Control of Process Operations and Monitoring of Product Qualities through Generic Model-based in Batch Cooling Crystallization

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Abstract
A generic model-based framework has been developed for crystallization processes, with applications aiming at the control of process operations and the monitoring of product quality. This generic model-based framework allows the systematic development of a wide range of crystallization models for different operational scenarios. This enables the design and control engineers to analyze various crystallization operations and conditions, thus facilitating the development of process control and monitoring systems (PAT systems) for crystallization processes. The generic framework has been implemented in the ICAS-PAT software which allows the user to design and validate PAT systems through a systematic computer-aided framework. The application of the framework is highlighted for batch cooling crystallization of paracetamol where the framework was applied for design of a process monitoring and control system to obtain a desired crystal size distribution (CSD).

Keywords: crystal size distribution (CSD), PAT, process monitoring and control, crystallization, paracetamol

1. Introduction
Crystallization is an important operation when manufacturing fine chemicals or pharmaceuticals. It is a widely used technique in solid-liquid separation processes to obtain solid products of high purity at relatively low costs. Requirements for crystal products are usually high purity, a specific crystal size distribution and a desired crystal shape [1]. Consequently many efforts have been made to model the crystallization process to support the development of appropriate process operations and control scenarios to meet specific end product demands. So far, the published crystallization process models have been problem specific, meaning that the models were developed with a certain crystal product in mind. Hence it is not surprising to notice that research on crystallization modeling emphasizes different issues such as crystal size distribution (CSD) or crystallization kinetics, depending on the aim of the specific modeling study. Furthermore, specific models employ numerous underlying assumptions, for example, on agglomeration and crystal breakage factors. As a consequence, there are many specific models available in the literature with different degrees of complexity, which makes their selection and use for a specific problem difficult if not confusing. There is therefore a need for the development of a generic crystallization model to assist the systematic and efficient development of appropriate models for specific crystallization processes.
Once an appropriate crystallization model has been developed, it can be used as a tool for process design, and for design of control and monitoring systems to ensure the desired end product quality. Such a process control and monitoring system is required for a pharmaceutical production process that is operated according to the Process Analytical Technology (PAT) guidance [2]. The objective of this work is thus to develop a generic model-based framework that allows the study of different crystallization operational scenarios, and which also supports the design, comparison and validation of process control and product monitoring systems. Since this framework will need to rely on process models, the framework will be extended with a tool to systematically develop crystallization models.

The use of the generic crystallization model, the PAT design framework and the associated tools is highlighted through the ICAS-PAT software. The application of the model-based framework is highlighted using a paracetamol batch cooling crystallization process as a case study, where the objective is to obtain a desired CSD.

2. Generic Model-based Framework

An overview of the extended framework for design of process control and product monitoring systems is shown in Fig. 1 where the generic model options have been added to the original [2]. The starting point for the design methodology is the problem definition in terms of process specifications and product quality specifications that is usually provided by the manufacturer or PAT system designer. A model library and a knowledge base have been developed and act as the supporting tools for the design of the process control and product monitoring system.

![Figure 1. Extended schematic representation of the PAT design framework [2]](image)

A systematic modeling framework (see Fig. 2) has been developed and implemented in the ICAS-PAT model library to create the various crystallization process/operation models from a generic batch cooling crystallization model. This modeling framework starts with the selection of the chemical system that needs to be investigated and the associated known information about its production scenarios. Then, the necessary balance equations and constitutive equations are extracted from the generic model library. The balance equations consist of population balance, overall mass balance and energy balance equations for the defined crystallization volume plus energy balance equations for the cooling jacket. The constitutive equations library contains a set of models of nucleation, crystal growth rate, supersaturation, saturation concentration,
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metastable concentration and physical properties corresponding to different types of crystallization processes. Subsequently a problem specific model is created which is verified through model analysis and solution. Finally the problem specific model is transferred to the ICAS-PAT model library through ICAS-MOT. In this way, based on the process and product quality specifications supplied by the user (Fig. 1), the generic model is adapted to reflect a specific case study and it allows the user to consider the necessary operational scenarios enabling thereby analysis of crystallization operations and conditions.

The developed design algorithm in the PAT design framework (see Fig. 1) relates the product and process specifications to the available supporting tools and subsequently generates a design proposal for the process monitoring and analysis system. If the obtained PAT system satisfies the requirements then it is selected as the final design of the process control and product monitoring system, which can then be subsequently implemented and used in practice to obtain the predefined product quality consistently.

3. Case study: Paracetamol crystallization process

The paracetamol crystallization process is adopted from the literature [1, 3]. The objective here is to design a PAT system for this process using the extended ICAS-PAT software. An overview of the features available in ICAS-PAT is shown in Fig. 3 [4].
3.1. **Problem specific knowledge base**: A knowledge base containing the information/data required for design of a PAT system for a crystallization process is created from a generic knowledge base. (see Fig. 3, top, left).

3.2. **Problem specific process model**: First a generic crystallization process model is selected from the model library (see Fig. 3, bottom), and then problem specific process models (paracetamol crystallization) are created from the selected generic crystallization process model (methodology illustrated in Fig. 2).

3.3. **Design of a PAT system**: The problem specific user interface (see Fig. 3, right) is used to design a PAT system for the paracetamol crystallization process. The design procedure consists of 9 hierarchical steps [2, 4] (see Fig. 3, bottom, right)

   **Step 1. Product property specifications**: The desired product is paracetamol with the following predefined qualities: paracetamol concentration: 0.012 g/g; mean crystal size: 100 µm; total crystal mass: 10 g.

   **Step 2. Process specifications**: The basic raw materials required include: Water as a solvent and paracetamol as a solute assuming that the pure paracetamol has been isolated with water during the organic synthesis step. The process equipment used is a jacketed batch crystallizer.

   **Step 3. Process analysis**: The process analysis provides a list of process points and corresponding process variables. A batch crystallizer is the only process point considered in this case and involves the following variables: solute concentration, mean crystal size, temperature, supersaturation, crystal growth rate and nucleation rate.

   **Step 4. Sensitivity analysis**: A sensitivity analysis based on open loop simulations is performed next to identify the variables that need to be monitored and controlled in order to assure the predefined end product quality. The process variable, solute concentration, is here considered as an example for the sensitivity analysis. As shown in fig. 4, the solute concentration profile was found to violate the operational limits, indicating thereby that this variable needed to be monitored and controlled. Repeating this procedure for all variables yielded a list of critical process variables: solute concentration and temperature.

   **Step 5. Interdependency analysis**: Interdependency analysis is performed for each critical process variable identified in Step 4 to select a suitable actuator.
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As shown in Fig. 5, a critical process variable (solute concentration) and the corresponding actuator candidates (coolant flow rate and inlet coolant temperature) were selected for analysis. The analysis indicated that inlet coolant temperature is more sensitive. Therefore, it was selected as an actuator to control the solute concentration in the batch crystallization (see Fig. 4). Repeating the procedure for all critical control variables yielded the same corresponding actuators (inlet coolant temperature).

**Step 6. Performance analysis of monitoring tools:** The available monitoring techniques and tools for each identified critical process variable are retrieved from the knowledge base. The performance of these monitoring tools (obtained from the knowledge base) is then compared (based on the selected specifications). ATR-FTIR was selected to monitor the concentration and the temperature is monitored by a thermocouple.

**Step 7. Proposed PAT system:** A feasible alternative of a PAT system is proposed based on the outcomes of the Steps 3-6. The critical process variables are solute concentration and temperature while the corresponding actuator candidate is inlet coolant temperature. The monitoring tools are ATR-FTIR for monitoring the concentration and thermocouple for temperature monitoring.

**Step 8. Validation:** A closed-loop simulation is performed to validate the proposed PAT system. This step involves controller configuration, control-monitor verification, sensitivity verification and product properties verification. The solute concentration will be controlled within the concentration set-point trajectory. The temperature will serve as an input to concentration set-point since the set-point trajectory is temperature dependant.

![Figure 4. Sensitivity analysis for the solute concentration](image)

![Figure 5. Interdependency analysis and control-monitor verification (closed loop simulation)](image)
Fig. 5 shows the closed loop response (PI controller with 2 inputs) of the solute concentration in the batch crystallizer. It can be concluded that although the solute concentration was beyond the upper limit initially, it stayed within the operational limits by the end of the operation. The concentration profile also satisfied the predefined product qualities specified in Step 1. Fig. 6 shows that the mean crystal size of 96 µm which is close to design target (100 µm) and the total crystal mass of approximately 9.5 g was also achieved.

Step 9. Final PAT system: A feasible alternative of the PAT system as shown in Fig. 6 was obtained. A cascade control system was used to control the solute concentration. The concentration is monitored by ATR-FTIR and the temperature is monitored by a thermocouple. The inlet water temperature is manipulated by blending hot and cold water.

Figure 6. Paracetamol crystallization process flowsheet with designed PAT system and product property verification

4. Conclusions

A generic model for crystallization process/operation has been developed and implemented in the ICAS-PAT software. This generic crystallization process model provided the means to generate the necessary crystallization process operational models for different production scenarios and thereby increased the model (re)usability. The application of the model-based framework in ICAS-PAT is highlighted through the paracetamol case study. The designed process monitoring and control system ensured that the critical process variables are measured and maintained within the operational limits and therefore predefined end product quality can be achieved precisely and consistently.

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References