



IFPRI Project Abstract

A Holistic Approach for the Model-based Control of Crystal Size, Shape and Purity in Integrated Batch and Continuous Crystallization - Wet Milling - Classification Systems

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Project Objective:

[2-3 sentence summary of original project brief]

The main aim of this project is to develop novel and integrated crystallization systems that can provide enhanced control over the properties of crystalline materials, such as crystal size and shape distribution as well as purity. The use of a cascade of MSMPR units, along with the integration of downstream wet mill and classification units that have recirculation streams, will broaden the achievable range of crystal size distribution (CSD) and enable continuous operation. The project will emphasize the use of Population Balance Model (PBM) based modeling, design, and model-based control approaches, with a focus on the critical role played by in-situ imaging-based monitoring tools.

Approach:

[2-3 sentence summary of project proposal (experimental/theoretical approaches)]

This project utilizes a model-based approach that relies on the use of a comprehensive population balance (PB) framework. 1D and 2D PBMs were developed for both batch and continuous integrated systems, which incorporate the impurity incorporation during crystallization. The generated model equations are solved using the high-resolution finite volume method (HR-FVM). The project also developed and executed a procedure for estimating kinetic model parameters for a representative model APIs that form high aspect ratio crystals during crystallization. Additionally, models for wet-milling and classification have also been developed and experimentally validated. The integrated system consisting cascade of crystallization units, wet milling, classification and recycle has been analysis and robust design spaces and attainable regions developed, considering the effect of recycle and other key process parameters on both critical quality attributes as well as overall process dynamics and startup duration.

Recent Results:

[Short summary of past year's progress and its significance, including one or two illustrative graphics (if useful)]

A framework was designed for an integrated system of continuous operations consisting of a cascade of MSMPRs, where wet mill and classifiers are used to have a larger number of degrees of freedom available to control certain CQAs such as crystal size and impurity. To find the allowed crystal size values with the current configuration set-up, a design space was developed. This provides an exemplary case study that demonstrates how process intensification by system integration and the use of model-based optimization can lead to significant process performance improvements. Then robustness studies were performed to observe kinetic parameter uncertainties on the system. This work was then compared to validation experiments to ensure this framework has accurately expressed the design space.

This framework was then applied to a commercial API (Atorvastatin calcium (ASC)). Parameter estimation was performed to use a model-based quality-by-design (mb-QbD) technique to obtain an attainable region along with kinetic parametric uncertainties and inlet crystal distribution uncertainties. This framework was implanted in an attempt to grow ASC crystals as the API is extremely nucleation dominated. However, it was observed that ASC crystals could not grow larger than $\sim 10\ \mu\text{m}$.

For this reason, spherical agglomeration of ASC is considered to grow the crystals and make downstream processing more efficient and also reduce the need for wet granulation. Design of experiment (DOE) for a 2-stage crystallization–spherical agglomeration system was performed to ensure stable polymorphic form of ASC is produced before spherical agglomerates are formed by adding a bridging solvent. Microscopic images and CSD of these agglomerates are shown in Figure 1.

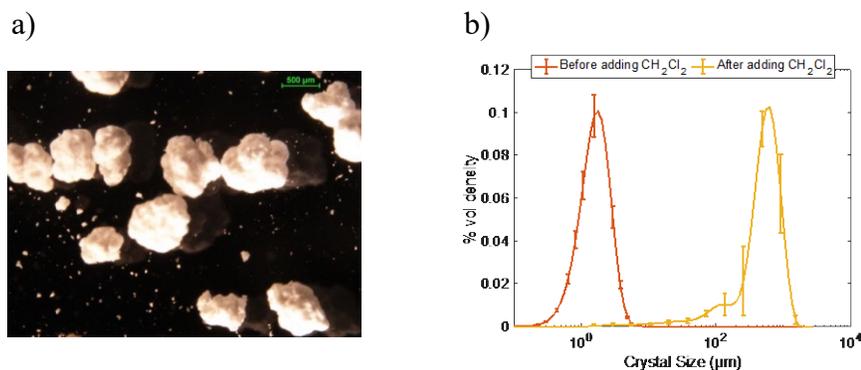


Figure 1. Spherical agglomerating results. a) Microscopic images of spherical agglomerates of ASC and b) CSD of ASC crystals before and after spherical agglomeration

Next Steps:

[2-3 sentence summary of where the project is headed in the next year. If the project is in its last year, a short summary of open questions.]

A complete model-based examination of pharmaceutical crystallization processes in an integrated MSMPR cascade system with recycle was reported. This work focused on the effect of recycle on crystal size, impurity and dynamic behavior. This work highlights the significance of advanced process design and control for consistent and robust operations of integrated MSMPR cascade with recycle.

In the ASC case, the next step in the research is investigating end-to-end manufacturing of ASC through spherical agglomeration. The addition of a continuous, intensified filtration-washing-drying unit to the system, along with a reactor, will complete the end-to-end system. Lastly, crystal characterization tests, including flowability, filtration and drying time, compaction, and dissolution, will be conducted.