ABSTRACT

Ganesh, Sudarshan PhD, Purdue University, May 2020. Continuous Pharmaceutical Manufacturing: Systems Integration for Process Operations Management.
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The Quality by Design (QbD) and Process Analytical Technology (PAT) initiatives of the United States Food and Drug Administration (FDA) have stimulated a paradigm shift in pharmaceutical product development and manufacturing since the mid-2000s. Specifically, there is taking place an accelerating adoption of computer-aided technologies in pharmaceutical discovery, development and manufacturing. The adoption of such technologies is driven by factors such as increasing expectations of product quality, accelerating time to market, combating drug shortages, achieving reduced operating and capital costs, personalizing medications and streamlining regulatory compliance. Continuous manufacturing has become one of these emerging technologies in the pharmaceutical industry; however, it presents numerous challenges in product and process design, as well as systems integration and operations.

This work addresses the implementation aspects of real-time process management (RTPM) in the continuous manufacture of oral solid drug products (OSD-CM). OSD-CM involves integration of multiple solids processing unit operations, process analyzers, and automation and information technology systems to enable the continuous flow and processing of both material and process data. Developments in OSD-CM since the 2000s have resulted in novel technologies and methods for material processing, designing and configuring individual equipment and PAT tools, strategies for active process control, as well as approaches for designing and operating integrated processes. As of late 2018, five drug products produced by early adopters of OSD-CM systems have received FDA approval. However, numerous challenges remain to be addressed in the implementation of individual subsystems, sensing methods and data architectures, to realize the all of the potential benefits of integrated manufacturing systems. To address these challenges, this thesis is focused on process monitoring and system integration while building on previous research in RTPM from our research group.

In the development and implementation of frameworks for robust process monitoring, two specific gaps in process monitoring of OSD-CM are addressed in this work. The first is the inline sensing of mass flow rate of particulate material, and the second, model-based data reconciliation for integrated OSD-CM processes. A novel x-ray-based sensor is studied, and the sensor's capability as an inline PAT tool to provide real-time measurements in OSD-CM is demonstrated. Further, a dry granulation system is investigated for material flow, assessment of established models and inline sensors, and the results applied to the development of a process data reconciliation and gross error detection framework.

The ultimate goal of system integration is to ensure that the individual system elements function reliably as a whole and meet the design performance requirements of the system. However, to date, there has been only limited discussion of the management of abnormal conditions during operations, to prevent unplanned deviations and downtime, and to sustain system capabilities in OSD-CM applications. Moreover, although the sourcing, analysis, and management of real-time data have received growing attention, under the label of Smart Manufacturing and Industry 4.0, there has been limited discussion of the continued verification of the infrastructure for ensuring reliable operations. Hence, this work introduces condition-based maintenance (CBM) as a general strategy for continued verification and sustainment of advanced pharmaceutical manufacturing systems such as OSD-CM. A vital implementation consideration for manufacturing operations management applications such as CBM is a systems architecture and an enabling infrastructure. Best practices for implementing such infrastructure are among the bottlenecks in operations management of advanced pharmaceutical manufacturing facilities, including OSD-CM. To this end, this work advanced the paradigm of Quality by Control (QbC), a hierarchical architecture for implementing QbD in pharmaceutical manufacturing. An infrastructure is implemented on the OSD-CM testbed at Purdue by utilizing commercially available automation systems, and by leveraging enterprise architecture standards. This thesis thus demonstrates an implementation of QbC as well as of the relevant features of the emerging operations management paradigm of Smart Manufacturing / Industry 4.0. It is envisioned that with the growth in digitalization technologies for design, development and implementation of OSD-CM processes, the promises of continuous manufacturing will be realized for a broad range of pharmaceutical products across the industry.