MODEL-BASED DESIGN OF PHARMACEUTICAL CRYSTALLIZATION PROCESSES

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Crystallization is the main particle formation and the first purification step in many industrial processes, especially pharma. Almost all the drug compounds which are called active pharmaceutical ingredients (API) are produced by crystallization processes in different modes such as batch or continuous. This step is crucial for dictating the downstream operations and final drug properties that are strictly regulated by administrations. Various studies have demonstrated that physical properties of the crystals such as crystals size, shape, polymorph, or chirality affect the drug bioavailability, operation of downstream units such as filtration and milling or the uniformity in tableting. To be able to control these key process parameters, it is crucial to have control and prediction power on crystallization process. In the light of this awareness and constant need in industry many studies have been focusing on the control and optimization of crystallization processes. Furthermore, with the industrial paradigm shift to Industry 4.0, model-based process design has become the focus of industry and crystal engineering research, and this also forms the motivation of this thesis.

This thesis is a collection of model-based crystallization design works for different compounds and different systems, presenting a methodological development of digital twins and how they are used for in-silico design of experiments (DoE) and process optimization. The systems studied are batch cooling crystallization with temperature cycling of a model compound (paracetamol) and an API, batch cooling crystallization with milling and temperature cycling for the shape optimization of the same API, and hot melt extrusion for amorphization of Bicalutamide. Novel contributions of this work can be listed as: 1) the introduction of a new formulation in the objective function during digital twin development to utilize a mainstream process analytical technology (PAT) tool data, 2) new formulation in the process model for size dependent crystal growth to match the broadening in the product crystal size distributions (CSD) of an API, 3) quantitative demonstration of the discrepancies in the needle-like crystals' CSD measurements, 4) immersion mill usage in batch cooling crystallization systems for crystal shape manipulation, and 5) a user interface to give

a platform. In each case study, a methodological framework is followed to show the benefits of model-based process design that is followed by experimental validation. It is emphasized that the model-based design should be the common practice under Industry 4.0 to discover more in the design space and what can be done for optimum operations while minimizing the time and valuable API spent on experimentation trials.