MODEL-BASED DESIGN AND CONTROL OF AN INTEGRATED PURIFICATION PLATFORM FOR CONTINUOUS PHARMACEUTICAL MANUFACTURING

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This dissertation illustrates the potential of flowsheet simulation and optimization frameworks for the digital design and advanced control in pharmaceutical manufacturing. The proposed digital twin framework supports hierarchical process control, maintaining product quality amid fluctuating conditions and process disturbances, specifically tailored to a novel continuous crystallization-filtration carousel (CFC) unit. This system serves as a critical interface between drug synthesis and drug product manufacturing.

The development of a digital twin, consisting of a robust mathematical model, is a cornerstone of this framework. An open-source pharmaceutical model library and digital design software tool PharmaPy, is developed to support this effort. The PharmaPy flowsheet for the continuous purification step, calibrated with laboratory-scale data, functions as a soft sensor for unmeasured critical quality attributes (CQAs), and is used to optimize critical process parameters (CPPs) and develop active control strategies to ensure product quality. For the first time, mechanistic models for continuous crystallization, filtration, deliquoring, washing, and drying are integrated into the PharmaPy repository, forming a comprehensive flowsheet for the purification of active pharmaceutical ingredients (APIs). The proposed quality-by-digital design (QbDD) framework demonstrates the advantage of using digital twins and digital design techniques in the initial phase of process development, by highlighting benefits such as elucidating the interaction between crystallization and filtration and designing simultaneous crystal-dry products, using *in-silico* simulations, in a resource efficient manner as compared to traditional experimental methods.

By combining the flowsheet with a two-way automated data exchange between physical and digital counterparts, a dynamic digital twin (DDT) of the systems is developed and implemented to the real process. A model-based control approach is developed, using moving-horizon-estimation (MHE) and Extended-Kalman-Filter (EKF) techniques, for the real-time estimation of the API purification performance, ensuring precise control by implementing a hierarchical control system to maximize throughput, reduce filtration time, and produce solid product with desired crystal size and solvent content. The real-time optimization (RTO) algorithm, in particular, demonstrates superior capability in maintaining product quality and optimizing process performance.

Overall, the work addresses challenges and opportunities in digital twin development for integrated modular pharmaceutical manufacturing systems and highlights the significant benefits of considering the

synergy of sensor-system-model integration, flowsheet modeling of integrated systems and the use of QbDD framework for advanced pharmaceutical manufacturing control, including reduced variability, enhanced product quality, and maximized productivity.