available, it can be used for simulation of the corresponding crystallization operations. If an established model for the desired kinetics is found within the model library, then this model is used. If not available, or in case a new model is desired, then identification of model parameters is performed. This identification step requires measured data, which may be available in different forms such as single crystal growth data or chord length measurements (for example, data from Focused Beam Reflectance Measurements, FBRM). Use of such data requires appropriate translational policies to convert measurements into one or more variables that are described by the model. A preliminary version has been developed and tested to obtain information about the development of crystal size distribution (CSD) in a given operation. The measurement types that can be handled through the modeling framework are continuously being expanded to accept more data types with information relevant for the crystallization operations. The measurements can be used for offline analysis and parameter regression. With an established kinetic model it is thus possible to translate the predicted model results into a form, which is directly comparable (and visualized) to the data available for evaluation of the model. Furthermore, if there is model – data mismatch, the measured data can be used for online parameter estimation.

The expanded model framework combined with the systematic approach to establish the kinetic models for use in general crystallization operations in combination with monitoring tools will be presented using case studies involving different scenarios for crystallization operations.

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