ABSTRACT

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Title: Development of Particle Size and Shape Manipulation Approaches for Crystallization Systems via Model Based Design and Process Intensification
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Crystallization is an important separation and purification step in the pharmaceutical manufacturing process. This operation is one of the last steps in the manufacturing of the drug substance which makes it a key process due to its impact on the properties of the active pharmaceutical ingredient that could affect the drug product efficacy and operational efficiency. Hence, it is critical to design and develop strategies to control crystal attributes such as size, size distribution, and shape. Extensive work has been done in control of crystal size in batch operation, however significantly less progress has been achieved in the control of crystal shape due to the lack of measurement and actuator technologies and efficient models and methods. The innovation in process analytical technology (PAT) tools has allowed for further advances in crystal size and shape studies. Additionally, the interest in continuous crystallization has increased due to the current trend to shift from batch to continuous operation in the pharmaceutical industry to achieve higher efficiency and consistency. The design of strategies for control of crystal size and shape is an area that requires development as the active ingredients get more complex and the pharmaceutical manufacturing moves towards integrated continuous systems.

This work presents a series of strategies for crystal size and shape control in batch and continuous crystallization systems. The first section describes the development and validation of a systematic classification approach for unseeded batch cooling crystallization systems. The approach is developed by analyzing the interplay between growth and nucleation kinetics and correlated with the achievable size and shape for various compounds. The study was extended to a multi-objective optimization framework in which optimal solutions for potassium dihydrogen phosphate (KDP) and paracetamol

were obtained. The framework showed similar trends as the classification approach, which further validates the observed simulation and experimental results.

The next sections of this thesis involve the design and evaluation of continuous crystallization systems. A multi-stage mixed suspension mixed product removal (MSMPR) system with fines destruction was proposed and validated via simulation and experimental studies. The result demonstrated that the incorporation of dissolution in the system allows for larger controllability of the crystal size and size distribution, while having minimum effect on the productivity. This work was extended by considering a multidimensional population balance model (PBM) under nucleation, growth, dissolution and binary breakage assumptions. Optimal batch and continuous systems were proposed and validated experimentally for controlling shape as the attribute of interest.

A model-based study was performed to evaluate the implementation of a PAT-based feedback control strategy on a MSMPR system. Direct nucleation control (DNC) is a model-free strategy commonly implemented in batch processes. Various DNC frameworks were proposed and the implementation in a single stage MSMPR system was investigated to determine the optimal structure for this type of continuous operation. Step changes and pulse disturbances were implemented to evaluate the performance of each DNC framework. This work shows the benefits of model-based studies for technology transfer from batch to continuous system.

The last portion of the thesis involves the development of novel crystallization strategies via process intensification. The first strategy proposed was an integrated continuous in-situ milling and crystallization platform. The integrated system was characterized via design of experiments to determine the impact of milling and crystallization process parameters on the steady state crystal size and size distribution. Then, a PBM model was proposed with a series of breakage kernels. The parameter estimation framework further validates the experimental observations. The second platform proposed is the crystallization in porous media. The main goal of the this work shown in the thesis involves the evaluation of controlled crystallization strategies. Linear and programmed cooling strategies were compared to scenarios in which DNC was implemented. The final

drug loading, internal crystals and the distribution of the drug in the porous matrix were evaluated.

In this thesis, a series of strategies for crystal size and shape manipulation for batch and continuous processes were proposed. The strategies were evaluated and validated via model-based and/or experimental studies. The main contribution of this work is to provide alternatives for crystal shape and size control that would allow for better design and control of crystallization processes where the design space in which the process could be operate can increase. In this way, agile and reconfigurable crystallization platforms can be designed and used in pharmaceutical applications.