Hybrid Modeling and System Analysis for Digital Twin Development of Continuous Pharmaceutical Manufacturing Processes

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With the goal from regulatory agencies to develop robust, flexible, and agile drug manufacturing lines with minimal supervisory oversight, the pharmaceutical industry is embracing a digitalization trend to better understand and control the manufacturing processes while striving for operational excellency. The trend has also supported by the recent development of Industry 4.0 technologies, aiming to build an integrated digital twin that can fully replicate the physical plant in a virtual environment. Such developments overlap with the emergence and adoption of continuous pharmaceutical manufacturing (CM) process, making the CM process an appropriate candidate for testing and implementing the new digital tools.

Shifting from batch to continuous for reduced footprint, rapid capacity adjustment, and better quality control, multiple processing routes have been developed for CM of oral solid dosage (OSD) products over the past two decades. Recently, with increasing research efforts and advancements of process systems engineering tools, significant progress has been made to realize the digital twin concept in CM. However, despite these attempts, some critical aspects still need to be considered for the practical application of an integrated digital twin, which include but not limited to the appropriate use of process data to develop models with better prediction accuracy and adaptability, the construction of flowsheet models for detailed system analysis, and the formation of effective optimization frameworks that can handle complex problems and save computational resources. The work presented in this dissertation focuses on the aforementioned aspects, with the research objective being to utilize process data and physical knowledge to develop efficient models and analysis tools for continuous pharmaceutical manufacturing process. The overall goal aims to enhance process understanding and facilitate implementation of digital twin framework for CM processes.

The first aim of this dissertation focuses on integrating available process data and physical understandings of CM unit operations for the development of hybrid and adaptive

models to improve overall model predictability and adaptability. The modeling methodologies are demonstrated for CM unit operations, and for a process analytical technology, namely a near-infrared spectroscopy model, adaptive strategy is also applied.

The second aim focuses on connecting the unit operations into fully integrated flowsheets capable of performing system analysis efficiently. Technology-economic analysis and sensitivity analysis for batch and continuous wet granulation lines concentrating on energy metrics are conducted to reveal the impacts on process conditions on energy consumption. The effects of introducing new plant data onto system analysis are also investigated with a case studies of continuous direct compaction line.

Finally, the third aim is to establish efficient workflows for system-based optimization of CM processes. This aim consists of developing workflows for 1) the optimization using hybrid model flowsheets with low computational cost, 2) a surrogate-based, feasibility-driven optimization with adaptive sampling method, and 3) an adaptive optimization framework. The methodologies are applied towards a continuous direct compaction and a continuous wet granulation process.

The developed modeling tools and system analysis workflows incorporate data and physical knowledge of the CM processes, further enhancing process understandings. The data connection between the *in silico* tools with physical process also facilitates the development and implementation of an integrated digital twin for CM processes, as the current state of the system can be better represented virtually.