ABSTRACT

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Title: Process Intensification Techniques for Combined Cooling and Antisolvent Crystallization of Drug Substances

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Crystallization is a key solid-liquid separation and purification technique used in pharmaceutical industry. Some of the critical quality attributes (CQAs) of a product from crystallization process include crystal size distribution (CSD), purity, polymorphic form, and morphology. Different size and polymorphs of a drug substance may have different dissolution profiles and different bioavailability, which can have adverse effect on human health. Therefore, it is important to design and control crystallization process to meet desired product CQAs. In recent years, drug substances are becoming more complex, often being heat sensitive, which may limit the temperature that can be used in the crystallization step. Consequently, the traditional cooling only crystallization may not be well suited to recover the high value drug substances. For these systems, antisolvent crystallization is typically employed to improve the yield. On the other hand, the solvent composition can significantly impact the polymorphic outcome. Therefore, designing combined cooling and antisolvent crystallization (CCAC) processes to solve the challenges of active pharmaceutical ingredient (API) crystallization in a highly regulated environment is a complex engineering problem.

Due to rising energy costs and intense price competition from generic pharmaceutical companies, the pharmaceutical industry is looking for ways to reduce the cost of manufacturing via process intensification (PI). This thesis focuses on different PI techniques for CCAC of drug substances. Continuous or smart manufacturing is gaining popularity due to its potential to lower the cost of manufacturing while maintaining consistent quality. Continuous crystallization is an important link in the continuous manufacturing process. The first part of the thesis shows PI of a commercial drug substance, atorvastatin calcium (ASC) for target polymorph development via continuous CCAC process using an oscillatory baffled crystallizer (OBC). An existing batch CCAC process for ASC was compared with the continuous CCAC in OBC and the newly designed continuous process was 30-fold more productive compared to the batch process. An array of

process analytical technology (PAT) tools was used in this work to assess key process parameters that affect the polymorphic outcome and CSD. The desired narrower CSD product was obtained in the OBC compared to that from a batch crystallizer.

Model-based PI techniques for efficient determination of crystallization kinetics of a polymorphic system in CCAC are also investigated in the thesis. A novel experimental design was proposed, which significantly reduced the number of experiments required to determine crystallization kinetics in a CCAC process. The kinetic parameters were identified, and the validated polymorphic model was used to perform an in-silico design of experiment (DoE) to develop a design space that can be used to identify operating conditions to achieve a desired crystal size and polymorphic form.

The final part of the thesis combines the experimental and model-based approaches for designing a continuous CCAC process for ASC in an integrated process consisting of a cascade of Coflore agitated cell reactor (ACR) and a three-stage mixed suspension mixed product removal (MSMPR) crystallization system. A combined artificial neural network (ANN) and principal component analysis (PCA) method was used to calibrate an ultraviolet (UV) probe, which was used to monitor ASC solute concentration in the cascade process. The crystallization kinetic parameters of ASC were estimated in ACR and MSMPR, which were used to build a digital model of the cascade process. The digital model was then used to obtain a design space with different temperature profile in the three-stage MSMPR that yielded narrow CSD of the ASC form I. Overall, this thesis demonstrates the benefits of applying PI in the CCAC of drug substances using a holistic approach including novel equipment, application of an array of PAT tools, and model-based digital design to achieve desired CQAs of the product.