CONTINUOUS PHARMACEUTICAL MANUFACTURING: SYSTEMS INTEGRATION FOR PROCESS OPERATIONS MANAGEMENT

by

Sudarshan Ganesh

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THE PURDUE UNIVERSITY GRADUATE SCHOOL
STATEMENT OF COMMITTEE APPROVAL

Dr. Gintaras Reklaitis, Co-Chair

Davidson School of Chemical Engineering

Dr. Zoltan Nagy, Co-Chair

Davidson School of Chemical Engineering

Dr. Stephen Beaudoin

Davidson School of Chemical Engineering

Dr. Marcial Gonzalez

School of Mechanical Engineering

Dr. Qi Zhou

Department of Industrial and Physical Pharmacy

Approved by:

Dr. John Morgan, Head of the Graduate Program

Dedicated to

my parents, Kala and Ganesh,

my late paternal grandparents, Seetha and R. Krishnan

my sister, Aishwarya, and my partner, Abhilasha.

Their unconditional love and support fuel my journey.

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ABSTRACT

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 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.

1 INTRODUCTION

1.1 Motivation

Technological progress in the pharmaceutical industry enables the promotion, restoration, and maintenance of public health by developing and providing access to medication that can be manufactured and administered effectively. Manufacturing innovations in the pharmaceutical industry have proliferated since the mid-2000s following the initiatives such as Quality by Design (QbD) and Process Analytical Technology (PAT) initiatives of the United States Food and Drug Administration (FDA) (FDA, 2004a; Ierapetritou et al., 2016; Troup and Georgakis, 2013; Yu et al., 2019). These are fostered not only by the requirement of consistent product quality but by the increased expectations for intensified product and process development, mitigating the loss of batches and recalls, accelerated time to market, reduced operating and capital costs, real-time quality assurance and streamlining regulatory compliance. Consequently, the industry is marching towards operational excellence and continuous improvement in the manufacturing space through the adoption of advanced technologies for the design and operations of integrated processes (Yu and Kopcha, 2017).

Continuous processing to manufacture drug substance and drug products, both in the small molecule and large molecule space is among the most notable recent developments in the pharmaceutical industry. These developments are driven by an increasing need for sustainable process operations, safety, asset utilization and quality risk assessment in process design and operations (Allison et al., 2015; CDER US FDA, 2019; Lee et al., 2015; Nasr et al., 2017; National Academies of Sciences Engineering and Medicine, 2019). Research efforts since the mid-2000s empowered by the QbD and PAT initiatives of the FDA have advanced model-based material development, improved equipment and process designs, innovations in process analyzers, and integration of unit operations in the systematic pursuit of continuous manufacturing (Kleinebudde et al., 2017). Some of the milestones include approvals of five continuously manufactured drug products by the FDA through late 2018, the recent draft guidance for continuous manufacturing (CDER US FDA, 2019) and growth in the technology providers. However, despite the steady advances in novel technologies and innovative methods addressing the individual technology

components, the implementation of advanced control in manufacturing facilities has faced technical and cultural challenges due to real and perceived regulatory hurdles, as well as an implementation gap for manufacturing readiness (Collins, 2018; Ierapetritou et al., 2016; National Academies of Sciences Engineering and Medicine, 2019). Importantly, drug shortages caused by numerous manufacturing challenges continue to persist (Yu and Kopcha, 2017).

To this end, the pharmaceutical industry is leveraging the recent growth of information technology in industrial automation, referred to as Pharma 4.0 (Binggeli et al., 2018; BioPhorum Operations Group, 2018; Ding, 2018; Markarian, 2018; Romero-Torres et al., 2017). The developments towards Pharma 4.0 is a consequence of the advances of the chemical processing industries towards the paradigms increasingly referred to as Industry 4.0 or Smart Manufacturing or industrial digitalization. Industry 4.0 practices are underpinned by enabling technologies in industrial automation and information technology towards applications such as real-time product and process risk assessment, asset management, quality assurance and workforce development. These rely on the ability to collect, store, share and utilize manufacturing data for manufacturing operations management; and necessitates architectures and supporting infrastructure for system integration, data management and process control (ISA, 2010a; Isaksson et al., 2018).

1.2 Overview

The central theme of this dissertation is the implementation considerations of real-time process management (RTPM) towards the advancement of pharmaceutical manufacturing. RTPM encompasses frameworks for process automation such as robust process monitoring, plant-wide control, and fault and knowledge management (Giridhar et al., 2011). The process of interest in this work is the continuous manufacture of powder-based oral solid drug products (referred to as OSD-CM). Notably, this work builds on previous research in RTPM from our research group towards the development and implementation of OSD-CM.

There are many system hardware and software components that, together, comprise the totality of an OSD-CM process (CDER US FDA, 2019). The unit operations used in OSD-CM are not fundamentally new compared to the traditional batch tablet manufacturing methods (García-Muñoz et al., 2017). The novelty and challenges in OSD-CM arise from the necessity to integrate

the component pieces not only for material flow and processing, but also data flow and processing (Almaya et al., 2017; Laske et al., 2017). Notably, the necessity to handle particulate material across a train of unit operations adds to the complexity of OSD-CM. Consequently, the implementation of such integrated processes is not trivial. The interoperability of the component pieces in the overall process not only involves combining individual system elements but also ensuring that they function collectively as a whole and satisfy the design properties or characteristics of the system of interest (SEBoK, 2019a).

This dissertation addresses four main aspects in an attempt to address implementation gaps in OSD-CM identified by the research and practitioners community, such as inline mass flow sensing and data reconciliation (Ierapetritou et al., 2016), systems integration (Myerson et al., 2015), and the considerations for maintenance (ASTM Committee E55, 2014; CDER US FDA, 2019; FDA, 2006). Notably, the objectives of this work were supported by grants awarded by the US-FDA for implementation considerations of OSD-CM to advance system architectures and operations management towards Industry 4.0 practices. The specific tasks addressed in this work are outlined below.

1. Investigation of a novel x-ray based sensor for particulate mass flow rate monitoring to advance sensing capabilities in OSD-CM processes.

2. Assessing a dry granulation process for integration in the continuous tableting process and for applications in robust process monitoring frameworks.

3. Implementing data architectures in the pilot-scale OSD-CM testbed for Quality by Control and Pharma 4.0 practices of operations management.

4. Introducing condition-based maintenance as a general strategy for continued verification and maintenance in OSD-CM operations management.

1.3 Organization

This dissertation is organized into 7 chapters and is structured as an amalgamation of edited sections from published, or to be published articles, or articles in preparation for submission.

Chapter 2 provides an overview on the modernization of pharmaceutical manufacturing, followed by the developments in RTPM for implementing OSD-CM. The chapter highlights the rapid evolutions in pharmaceutical manufacturing since the mid-2000s resulting in integrated process operations and subsequent advances towards Pharma 4.0. Notably, this chapter is an extract from a submitted (under review) book chapter entitled 'Advancing Smart Manufacturing in the Pharmaceutical Industry' in 'Smart Manufacturing: Applications and Case Studies', to be published by Elsevier in 2020. The developments from this thesis towards process monitoring, abnormal events management and systems integration are also included in relevant sections.

Chapter 3 details the X-ray sensor study and its early stage implementation in the pilot plant facility. The majority of the contents of this chapter are reproduced from the article entitled 'Application of X-Ray Sensors for In-line and Noninvasive Monitoring of Mass Flow Rate in Continuous Tablet Manufacturing' in 'Journal of Pharmaceutical Sciences' (Ganesh et al., 2017). Further, advances in the utility of the sensor in the tablet line is highlighted.

Chapter 4 describes the roller compaction study. The contents of this chapter enabled the work of our research group towards robust process monitoring systems. The subsequent utility and applications from this work are partly published as articles entitled 'Sensor Network for Continuous Tablet Manufacturing' in 'Computer Aided Chemical Engineering' (Ganesh et al., 2018a) and 'Sensor Network Robustness Using Model-Based Data Reconciliation for Continuous Tablet Manufacturing' in 'Journal of Pharmaceutical Sciences' (Moreno et al., 2019).

Chapter 5 presents excerpts from the article entitled 'A perspective on Quality-by-Control (QbC) in pharmaceutical continuous manufacturing' published in 'Computers and Chemical Engineering' (Su et al., 2019c). The excepts discusses the development of Quality by Control, which is briefly, an architecture to implement QbD. As a second author in this article, contributions from this dissertation included developing the systems integration architecture to demonstrate the

QbC framework. These implementation considerations also supported additional RTPM applications pursued by the research group, culminating in published works (Moreno et al., 2019; Su et al., 2019a, 2018b).

Chapter 6 establishes the requirement of proactive considerations for maintenance strategies in OSD-CM. Herein, Condition-based Maintenance (CBM) is introduced as a strategy for leveraging the advances in RTPM of OSD-CM for continued verification and sustainment of process operations. Such use of real-time data for maintenance management is one of the main benefits of integrated data architecture in the ongoing Industry 4.0 or Pharma 4.0 practices of operations management. CBM builds on the concepts from previous work of the research group in exceptional events management to include considerations for infrastructure failures, aside from faults arising from material handling and process disturbances. The aspect of systems architectures, a vital consideration for the robust process operations is further discussed, along with illustrating the developments in implementing the infrastructure in the pilot scale advanced manufacturing tablet manufacturing testbed. The contents of the Chapter are to be submitted for publication in an article entitled 'On Condition-based Maintenance for Process Operations Management in Pharmaceutical Continuous Manufacturing.'

Chapter 7 concludes this dissertation by emphasizing the lessons learned and subsequent considerations for future work in the area of process operations management in pharmaceutical manufacturing. OSD-CM has considerably matured for industrial applications and regulatory considerations. This growth necessitates solutions for process safety, training and development of best practices, along with considerations for improved sensing, equipment innovations and strategies for operations management.

2 ADVANCING SMART MANUFACTURING IN PHARMACEUTICAL PROCESS OPERATIONS

2.1 Introduction

Smart Manufacturing (SM) and related ongoing industrial automation advances such as Industry 4.0 are reshaping manufacturing operations management driven by expectations for improved safety, security, quality, asset utilization, time to market, regulatory compliance and enhanced customer relations across multiple industries (Baur and Wee, 2015; Moyne and Iskandar, 2017). This advent of SM in the chemical processing industries for 'manufacturing intelligence' is a manifestation of cultural and mindset change in utilizing the technological advances in communication and information technology, and builds on decades of progress in process systems engineering (Bagajewicz, 2009; Christofides et al., 2007; Davis et al., 2015; Edgar and Pistikopoulos, 2018; Venkatasubramanian, 2019). SM benefits from multiscale modeling, advanced sensors, and equipment-process-enterprise integration achieved in the manufacturing space over decades of progress in digital process operations; and is enabled by the integration of unit operations with the business units through the progress in digitalization, referred to as the Operations Technology and Information Technology (OT/IT) integration (Isaksson et al., 2018). Notably, SM relies on underlying components of product and process understanding, process monitoring and control, and systems integration; as well as cultural drivers and advances in the enabling technologies for systems integration.

In this chapter, an overview of the advances in operations management in pharmaceutical manufacturing towards SM by focusing on the developments in OSD-CM. The cultural advances and several technological developments in the underlying RTPM component areas, including process monitoring and control, fault-tolerant control, exceptional events management, knowledge management, and systems integration, are discussed. It must also be noted that significant progress along the Industry 4.0 concepts has been achieved in digitalization of pharmaceutical facilities and is increasingly referred to as Pharma 4.0. The early stages of Pharma 4.0 is seen in development laboratories, supply chain, clinical trials, continuous manufacturing of drug substances, end-to-end integration of drug substances and drug product manufacturing, and bioprocessing (Herwig et

al., 2017; OSIsoft LLC, 2017; Romero-Torres et al., 2018; Steiner and Jornitz, 2017), however these topics are beyond the scope of this work.

2.2 Modernization of Pharmaceutical Manufacturing

2.2.1 Quality by Design

While the discovery of the drug substance or the active pharmaceutical ingredient (API) has been the traditional focus of the pharmaceutical industry, the development of an effective product formulation for the delivery of the API and of the design and operation of processes that will consistently and profitably manufacture the product has in recent years drawn increased efforts. Drug products include tablets, capsules, film strips, soft gels, skin patches, injectable, etc., where the choice of product form is based on the desired drug delivery profiles within the body, the mechanical and chemical constraints of the API and patient compliance. Oral solid doses, particularly tablets, are the most common form of a drug product as tablets are cheap to manufacture, are mechanically and chemically stable and are most convenient to self-administer. The manufacturing process, however, requires many capital-intensive, complex steps that use numerous associated resources, including equipment, material, and labor; and the associated costs constitute about 27% of the cost of a brand name drug product and almost half the cost of a generic drug product (Basu et al., 2008). The reader is referred to (Khinast and Bresciani, 2017) for an overview of the unit operations involved.

By recognizing that drug shortages and recalls commonly begin with a supply disruption related to a product or facility quality, regulatory encouragement towards science and risk-based manufacturing has led the developments towards agile, flexible, and robust systems to mitigate failures within manufacturing facilities (Lee et al., 2015; Yu and Kopcha, 2017). Importantly, these manufacturing failures as well as the limited ability to scale production during emergencies are considered a potential threat to public health. The ‘Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach’ and the ‘PAT – A Framework for Innovative Pharmaceutical Development Manufacturing and Quality Assurance’ documents by the United States Food and Drug Administration (FDA, 2004b, 2004a) in the early 2000s envisioned modernization of the pharmaceutical industry through the adoption of innovative manufacturing technologies. Scientific

and risk-based approaches to product development and manufacturing along with the pursuit of operational excellence to benefit patients by providing essential medication at consistent quality in a timely manner, and the potential to reduce manufacturing associated shortages, recalls and costs have driven a paradigm shift in the modernization of pharmaceutical processes.

2.2.2 Towards cyber-physical systems

The QbD and PAT initiatives have launched a cultural change serving as innovation drivers by encouraging scientific and risk-based approaches to product and process development and manufacturing and a departure from the traditional checklist-based operations. QbD and PAT encouraged the design of manufacturing systems that could operate in a design space within which predefined quality target product profile (QTPP) could be assured using advanced process monitoring and control technologies.

Attaining predefined quality, safety, and efficacy is based on product and process understanding, and the enabling control strategies. This is achieved by utilizing knowledge gained from first principles and empirical modeling, a risk assessment of the processing routes by identifying the Critical Quality Attributes (CQAs) and corresponding Critical Process Parameters (CPPs) that could impact the product and the implementation of PAT. The control strategy involves a planned set of controls, including that of process parameters, process attributes, facility and equipment operating conditions, and process testing that ensures process performance and product quality to be within the design space. The PAT guidance (FDA, 2004a) and International Council for Harmonization guidelines ICH Q8 (R2) Pharmaceutical Development, ICH Q9 Quality Risk Management and ICH Q10 Pharmaceutical Quality Systems laid the foundations for the modernization of pharmaceutical industry via advanced manufacturing methods, including real-time assessment of process performance and product quality.

The fundamental understanding of the product and the process, and the ability to measure and control CQAs is the basic principle for development and manufacturing under QbD principles. Hence, this necessitates the systematic integration of physical and cyber capabilities throughout the life cycle of product development and manufacturing. These include product and process modeling, online sensing and process control, knowledge management, and the use of automation

systems for implementation. Moreover, such innovations in Chemistry, Manufacturing, and Controls (CMC) require effectively sourcing, managing and utilizing the volume, velocity, veracity, and variety of the data from equipment and analyzers at multiple scales of operations spanning laboratory, pilot-scale development, manufacturing facilities as well as of contract manufacturers and suppliers. Moreover, prior CMC knowledge is valuable to accelerate new drug development as well as the regulatory review process (Hussain et al., 2019). Knowledge management and quality risk management are hence highlighted in ICH Q10 as key enablers for the development and implementation of the pharmaceutical quality system to record and manage process data as well as observations such as failures, material clogging, cleaning frequency, etc. during the product's life cycle. Furthermore, capture of the knowledge about the products and processes, requires linking experimental data and predictions with suitable models.

Process models play an essential role in the progress towards the modernization of manufacturing systems (Chatterjee et al., 2017). Under the QbD paradigm, mathematical models are essential for encoding pharmaceutical process understanding and can be used effectively throughout development and manufacturing, including process design, scale-up, process monitoring, control, and continual improvement. The models may be broadly classified into mechanistic or first-principles models, empirical models, and semi-empirical or hybrid models. Many data-driven and mechanistic models have been implemented in pharmaceutical process development and manufacture, and these modeling approaches are further evolving for multiple objectives. The efforts towards improved agility, flexibility, and robustness in manufacturing methods to mitigate the loss of batches, recalls and inconsistent product quality is already resulting in a paradigm shift towards model-based approaches to product and process development, process control and operations management. Data-driven models are crucial for quantitative monitoring using PAT tools as well as the implementation of multivariate statistical process control (MSPC). Advances in process understanding are further facilitated by first-principle and hybrid modeling of the system. The models are leveraged for reliable process operations in monitoring and forecasting systems, open and closed-loop decision support, and plant-wide automation. These advancements are ushering pharmaceutical manufacturing into the big data era to leverage models and predictive analytics for driving innovations in product development and intensification of process operations. As a consequence of business, social and regulatory drivers, and importantly,

a deeper understanding of the manufacturing system and its components, these efforts lead towards operational excellence and continuous improvement of manufacturing systems. The reader is referred to the article (Yu et al., 2014) and the book 'Comprehensive Quality by Design for Pharmaceutical Product Development and Manufacture' (Reklaitis et al., 2017) for an overview on QbD concepts and applications.

2.2.3 Quality by Control

The QbD guidance and the ICH Q8, Q9 and Q10 promoted the systematic generation of the essential product and process knowledge required to implement continuous operation by identifying the critical material/quality attributes, process parameters, and the control strategies required to maintain the process operation and the quality of the product under a state of control. This was an advancement from Quality-by-Testing (QbT), the quality control approach to testing the quality attributes of in-process material or final product at the end of each batch processing step. The concept of Quality by Control (QbC) for a model-based paradigm in the systematic implementation of QbD approaches following hierarchical control layers was recently introduced by our research group (Su et al., 2019c). QbC in pharmaceutical manufacturing envisions that quality should not only be designed initially using product and process understanding based on QbD, but more robust processes ought to be implemented using active process control approaches by benefiting from the increasing product and process knowledge, enabled by state-of-the-art industrial automation technologies.

2.2.4 Continuous Processing

The regulatory push towards advanced manufacturing opened the doors for innovations including in existing unit operations emerging from the systematic integration of product and process knowledge, instrumentation and automation systems, compliance protocols and real-time process management. Continuous manufacturing promotes the physical integration of two or more unit operations with the implementation of real-time monitoring and process control (CDER US FDA, 2019). Driven by the expectations of achieving reduced operating and capital costs, lowering material inventory, improved product quality and reduced batch to batch variability, safety and increased reliability, the development of advanced technologies for the intensification of product

development, manufacturing processes and supply chains ensued in earnest. The progress in material development further enables reducing the number of processing steps and need for human handling during intermediate stages.

Moreover, the expectations of utilizing smaller equipment for longer run durations translates into flexibility in scale-up and significantly reduces the size of the manufacturing facility. The shift from traditional batch manufacturing and end of line product quality testing to the development of continuous manufacturing systems and real-time quality assurance pave the way for real-time release testing (RTRT) (OConnor and Lee, 2016). These upgrade the value of process data from merely being utilized for end-of-batch quality checks to exploitation in advanced process control, process intensification, and model-based development of new products and processes. As opportunities emerged to benefit business needs, five drug product filings which employed continuous tablet manufacturing processes have received FDA approvals namely, Orkambi from Vertex in 2015, Prezista from Janssen in 2016, Verzenio from Eli Lilly and, Symdeko from Vertex in early 2018, and Daurismo from Pfizer in late 2018. Generally, continuous manufacturing facilities enjoy economies of scale; that is, the investment and operating cost per unit of production decrease as the plant design capacity is increased. However, the incentives for continuous manufacturing in the pharmaceutical industry are not the same in all aspects as they may be for the other industry sectors. The reader is referred to the article by (Steiner and Jornitz, 2017) in the book 'Continuous Manufacturing of Pharmaceuticals' (Kleinebudde et al., 2017) for a comprehensive description of the benefits and historical developments towards continuous processing in the pharmaceutical industry.

This modernization journey towards advanced manufacturing technologies is enabled and accelerated as a result of significant efforts in overcoming technical, cultural and regulatory challenges since the early 2000s, with contributions from multiple academic, industrial and regulatory groups. For example, under the US National Science Foundation supported Engineering Research Center for Structured Organic Particulate Systems (NSF ERC-SOPS), multiple manufacturing process testbeds for solid oral drug products have been developed. Also, the Novartis-MIT Center, the Research Center for Pharmaceutical Engineering in Austria and several additional research centers and industry-academia-regulatory partnerships have enabled the

modernization of pharmaceutical manufacturing in earnest. Importantly, community interactions through symposia and forums such as the International Symposium on the Continuous Manufacturing of Pharmaceuticals (ISCMP), American Institute of Chemical Engineers (AIChE) Pharmaceutical Discovery, Development and Manufacturing (PD2M) Forum, the International Forum for Process Analysis and Control (IFPAC) among others, and working groups in multiple organizations such as the FDA Emerging Technology Team, the ASTM E55 Committee, the International Society for Pharmaceutical Engineers (ISPE) Continuous Manufacturing Subcommittee and Pharma 4.0 Special Interest Group, BioPhorum Operations Group, the National Academies of Sciences, Engineering and Medicine continue to foster developments in modernizing pharmaceutical manufacturing using digital technologies.

Notably, the advances in continuous manufacturing in the small molecule space provided the initiatives to advance manufacturing sciences and have received FDA approvals. These advances have been instrumental towards the harmonization of regulations across multiple global agencies and address the barriers to continuous manufacturing. Furthermore, it has provided the necessary encouragement for process intensification achievable through automation and advanced manufacturing methods. The lessons learned in small molecule applications of continuous manufacturing are stimulating similar developments in the more complex biological products domain, where technologies for real-time monitoring of CQA's are in early stages of development, and contamination monitoring and control are quite challenging (National Academies of Sciences Engineering and Medicine, 2019). In the forthcoming years, developments through the Industry 4.0 initiatives are positioned to impact the design, deployment and sustainment of the processes and facilities that produce the next generation of life-saving medication.

2.3 Continuous tablet manufacturing

Continuous manufacturing processes are a system of systems. In this subsection, the integration of existing tablet processing technologies to form a 'continuous manufacturing' system is discussed. Further, the considerations for such a complex system are briefly highlighted, along with the considerations for leveraging the advances in OT/IT integration to progress in this journey.

2.3.1 Process

Oral solid dose manufacturing involves the use of a sequence of unit operations for processing drug substances as well as additional ingredients such as excipients, lubricant, and coatings to result in the final dosage form. The drug substance is usually a small-molecule organic compound manufactured using classical reaction and separation operations to result in a particulate solid, often crystalline, at ambient conditions. The manufacturing steps for the drug substance are referred to as primary manufacturing. The excipients, lubricants, and other therapeutically inert components used to facilitate product handling, manufacturing, administration, dissolution, and delivery to the patient, are also particulates at ambient conditions. The downstream manufacturing or secondary manufacturing involves the blending of the powders comprising the product formulation and compressing the blend into tablets. The secondary manufacturing process traditionally follows one of three routes - direct compaction, wet granulation, or dry granulation for production of tablets (or capsules). The granulation routes involve additional solids handling processes depending on the desired formulation and material properties. Powders that flow well and have no segregation issues may be directly compressed after blending. Powders that flow poorly or segregate are formed into granules, either using dry granulation which involves pre-compression into a ribbon followed by milling or using wet granulation which involves agglomeration of the particles using a liquid binder, possibly screening to control granule size, followed by drying. The secondary manufacturing of powder-based oral solid doses is the manufacturing route used as an example in the subsequent discussion.

Several of the unit operations in tablet manufacturing such as dry granulation and tablet compression are inherently continuous processes, however, they are operated in semi-continuous fashion. In particular, these unit operations have traditionally been utilized in recipe-based batch processes, by processing a defined amount of input material. The required product quality assurance such as blend uniformity, particle size distribution, tablet hardness, and others are performed at the end of each of the processes. Various monitoring and control strategies proposed for such batch manufacturing relied on a priori determined optimal or nominal process operation trajectories or recipes. However, the quality testing performed at the end of the process could result in the loss of the entire batch since remedial control actions can only be implemented for subsequent batches. Rework of nonconforming batch of product is technically challenging and not

acceptable from a regulatory perspective. As a result of such batch-to-batch control strategies, significant waste and substantial time delays are encountered before product quality improvements are realized.

The advances in material development, process modeling, integration of unit operations, and the ability to source and exploit data in real-time for process control and manufacturing operations management facilitates process intensification in tablet manufacturing. A continuous flow of materials between unit operations driven by equipment innovations and real-time process operations management leads to continuous manufacturing of tablets (referred OSD-CM in the subsequent discussion). Advances enabled by leveraging process systems engineering methods have bolstered the developments in the design of individual unit operations and integrated processes, online measurements, and supervisory control for real-time quality assurance (García-Muñoz et al., 2017; Giridhar et al., 2014; Laske et al., 2017; Markl et al., 2013; Oka et al., 2017; Reklaitis et al., 2017; Singh, 2018; Singh et al., 2014; Su et al., 2019c).

The primary solids processing unit operations for OSD-CM are continuous powder feeding using loss-in-weight feeders continuous blending, and tablet compression. Loss-in-weight (LIW) feeders are used for feeding the API, excipients, inert additives, etc. into the continuous blenders. Depending on material properties and formulation, unit operations such as roller compaction, milling, wet granulation, drying, and coating could be employed before tableting. OSD-CM requires the systematic integration of these solids processing unit operations, along with analytical systems, process knowledge, and automation methods (CDER US FDA, 2019). The sensor network for active process control and real-time quality assurance is composed of sensors built into the unit operations equipment to measure CPPs and process analyzers which measure CQAs. The systems integration of equipment and sensors into a supervisory control system enables the plant-wide control of the process. A conceptual process schematic, incorporating direct compaction and dry granulation alternatives as implemented in the pilot plant testbed at Purdue University is shown in Figure 2-2 (Ganesh et al., 2018a).

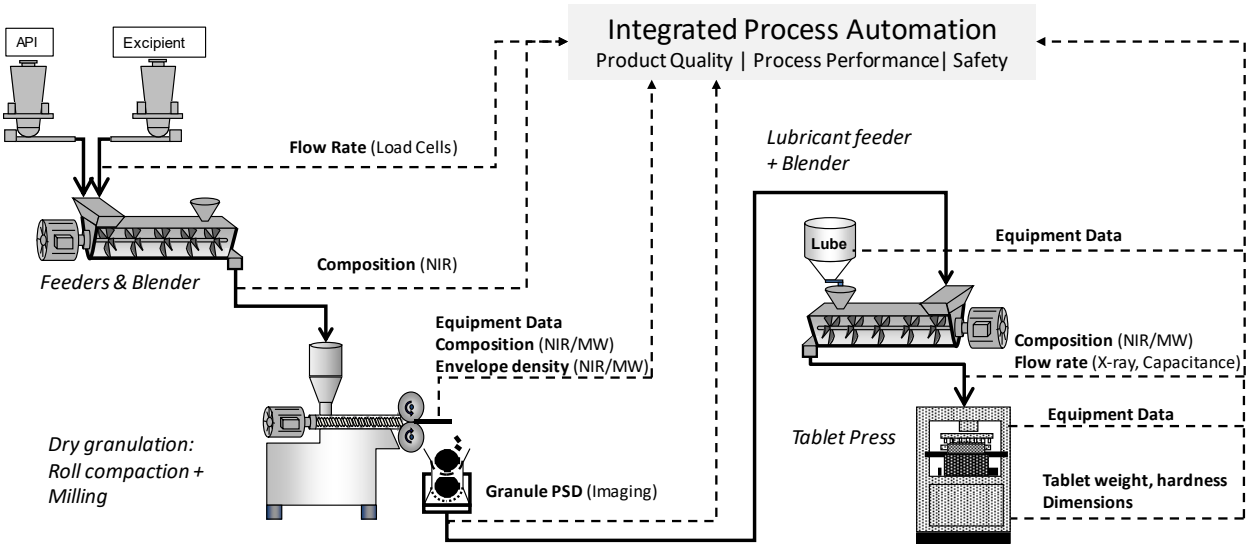


Figure 2-1: Schematic of OSD-CM with direct compaction and dry granulation processing routes (Ganesh et al., 2018a)

2.3.2 A complex system of systems

Advanced manufacturing systems such as OSD-CM integrate efficient subsystems to achieve overall system effectiveness, or simply stated, to ensure that the whole is greater than the sum of parts. To assure that products with the desired quality are consistently manufactured over time, OSD-CM processes need to operate under a state of control, i.e., to maintain the deviations in the process input and output variables within the design space. The first step towards effective process operations management thus lies in the development and implementation of multiple levels of control strategies. These strategies enable real-time manufacturing decision making by sourcing, contextualizing and analyzing massive amounts of sensor data available at higher scan rates from individual equipment, analyzers, knowledge management of the process and product, and the supervisory distributed control of efficient equipment (Giridhar et al., 2011). This requires effective RTPM, broadly involving process control and manufacturing operations management. Key considerations include design, development, maintenance, and improvements in process operating conditions, refill scheduling, asset operability, scale-up, material tracking, and deviation management. The control strategies are generally supported and executed using PAT tools, process control, and intelligent alarm management systems, and knowledge management systems. At a more advanced level, these essential functions manifest into start-up and shutdown considerations, RTRT, Quality Risk Management (QRM), and real-time optimization (RTO) capabilities.

The PAT initiative (FDA, 2004a) led to the development and implementation of an integrated automation system for product quality assurance by designing, analyzing, and controlling manufacturing through timely measurements of quality attributes of raw and in-process materials and process conditions. The real-time monitoring of process performance and quality attributes of in-process materials employ a combination of methods for process data analytics. Product quality information is obtained using in-line, at-line and off-line sensors, as well as virtual sensors. Virtual or soft sensors use data-driven, mechanistic or hybrid models for predicting the values of the unmeasured or unmeasurable material attributes and process conditions from the available measured variables. The soft sensing methods are particularly important as the manufacturing CPPs, and CQAs are typically only surrogates for clinically relevant quality measurements.

The subsystems and components for implementation involving the equipment, analyzers, models, control systems, and communication technologies result in OSD-CM as a complex system of systems. The overall system is leveraged to achieve the desired product quality, along with the expected social, business, and regulatory objectives. However, the underlying components of complex systems have a lifecycle and demand consideration of failure modes by recognizing their limitations to achieve the intended benefits of an integrated system. The complexities warrant a comprehensive effort for preventing systemic failures (Venkatasubramanian, 2011). Failures in integrated systems such as OSD-CM processes lead to uncertainty in product quality assurance, resulting in the requirement for increased offline quality testing, time to market, hence impact consumer reach. Consequently, this limits the utility of OSD-CM technology.

An effective integrated operations management system design must ensure the robustness of monitoring and control systems during manufacturing considering expected and unexpected variations, hence must include considerations for system performance monitoring, utilization of redundant systems, calibration verifications and device maintenance (ASTM Committee E55, 2014). Further, the possible long run times for OSD-CM systems warrant additional considerations for qualification, maintenance, and cleaning to maintain individual physical assets and the overall OSD-CM system in a validated state (CDER US FDA, 2019; Giridhar et al., 2014; Hamdan, 2010). To complement the efforts in designing and configuring efficient individual equipment, PAT tools,

and process control strategies, managing non-random abnormal conditions in material flow and asset operations is essential by establishing process alarms, and corrective and preventive actions. While regulatory process control is essential for ensuring the optimal operations of the process, statistical process control methods add value for assessing the batch to batch variations in process performance and product quality, and further establishing the corrective and preventive action plans. This leads to actionable improvements, such as utilizing control performance monitoring for control structure re-organizing and proactive maintenance of the system. Numerous methods can be implemented for fault detection and diagnosis using specialized hardware systems or soft sensing methods. The Guidance for Industry Q9 Quality Risk Management (FDA, 2006) has highlighted multiple such tools for risk management. A risk-based assessment of process automation and control system design to ensure robust operation and RTRT should include the implementations of standards and community guidance such as Code of Federal Regulations (CFR) 21 Part 11, ISA-88 Batch Control Standard, ISA-95 Enterprise-Control System Integration Standard, or the ISPE GAMP 5.0 Good Automation Manufacturing Practice. Hierarchical control strategies have been proposed to maintain the quality of the product in response to potential variations or disturbance in the process, equipment conditions, incoming raw materials, or environmental factors over time (Yu et al., 2014).

A holistic approach to developing control strategies is addressed through the three stages of process validation described in (FDA, 2011) for process design, process qualification, and continued process verification. The process design stage involves the development of a control strategy for achieving the manufacturing process performance and quality expectations. The process qualification stage involves assessing the robustness and reproducibility of the integrated system, its components as well as the facilities and utilities. The first two stages of the process validation provide the necessary understanding of the manufacturing process and associated analytical methods. The continued process verification stage involves the assessment of the system to be within the state of control during manufacturing. The ability to utilize data from process equipment and analyzers for continued process verification would enable real-time assurance of process performance, hence of product quality in leading to proactive manufacturing operations management such as RTRT.

2.4 Developments in OSD-CM Operations Management

In this subsection, recent progress and perspectives towards the RTPM aspects in OSD-CM (Giridhar et al., 2014, 2009) are described. Herein, advances in-process monitoring, and control, fault-tolerant control, abnormal events management, and knowledge management are outlined. These underlying components pave the way for the implementation of OSD-CM and benefiting from the digital evolution.

2.4.1 Process Monitoring

The development in real-time process analyzers employed in OSD-CM includes those based on the use of near infrared (NIR), Raman, ultrasound, x-ray, microwave, capacitance, imaging, and laser light scattering signals. While most inline nondestructive measurements employ reflectance methods based on NIR and Raman spectroscopy, the developments towards transmission measurements such as microwave and x-ray technologies have recently been demonstrated for OSD-CM (Austin et al., 2013; Gupta et al., 2015). Further, ensuring material balance closure is crucial to maintain robust and profitable continuous operations, and the use of x-rays for inline mass flow monitoring was recently reported (Ganesh et al., 2017). These sensing technologies are configured to provide non-destructive information related to physical, and chemical attributes of the materials based on spectral analysis. These process analyzers are comprised of electronic and mechanical components, light sources, optic cables, measurement probes and interfaces, and importantly, the methods and software to acquire and analyze the data, in real-time. The measurements depend on factors such as the working principles of the sensor, probe choice, and locations, material, data filtering, calibration models, etc. Irrespective of the technology, the adaptation of methods for real-time monitoring involves significant efforts for material sampling, and the collection and utilization of data. This requires extensive amounts of materials for calibration and validation. Furthermore, non-random operational challenges such as material blockage, sticking, frequent and persistent fouling of inline analyzers, device age, calibration models, etc. affect the real-time measurements provided by these sensing systems. At-line sensors usually involving technologies that are more robust are employed as reference methods for the in-line CQA sensors, however, these sensors require a more extended period to arrive at a measurement relative to the dynamics of the process and may employ destructive testing

of the samples. Nevertheless, the at-line sensors aid in near real-time assessment of process performance capabilities using statistical quality control methods; validate CQAs to enable RTRT and aid in checking for calibration drifts in the in-line measurement systems. To overcome the challenges in configuring individual process analyzers, developments leading to configurations for smart or intelligent sensors to simplify device calibrations and automating diagnostics to manage non-random events such as fouling (Fonteyne et al., 2015). We refer the reader to a recent review (Laske et al., 2017) for additional reading on the PAT tools available for tablet manufacturing.

The developments of such sensing technologies are essential to not only provide a measurement of the system for a high level of product and process understanding during development but benefit the monitoring and control of the integrated system during manufacturing. Importantly, the real-time implementation of control strategies leading to operational excellence requires accurate and reliable inline measurements, overcoming the random and non-random errors in measurement. This necessitates a sensor network setup comprising of not only the reliable individual sensors for product quality monitoring but also for holistic process automation. Robust process monitoring capabilities using systematic sensor network designs are essential for the timely detection of process deviations and initiating some form of intervention to assure process performance and product quality. The data-driven and mechanistic modeling of OSD-CM along with the development of real-time sensing technologies enable the developments towards robust model-based process automation of the integrated process.

Methods such as univariate statistical quality control, MSPC, and data reconciliation (DR) and gross error detection (GED) serve to track individual attributes or variables by subjecting the time series measurements to statistical tests for detecting actionable deviations. These methods use the real-time data, along with prior information about the statistically characterized error in the measurements and a model of the process to predict the most likely state of the process. While MSPC methods rely on data-driven models, the utility of mechanistic models in process operations leads to DR, GED, and state estimation. The mechanistic models are mostly the component material balances, property relations and compaction equations. These methods serve to ensure the observability of the process through real-time verification of raw measurements. GED or sensor validation refers to the identification of faulty or failed sensors in the process. DR or data

rectification is the task of providing estimates for the true values of sensor readings using redundancy in the sensor network. This requires a minimum number of sensors such that on the occurrence of a measurement failure, the network is still observable. Multiple measurements of the same process variable can improve the reliability of that measured variable; however, it does not affect the observability of the unmeasured variables. Moreover, sensors using the same technology can miss certain process features which can only be seen via measurements utilizing a portfolio of alternative technologies. Although the blend uniformity is the primary concern for a continuous tableting process, integrating available mechanistic understanding with sufficient measurements to maintain network redundancy and observability of unmeasured variables is essential for reliable continuous operations. MSPC methods applied to the integrated OSD-CM process for monitoring process performance and product quality are reported (Almaya et al., 2017), and the process data analysis methods of robust state estimation, DR and GED were recently introduced and demonstrated for OSD-CM applications (Ganesh et al., 2018a; Liu et al., 2018; Moreno et al., 2019, 2018; Su et al., 2019a).

2.4.2 Process Control

Reliably operating a OSD-CM process requires a robust and fault-tolerant supervisory control system to manage the effects of common cause disturbances and abnormal events by leveraging the capabilities of efficient automated equipment for producing the material at desired quality attributes (Su et al., 2018b). The powder processing unit operations are characterized by fast dynamics with time constants of seconds or minutes, thereby requiring fast responses from the control system. There is also a limited hold-up in each unit operation, and thus the buffering provided by material inventory is limited. Additionally, stream recycling or substantial back mixing in the process must be avoided in the highly regulated pharmaceutical secondary manufacturing process due to the requirements of material tracking. Therefore, aggressive control responses are often required to address process disturbances, potentially posing safety threats due to dust-generation in the manufacturing process (Singh et al., 2015). Furthermore, variability in raw materials upstream also has a rapid and direct impact on downstream processes, which affects the in-process materials and final drug product qualities, thereby challenging production. Systematic design and implementation of plant-wide control system employing feedback, feedforward or multivariable control strategies based on the use of predictive process models are

hence crucial to the success of OSD-CM by manipulating the process input variables for achieving the target set-points of the controlled variables within their target design space ranges. Plant-wide control aims for controlling important plant operating variables, while maintaining safe operating conditions, e.g., maintaining the production rate and material quality attributes at desired set point by manipulating the necessary operating variables within equipment safety limits. Supervisory distributed control systems (DCS) are employed for implementing controller designs such as single/multiple-loop controllers, using simple feedback proportional, integral and derivative (PID) control, feedforward ratio control, or the advanced model predictive control (MPC) in case of strong variable interactions and highly nonlinear process dynamics. It is important to note that the developments of appropriate measurement systems leads to the implementation of such regulatory and supervisory control strategies.

Architectures to systematically control integrated processes using equipment level controllers and supervisory controllers for maintaining the normal operating conditions and product quality specifications was recently introduced by the research group and established as the Quality by Control framework (Su et al., 2019c). QbC is defined as 'The design and operation of a robust manufacturing system that is achieved through an active process control system designed in accordance with hierarchical process automation principles, based on a high degree of quantitative and predictive product and process understanding.' QbC in general enables reliable batch and continuous process operations, especially the real-time release in continuous manufacturing of pharmaceutical products. A risk-based evaluation framework was further proposed to assess the risk of each control layer and determine the most appropriate approach to reduce the occurrence and impact of commonly occurring risks (Su et al., 2017). A risk map for the manufacturing process can be presented in the form of a matrix, which characterizes the likelihood that a risk event will occur and describes its impact on the manufacturing system. Only the nominal risks that are acceptable to continuous manufacturing are investigated at the control design. An acceptable risk is a risk that is understood and tolerated usually because of the cost or difficulty of implementing an effective permanent countermeasure exceeds the expected impact of the risk event on process operations.

Despite the progress in model-based process control for OSD-CM systems, there are key challenges that were highlighted in (Su et al., 2019c), such as lack of shared understanding of control theory for broader application in the industry, challenges in developing and implementing inline sensors, lack of standardization, and the real and perceived regulatory hurdles for implementation of advanced control in manufacturing facilities. Nevertheless, the advances in process control for OSD-CM and the growth of enabling tools facilitated by the digitalization of manufacturing operations opens the door to process automation and continuous improvement at multiple levels, including predictive maintenance, control performance monitoring and structure reorganizing. Such improvements can be targeted to achieve tighter tracking of CQA and more robust plant-wide control, which will maintain the process within its designed operating space.

2.4.3 Material Tracking

Material tracking is of critical importance in pharmaceutical manufacturing and associated supply chain and distribution channels. It forms a safeguard for tracing the life cycle of the product, as well as aid in resolving the consequences when a drug recall is necessary. For example, when an identified drum of API is introduced into the process train, the number of subsequent lots of drug product that contains API from this drum could be tracked and quantified (Billups and Singh, 2018). In addition, by 2023, the United States Drug Supply Chain Security Act will require that the pharmaceutical industry implement end-to-end traceability. The availability and access to real-time data enables potential innovations in quantitative and predictive material tracking in continuous processing (Bylo, 2017). The conventional definition of a drug product lot using the batch size can be adapted in continuous manufacturing, however, operationally it requires additional steps to assure true lot identity. While a lot in batch manufacturing in principle experiences the same processing history since the operation is confined to that batch of material, a lot in continuous manufacturing is collected over a certain period of time during which ideally the material is subject to same operating conditions. Hence, the identity of a lot of product in continuous manufacturing can be either defined using an a priori criterion (mass of product or duration of a run) or if the need arises, dynamically. In any case, as the material proceeds through the process train, its progress must be recorded in terms of measured properties at each point in the sensor network, monitored against the allowed design space, and the residence time in each equipment based on model predictions or measurements. At the first departure from allowed

ranges, the material must be flagged as nonconforming, the termination time of a lot of preceding material recorded, and nonconforming material tracked until satisfactory conditions are reestablished. These functions require the informatics system under the smart manufacturing umbrella to accumulate dynamic data on lot and nonconforming materials statistics, including the identity of stages at which departures leading to nonconformance was observed since these can offer insights on points and modes of failure, as well the process variation and its propagation.

Among the topics of active research in OSD-CM is that of the material residence time and its distribution in each equipment, viz., the residence time distribution (RTD). This vital concept in chemical and reaction engineering, has been a focus of attention recently as a tool for material tracking in pharmaceutical continuous manufacturing. For example, a statistical approach is often adopted for material RTD studies. Typically, the response of a step-change in API concentration or the downstream propagation of a tracer composition is experimentally or numerically characterized to develop RTD profiles (García-Muñoz et al., 2017; Rogers et al., 2013), dimensionless RTD models (Tian et al., 2019), or empirical RTD models based on transfer functions (Rehrl et al., 2018). Usually, this RTD understanding corresponds to nominal steady-state operating conditions, the drawback is that it is not representative of the actual dynamics of operations. In the context of continuous manufacturing with active process control as discussed in the above section, it is imperative to understand and characterize RTDs under dynamic operating conditions. This dynamic feature is useful because material tracking, and product diversion usually occur during start-up/shut down or subject to process disturbances that are under dynamic transient conditions and the process is actively controlled until reestablishing satisfactory conditions.

Overall, with both the real-time information flow from the sensor network and the residence time distribution from the material flow integrated within the smart manufacturing framework, the digitalized material tracking capability provides more credible traceability in continuous process train, along with a deeper understanding of the root causes of process variation.

2.4.4 Abnormal Events Management and Maintenance

To complement the efforts in designing and configuring efficient individual equipment, PAT tools, and control strategies for product quality, managing non-random abnormal conditions

in material flow and assets such as flow blockage, automation system malfunctions, or equipment performance degradation is essential. This requires establishing process alarms based on qualitative and quantitative indicators, and further the corrective and preventive action plans for sustainment of the process.

Recently, exceptional events management (EEM) and intelligent alarm system (IAS) frameworks were introduced to OSD-CM applications to address the issues of fault detection, diagnosis and mitigation of abnormal events (Gupta et al., 2013; Hamdan et al., 2012, 2010). Qualitative model-based methods such as signed directed graphs, and process history-based qualitative trend analysis and quantitative methods such as wavelet analysis and principal component analysis were demonstrated to detect faults mainly caused by material blockage and buildup. Further, configuring alarms following ISA-18 Standard on Alarm Management in the Process Industries (ISA, 2016) and knowledge management using ontologies were discussed.

Furthermore, the process equipment such as feeders, granulators, and tablet presses require efficient functioning of their corresponding subsystems and components, such as load cells, solenoids, wear strips, gaskets, punch retainers, motors, bearings, lubrication systems, electrical connections, and internal controllers among others. In addition to the risks associated with particle handling such as fouling, caking, segregation, ratholing, etc., these components wear resulting from the use of the equipment. Wear in tooling such as the tablet punches, the leveling changes in the tablet press turret due to equipment age manifest into structural malfunctions. These structural malfunctions that occur due to wear in the individual equipment could result in a change in the information flow between various variables (Venkatasubramanian et al., 2003c). Hence, verification of equipment performance during operations as well as between runs after cleaning cycles is imperative for ensuring reliable conditions of the equipment and implement strategies to avoid the need for unplanned shutdown as well as for robustness in process operations. Real-time monitoring of the equipment components considering potential failure modes could benefit the implementation of system health monitoring tools and proactive maintenance strategies such as Condition-based Maintenance (Ganesh et al., 2018b; OSIsoft LLC, 2017; Vann et al., 2018). Standards such as the ISA-108 Technical Report for Intelligent Device Management (ISA, 2015a)

provides further guidance for configuring intelligent devices such as the equipment and sensors already used in OSD-CM systems.

Progress towards data-driven practices for maintenance management stands to benefit the sustainment and operations of OSD-CM processes. Furthermore, the systematic integration with the process-control and real-time optimization layers to facilitate timely execution of mitigation strategies or when needed, initiate nonconforming materials tracking and control procedures, are important considerations in the design and implementation of robust frameworks for abnormal events management.

2.4.5 Knowledge Management

Knowledge management frameworks for managing the process data and metadata from the OSD-CM process in a systematic manner is vital to support the manufacturing operations management functions and the research and development objectives. The information must be stored in a structured, semantically rich fashion, to begin with, else it becomes costly, and sometimes impossible, to retrieve the desired items of information later, much less in real-time (Joglekar et al., 2017, 2014). Notably, capturing development and manufacturing knowledge and experience at runtime helps improve production and reduce quality events.

A conceptual design of a knowledge management system for a QbD in drug product development was demonstrated as the Knowledge Provenance Management System (Joglekar et al., 2017, 2014). The complete provenance of knowledge was captured by modeling the details of the associated knowledge generation steps as a combination of hierarchical scientific and business workflows. A repository of the process and sensor data along with the recorded metadata of the experiment or production run constitutes the workflow. This systematic recording results in the provenance of information. Automated recording of process and sensor data and timely annotations of troubleshooting activities in a workflow-based repository would provide the information base for process development. In addition, such a library benefits manufacturing intelligence during process operations to provide timely alerts to operators, and further for the development of future products. A workflow also facilitates the ease of access to experimental (or process) data, in addition to the accessibility of information between researchers working in the

same product or process development group at different times. Finally, it could provide the information base for identifying and tracking both lots of good material and lots of nonconforming material. Standards such as the ISA-88 Standard for Batch Control (ISA, 2010b) could benefit from standardizing workflow tasks.

Ontologies developed for pharmaceutical development and manufacturing decision support (Hailemariam and Venkatasubramanian, 2010a, 2010b; Venkatasubramanian et al., 2006) were illustrated in fault detection and diagnosis in a OSD-CM subsystem using roller compaction (Gupta et al., 2013; Hamdan et al., 2012, 2010). Workflows for capturing the knowledge provenance for drug product processing were recently discussed (Joglekar et al., 2014).

2.4.6 Systems Integration

Much has been accomplished since the early 2000s in pursuit of QbD and continuous manufacturing. The systematic development and integration of unit operations, analytical systems, process knowledge, and automation methods has served to raise the visibility and acceptance of modern process systems engineering tools, such as process modeling, online sensing and intelligent monitoring, active process control, fault diagnosis, material tracking, and real-time risk assessment for advanced manufacturing. Recent works in OSD-CM address the integration of the systems from an implementation viewpoint (Bhaskar et al., 2017; Giridhar et al., 2014; Markl et al., 2013; Moreno et al., 2019; Singh et al., 2014; Su et al., 2019a). These conceptual developments in continuous manufacturing have resulted in the demonstration of advanced process control, however, manufacturing operations management functions such as process performance monitoring, deviation management and materials tracking functions further require the vertical integration of the process and local control systems to facility and enterprise systems through reliable information technology platforms.

2.5 Digitalization of Process Operations

Despite the advances in novel technologies and innovative methods addressing these components, the implementation of advanced control in manufacturing facilities face technical and cultural challenges (Collins, 2018; Ierapetritou et al., 2016). The development, implementation,

and operations of these integrated systems are more complicated than operating individual equipment, and the control strategies have become increasingly difficult to maintain due to a lack of knowledge management among early developers, system integrators and implementers. Moreover, the palette of computer tools deployed for these functions, which could often be geographically distributed across a site require considerations for systematic data architecture. In addition, the lack of enabling technologies and standardization for data management and information technology are among the critical bottlenecks in implementing advanced process control in pharmaceutical facilities (Romero-Torres et al., 2017). Moving forward, with the increase in assessment, adoption, and development of OSD-CM systems to address business objectives, as well as the developments towards plug-and-play systems and a vision of facility control rooms in pharmaceutical manufacturing, a unified effort towards implementation and manufacturing operations management functions is essential. Some of the expectations and ensuing challenges for further advancing the manufacturing readiness level of enabling technologies for advanced manufacturing in pharmaceutical processes can be addressed by leveraging the cross-industry advances and best practices in industrial automation.

Smart Manufacturing and related ongoing industrial automation evolutions such as Industry 4.0 have the potential for implementing the technological developments in pharmaceutical manufacturing through the application of state-of-the-art process operations tools, architectures and automation methods. As pointed out in (Moyne and Iskandar, 2017), the progress in IT systems integration and automation have been critical for the progress of semiconductor manufacturing, an industry that has some parallels with pharmaceutical manufacturing in requiring precision manufacturing, with high expectations for product quality, while also meeting challenging safety and profitability targets. Moreover, the decades of learnings in the implementation of automation systems in chemical processing industries captured in multiple International Society of Automation (ISA) standards can be leveraged to leapfrog the old generation of process data management tools and structures in pharmaceutical manufacturing with state-of-the-art implementation using new tools and architectures. For example, architectures following ISA-95, ISA-99 and ISA-108 provide the ability to make asset data available for relevant manufacturing operations management analyses in real-time by facilitating connectivity between isolated functional groups across hierarchies.

3 APPLICATION OF X-RAY SENSORS FOR MASS FLOW RATE IN CONTINUOUS TABLET MANUFACTURING

3.1 Introduction

Previous work in the research group identified SETXVue XP-300, designed by En'Urga Inc. (West Lafayette, IN), as a potential inline and non-invasive particulate mass flow rate sensor. In this chapter, the sensor study for utility in OSD-CM with model materials and flow rates as used in our pilot scale advanced manufacturing testbed for OSD-CM is described. The offline study for sensor integration is published as a peer-reviewed journal publication (Ganesh et al., 2017). Additional developments for the integration of the sensor into the pilot plant is discussed. Notably, this work was the first application of an inline sensor for mass flow measurement in OSD-CM.

3.1.1 Requirement of mass flow sensor

Continuous downstream tablet manufacturing integrates multiple unit operations for solid handling and processing of crystallized and dried drug substances, excipients, lubricant etc. into tablets. Excipients and the active pharmaceutical ingredient (API) are fed into a continuous blender using loss-in-weight (LIW) feeders. Appropriate selection and setup of LIW feeders is extremely important to have consistent blend uniformity and feed into the downstream unit operations(Cartwright et al., 2013; Engisch and Muzzio, 2012). The powder blend is then fed continuously into a tablet press for compaction. Blend uniformity, material handling and blend compaction properties are key challenges in processing dry powders. To address these challenges, additional unit operation of dry or wet granulation may be employed prior to tablet compaction.

The stream flow rates are key process variables in a continuous processing line and inline measurements of the same are critical for monitoring the throughput, residence time, equipment holdup, fouling, leakage and thus, the desired operation of the process. In-line mass flow rate measurement of the particulate material in continuous tablet manufacturing is critical at two locations – the exit of the API-excipient feeder-blender system and the entry of the tablet press.

The material composition and the mass flow rate are the control variables for the feeder-blender process, in order to implement a ratio control structure that would ensure blend uniformity (Su et al., 2017). This flow rate at the exit of the blender is ideally the sum of the flow rates from the LIW feeders, and the composition can be calculated from the ratio of the flow rates. The throughput from LIW feeders, however depends on the tuning of the feeders done at a set flow rate, for a given composition. This also requires appropriate selection and operation of the screw conveyor and internal attachments of the LIW feeder. In addition, an appropriate averaging time for the loss of material mass in the feeder hopper that are measured using load cells is essential, which is again material dependent. Variations in bulk density of the powders in the feeders owing to a new lot of raw material or added glidant in the system, could result in a variation or a change in the actual flow rate into the blender. In addition, measurement redundancy is essential in continuous processing for gross error detection and data reconciliation, an important data analysis step in real-time process management(Narasimhan and Jordache, 1999). Because of the variations of the throughput from the LIW feeders, and the dynamics of the blender, inline monitoring of the control variables viz. the flow rate and composition, at the exit of the blender is critical for ensuring process measurements with minimal error, and hence a robust control structure.

The exit flow rate from the blender is a disturbance variable for the downstream processes, both for the tablet press in a direct compaction line or for granulation processes. In addition, transforming an existing tableting setup to a continuous plant may require use of belt conveyors and other material conveying lines, as end-to-end gravity flow between all units in the facility may not be feasible. This results in additional time delays and possible variations in material bulk density at the tablet press inlet. Hence, monitoring the flow disturbances at the tablet press inlet is crucial for furthering the design of robust feedforward control structures. For processes incorporating dry or wet granulation, the mass flow rate at the inlet of the tablet press must account for the dynamics of the granulation process, and thus measuring the flow rate is imperative at the exit. Moreover, monitoring the mass flux in continuous processing is critical for material tracking through the system in addition to the development of control system designs for ensuring robust process performances.

3.1.2 Mass flow sensors

Volumetric flow measurement of particulate streams is challenging as the bulk density of the particulate stream depends not only on material properties but also on storage and transportation of the material and its processing history(Hopkins, 2006). A direct mass flow measurement accounting for the variations in bulk density is extremely important when one considers the limited holdup volume of the equipment downstream (Su et al., 2017).

Mass flow rate measurement of particulate material is more challenging than fluid stream measurements because of the complex properties of particulate streams. As a result, this is typically achieved by indirect methods such as impact measurement, optical measurement and radiation measurement (Grift, 2003). In such methods, the mass flow rate is evaluated as $Q(t) = A * \rho * \beta(t) * v(t)$, where A is the cross-sectional area of the conduit, $\beta(t)$ is the solids loading in the system, $v(t)$ is the velocity of particle flow and ρ is the true density of the particles(Yan, 1999). The solids loading of the system is essentially the cross-sectional area occupied by moving solids normalized with respect to the conduit cross sectional area.

Impact measurement, optical measurement and radiation measurement techniques are some of the methods used for inline mass flow rate measurement of particulate material. Because of the vibrations that can arise from the operation of feeders, blender and tablet press and the occurrence of materials with wide particle size and shape distributions, impact measurement and optical measurement may not be as robust as radiation-based methods for flow rate monitoring in a pharmaceutical tableting line. Radiation methods have the advantage of being non-invasive and not having moving parts; however, they require appropriate safety arrangements and infrastructure. In radiation sensing, a constant level of radiation in the form of microwaves, x-rays or γ-rays is measured in the conduit. The measured intensity level decreases during flow, in comparison to absence of any mass flow. This intensity can be assumed proportional to the mass flow density and is independent of the particle size distribution within the beam, assuming relative uniformity in the material true density. Soft x-ray fields can penetrate the tube material and yield reasonably high radiation attenuation, making the system applicable to measuring the particulate flow in the tableting system, which have solids loading at about 2%, making it essentially a dilute-phase conveying system. The transmitted intensities of the electromagnetic waves after attenuation by

particulate flow and without any material flowing obey Beer-Lambert's law which relates it to the material properties and the planar concentration of material (Yan, 1999).

3.1.3 Purpose

The current work discusses the feasibility of using an x-ray-based sensor for real-time mass flow rate monitoring of dry powder blends and granules using offline steady state conditions. The conditions and formulation of the powder blends are such as arise in pilot scale continuous tablet manufacturing facilities. The manuscript also discusses the working principle of the sensor, and the measurement precision and accuracy observed at these conditions. To the authors' knowledge, the use of a radiometric sensor as a PAT tool for in-line mass flow rate monitoring in continuous tablet manufacture has not been previously reported.

3.2 Materials and equipment

3.2.1 Materials

Acetaminophen (APAP) Grade 0048 (courtesy Mallinckrodt, NC, USA), Avicel microcrystalline cellulose (courtesy FMC BioPolymer, PA, USA) grades PH-102 (MCC-102) and PH-200 (MCC-200), lactose monohydrate grade 310 (courtesy Kerry Inc., WI, USA), magnesium stearate and silicon dioxide in varying proportions are used to evaluate the performance of the sensor. 2 kg blends consisting of the desired quantities of excipient and APAP are blended offline in a 5L Tote bin blender at 16 rpm for 15 minutes. Lubricant or glidant is then added and blended for further 5 minutes. Powder blends comprising of the excipient and APAP are processed to granules using Alexanderwerk WP120x40 roller compactor at 10 kg/h flowrate, with compaction pressure of 50 bar and milling speed of 45 rpm. True density of the powder blend and granules are measured using AccuPyc II 1340 pycnometer (Micrometrics Instrument Corp., Norcross, GA), with helium as the displacement fluid.

3.2.2 Sensor description

The SETXVue XP-300 mass flow meter used in this work is designed by En'Urga Inc., (West Lafayette, IN) and has been demonstrated to effectively measure the flow rate of food grains, slurries and other multi-phase systems (En'urga Inc., 2014). The instrument is comprised of a soft

x-ray point source (10-50 keV) at one end while the other end has an array of horizontal sensors for obtaining total planar concentrations and an array of vertical sensors for obtaining the particulate flow velocity, in a divergent beam geometry configuration, as shown in Figure 3-1. Beam hardening may increase the uncertainty of measurement; however, the effect of beam hardening is small as long as the x-ray attenuation is about 5%. Appropriate physical arrangements for minimizing effects of beam hardening is made in the lead encased aluminum container that houses the equipment. The sensor measurement frequency is 1000 Hz and a suitable sampling time required for mass flow monitoring of particulate systems can be defined.

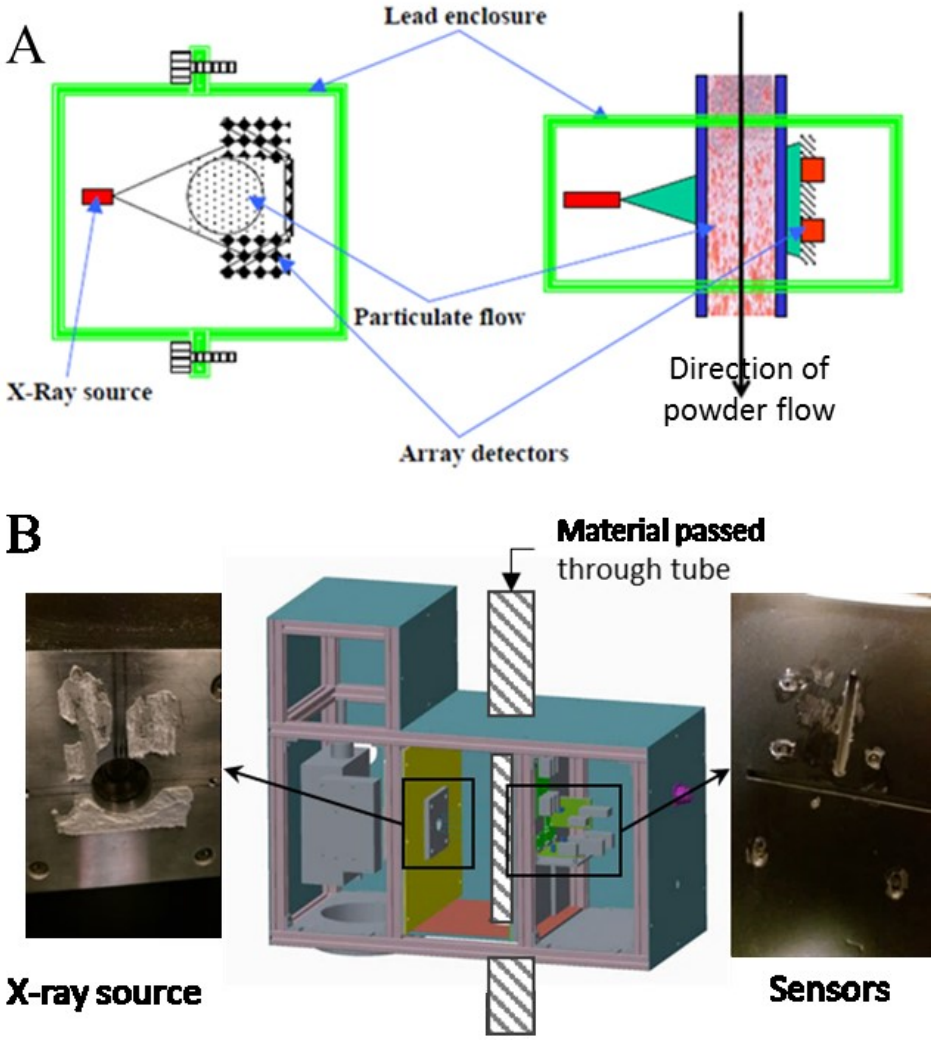


Figure 3-1: Schematic representation of the x-ray sensor SETXvue XP-300, En'Urga Inc.

The horizontal arrays measure the X-ray absorption, which is related to the material flowing through the system following Beer-Lambert's law, as given in Eq. 3-1.

$$\frac{I}{I_0} = \exp\left[-\left(\frac{\mu}{\rho}\right)x\right] \quad \text{Eq. 3-1}$$

Where I_0 and I are the intensities of incident and transmitted x-ray waves respectively, x is the mass thickness that relates to the effective thickness of the material traversed along the wave and μ/ρ is the material dependent mass attenuation coefficient. For a given x-ray energy level, the mass attenuation coefficient can be evaluated according to the chemical composition of the compound as a weighted average of the mass attenuation coefficients of the constituent elements (Hubbell and Seltzer, 2004). The signals from the array of horizontal sensors are integrated according to the Eq. 3-3 to obtain the total mass/unit length, with r being the radius of the conduit and -R to R defining the extent of flow. This integrated thickness as measured by the sensor is further analyzed as the absorption value, corresponding to the material and the flow rate.

$$\frac{I}{I_0} = \exp\left[-\left(\frac{\mu}{\rho}\right)x\right] \rightarrow\ x = -\frac{\ln\left(\frac{I}{I_0}\right)}{\frac{\mu}{\rho}} \quad \text{Eq. 3-2}$$

$$Integrated\ Thickness: \int_{-R}^{R} x dr = \int_{-R}^{R} \ln\left(\frac{I}{I_0}\right)\left(-\frac{\rho}{\mu}\right) dr \quad \text{Eq. 3-3}$$

The vertical sensors are primarily electrodynamic sensors that are at known distances apart from each other. The transit time taken by the particles from the upstream sensor to the downstream sensor is measured by cross-correlating the absorption signals using a signal correlator. This yields the velocity measurement for the stream of particles. A detailed description on the working of cross correlation velocimetry is succinctly presented in (Yan et al., 1995).

The equipment is subject to measurement errors resulting from the geometry, system design, calibration, material flow properties and the flow rate of the material through the system. (Mennell et al., 2000) identify and describe the errors of measurement from a radiometric sensor. The current study evaluates the feasibility of SETXvue XP-300 as designed and made available by En'Urga Inc. for use in real-time monitoring of flow rate for powder blends and granules.

3.2.3 Experimental Setup

The adaptation of sensors for real-time measurements in an industrial setting requires understanding of the dynamics of the attribute being monitored, which is not straightforward and requires a systematic study for calibration (Ierapetritou et al., 2016). The assessment of the utility of the x-ray sensor for measuring mass flow rate in real-time includes an experimental setup which consistently feeds particulate blends, collects x-ray absorption and velocimetry data from the sensor, measures the actual flow rate and analyzes the data to obtain the relationship between the sensor measurements and the actual flow rate. This offline arrangement mimics the setup in a continuous tableting line, where the flow rate of powder blends at the exit of the feeder-blender system or that of granules requires measurement. The mass flux of the particulate stream is proportional to the product of velocity with the effective planar mass concentration estimation from the horizontal sensors,

$$Q \propto velocity * x - ray\ attenuation \qquad \text{Eq. 3-4}$$

The study was carried out in a standalone setup. The powder blends and granules prepared offline are loaded into the hopper of the loss-in-weight feeder (KT-35, Coperion K-Tron, Inc., Pitman, NJ). The material is fed into a nylon 6,6 tube of 0.75” or 1” outer diameter and 0.0625” thickness that is passed through SETXvue XP-300 for monitoring the mass flow rate. This arrangement ensures dilute nature of the flowing material for precise measurements from the sensor. A Mettler-Toledo ME 4001E weighing scale was used at the exit of the sensor to provide an independent measurement of the actual particulate flow rate. The experimental system, as shown in Figure 3-2, is also used to calibrate the mass flux sensor and to predict flow rates, which are within the calibration range. The assessment of the LIW feeder performance is beyond the scope of this work.

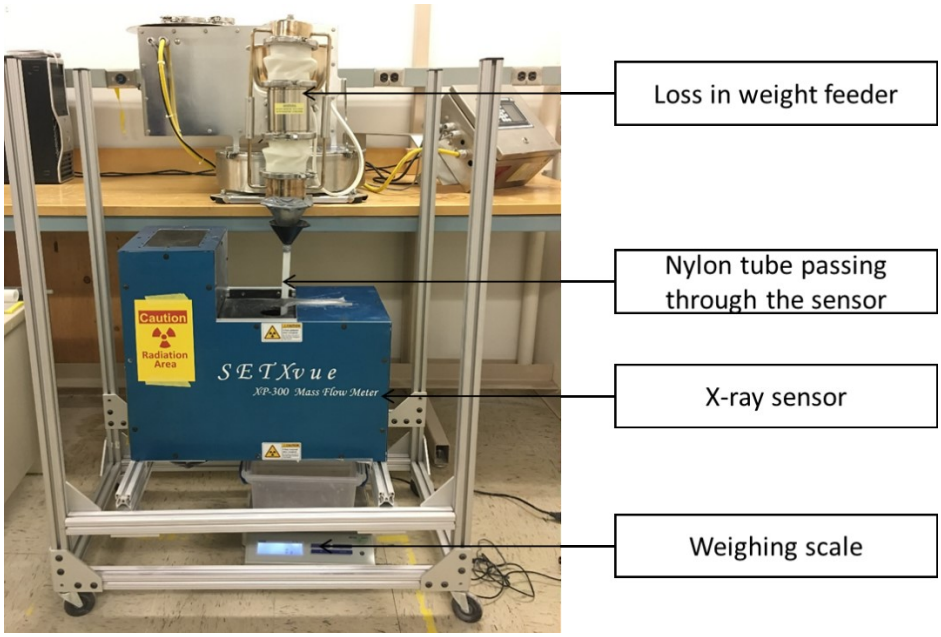


Figure 3-2: Off-line setup of the x-ray sensor for understanding the usability for inline mass flow rate monitoring in a continuous tablet manufacturing line

3.2.4 Procedure for sensor monitoring

The x-ray attenuation and velocimetry results are determined using SprayQC, a Microsoft Foundation Class based software developed by En'Urga Inc. that accompanies the equipment. The x-rays are generated at 30 keV and 0.8 mA. A background reference with no particulate flow is carried out and averaged over 5 seconds. The measurements are recorded in real-time every second using a National Instruments data acquisition board with a TCP/IP connection to MATLAB. Given the use of a loss-in-weight feeder, the flow rate of the powder blend in the tube passing through the sensor is assumed to be at steady state. The average flow rate determined from the weighing scale measurement is used for calibrating the sensor to enable prediction of an unknown flow rate.

The general procedure for flow monitoring using the sensor is as follows:

1. Establish background reference with no material flow through the sensor.
2. Feed material using LIW feeder and collect material at the exit of the sensor on a weighing scale to independently monitor the actual flow rate through the sensor.

3. Start real time monitoring available on SprayQC software and monitor the x-ray attenuation and velocimetry for 30 seconds, with measurements collected at every 1 second.

3.2.5 Analysis of sensor data

The x-ray attenuation and velocimetry data is obtained at 1 second intervals from the sensor using the SprayQC software. The data is recorded in Matlab using a TCP/IP connection setup for 30 seconds, assuming the powder/granule flow is at steady state during that time interval. The data is used as collected or by averaging every two, five or ten seconds to check the measurement variation of the sensor over the 30 seconds of monitoring. The relative standard deviations of the x-ray attenuation and velocimetry data for a given time average are computed and recorded. The flow rate recorded using the catch scale is calibrated to the 30 second averaged data.

Using the relationship of the sensor measurements, the actual vs predicted flow rate of the calibration data is presented. The calibration can then be used to predict flow rate of steadily flowing material for an *unknown* flow condition. The root mean square error of the calibration and prediction data sets are computed and reported.

3.2.6 Conditions examined

The materials and flow rates used for evaluating the sensor are of interest to the continuous tablet manufacturing studies being conducted in the pilot plant facility at Purdue University. The composition of the powder blends and their purpose are described in Table 3-1. Three LIW feeder set points are used for demonstrating the precision of the sensor and calibration. The flow rates at these set points are measured using the weigh scale for each condition. Additional LIW feeder set points are used for predicting the flow rate using the sensor measurements and the appropriate calibration.

Table 3-1: Blend compositions and their purpose for the study

Blend Composition	Abbreviation Used	Purpose
100% MCC-200	PH0-(1)	Effect of multiple passes of material Real time flow monitoring
0, 2, 5, 10% APAP + MCC-200	PH0-(2), PH2, PH5, PH10-(1)	Effect of small changes in composition
0, 10, 25% APAP + MCC-200	PH0-(2), PH10-(2), PH25	Effect of tube diameter
10% APAP + 0.5% MgSt + MCC-200	PH10-L	Effect of addition of lubricant
10% APAP + 0.2% SiO_2 + MCC-200	PH10-G	Effect of addition of glidant
10% APAP + MCC-102	G10	Effect of granular material Real time flow monitoring
10% APAP + MCC-200	PH10-(3)	Real time flow monitoring
10% APAP + 45% Lactose + 45% MCC-200	LP10	Effect of poorly flowing and sticky material

3.3 Results and discussion

3.3.1 Sensor measurements

The sensor measurements of the x-ray absorption and velocimetry of the flowing material are captured in SprayQC. Measurement of the x-ray attenuation is displayed as an absorption plot, which indicates the integrated mass thickness of particulate presence along the path of the x-rays. This measurement represents the cross section averaged solids loading of flowing material in the sensing window. A cross-correlation velocimetry plot for velocity measurement in the conduit is also recorded.

Representative sensor measurements for x-ray attenuation and velocimetry obtained every second using blends PH10-(3) and G10 are displayed in Figure 3-3A and 3-3B respectively. The flow rate of blend PH10-(3) ranges from 6 to 10.5 kg/h and that of G10 ranges from 10 to 17 kg/h. The real time velocimetry plots for PH10-(3) and G10, as shown in Figure 3-3, indicate good precision in velocity measurements for the entire range of flow rates observed. Precision in a 30 second averaged velocity for all the flow rates observed for a given material is evident as a relative standard deviation of under 3% is observed for both powder blends and granules, as indicated in Figure 3-4. This is intuitively expected for a given material in a given physical setup, as the

particulates are free falling and would have attained the same terminal velocity in the sensor window. Possible variations might arise by virtue of the drag caused by varying particle sizes, collisions with other particles and the presence of any obstructions in the path of flow. The absorption for G10 and PH10-(3) as shown in Figure 3-5, demonstrate the real-time measurement for two of the feeders set points for each condition for 30 seconds of monitoring. The x-ray absorption can be observed to be dependent on the flow rate of the particulate stream. As expected, an increase in x-ray attenuation is observed with an increase in the particulate flow rate, as a result the presence of additional material in the sensor window. The figure also indicates the precision in average attenuation for flow rates at the same feeder set point that results in a similar throughput of the materials handled.

Theoretically the mass attenuation coefficient of a compound could be calculated using a weighted sum of the elemental mass attenuation coefficients (Hubbell and Seltzer, 2004). However, a direct measurement is used in this study. The attenuation coefficients are computed at 30 keV, the condition at which the sensor is used at our facility. The blend compositions used in this study have similar mass attenuation coefficients. The positioning of the tube in the sensor also determines the velocimetry and absorption measurements in accordance with the divergent beam geometry assumptions. A linear relationship for the same is used in the sensor's model. Hence, the mass attenuation coefficient along with the dependence on the setup can be lumped together and determined experimentally.

The true densities of the material blends used in the study are in the range 1.52±0.03 g/cc. In addition, the sensor measurements for x-ray attenuation and velocimetry in a fixed physical setup indicate the linear dependence of the particulate flow rate on the x-ray attenuation for a given material, with velocity nearly constant for a given material. Considering marginal variation in the true density of the materials for a given blend composition, and the velocimetry precision for a given setup, the sensor calibration can thus only reflect the dependence of the flow rate on the corresponding x-ray attenuation. However, real-time velocity monitoring enables monitoring disturbances, such as no flow or material buildup in the conduit.

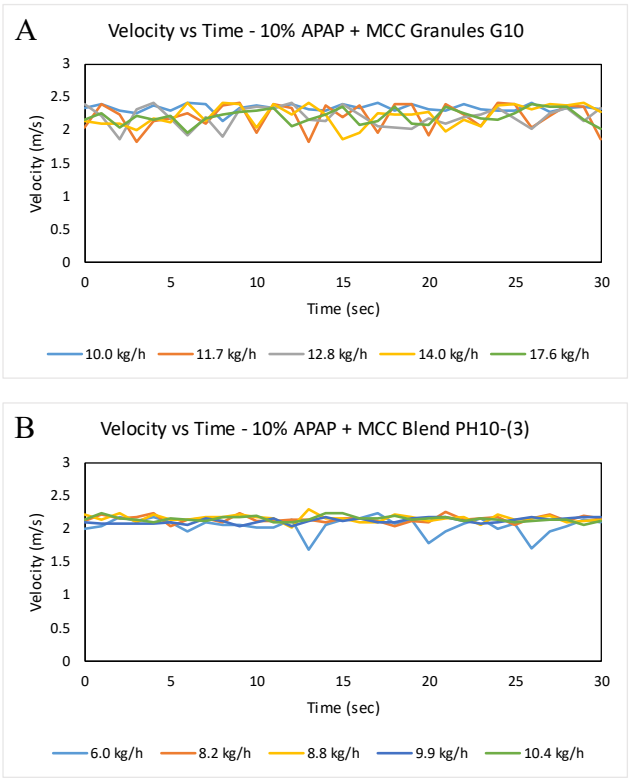


Figure 3-3: Representative sensor velocity measurements over 30 seconds. A: 10% APAP + MCC PH-102 granules G10; B: 10% APAP + MCC PH-200 blend PH10-(3)

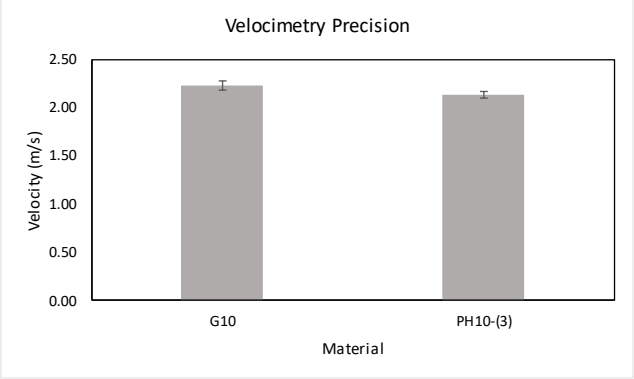
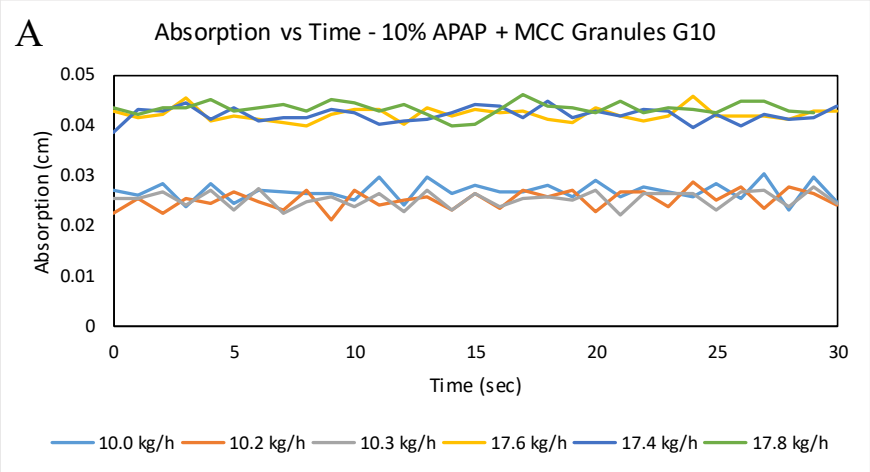


Figure 3-4: Average velocity measurements for G10 (19 samples. Flow rate 10 to 17 kg/h) and PH10-(3) (19 samples. Flow rate 6 to 10.5 kg/h)



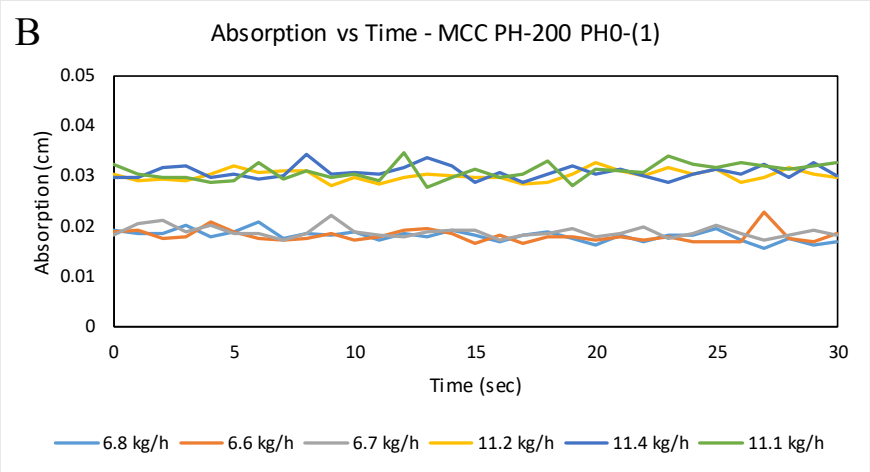


Figure 3-5: Representative sensor absorption (x-ray attenuation) measurements over 30 seconds. A: 10% APAP + MCC PH-102 granules G10; B: 0% APAP + MCC PH-200 blend PH0-(1)

The variation in x-ray attenuation decreases with an increase in the measurement averaging time to 2, 5, 10 seconds, which is calculated by averaging the sensor observations from the said number of previous observations, as intuitively expected and as shown in Figure 3-6. Averaging the measurements over an increased time window reduces the variability in the sensor measurement and this is particularly important at flow rates that do not result in a continuous stream of solids, or cohesive materials that result in irregular particulate flow. However, given the fast dynamics of the continuous tableting line, an in-line monitoring system with an averaging window of less than 5 seconds is desired for process control implementation and a trade-off for measurement precision with real-time measurement availability is necessary. Quantification of the

relative standard deviation for x-ray attenuation at a given flow rate depends on the material flow properties and the dynamics of the feeder used in the system. A representative measurement relative standard deviation plot for G10 with three observations at each of the mentioned flow rates is shown in Figure 3-7. A careful assessment of the relative standard deviation is important in every individual setup, as the sensor measurements are affected by the physical location of the sensor and the dynamics of the stream at the inlet of the sensor. This emphasizes the requirement to experimentally evaluate the sensor to capture the dynamics of every individual sensor application, for obtaining robust flow rate measurements during operation.

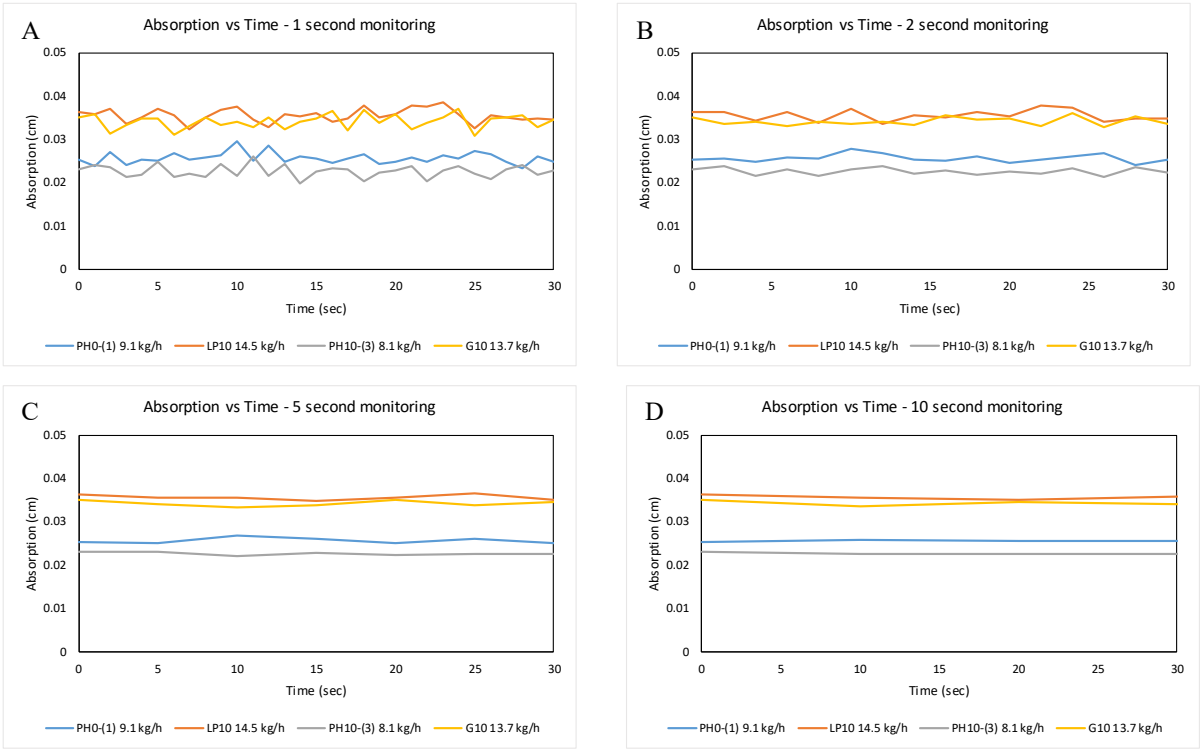


Figure 3-6: Effect of increasing sampling time on monitoring variations

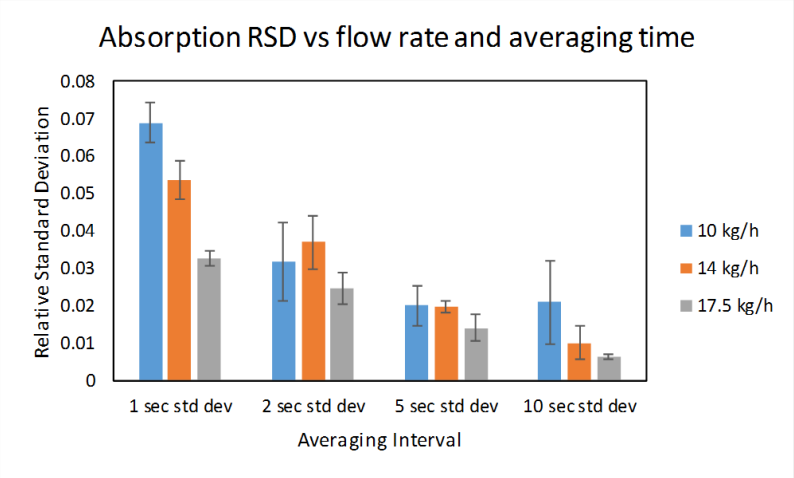
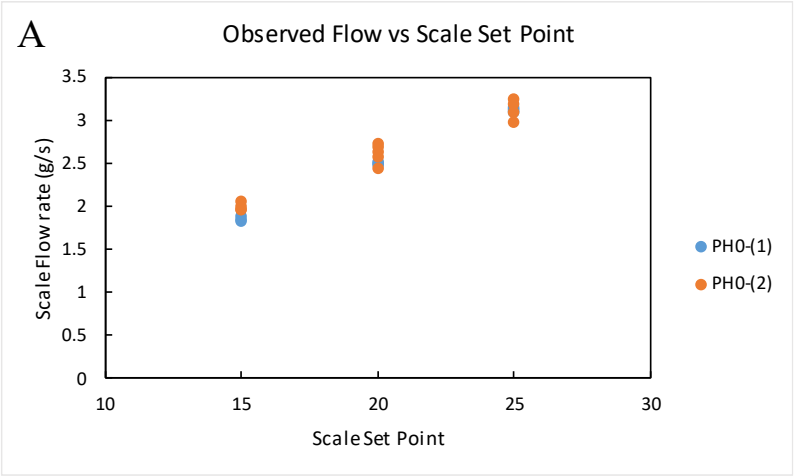


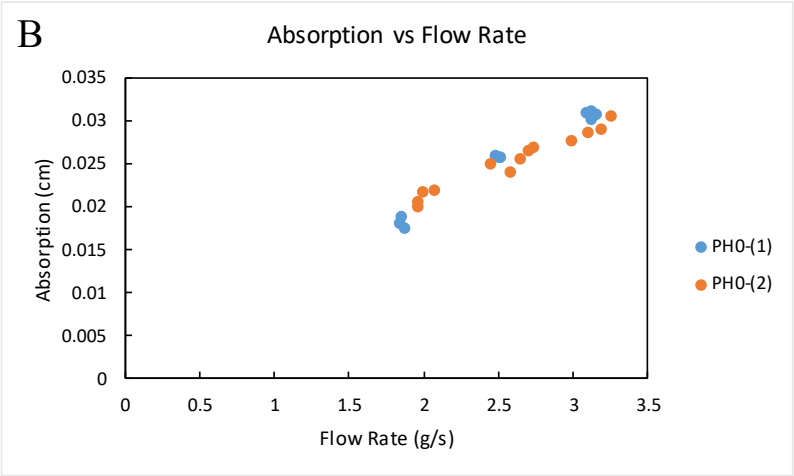
Figure 3-7: Changes in measurement RSD based on sampling time. Material displayed: G10

3.3.2 Effect of reusing material for calibrating the sensor.

Effects of multiple passes of the powder or granular blend on the measurement of the x-ray attenuation is investigated using MCC -200. Multiple passes of the powder are carried out by collecting and refilling the LIW feeder hopper with the material. Reuse of material can result in a change in the flow properties of the blend. This is evident from the variation in the actual flow rate of the feeder at the same set point, as shown in Figure 3-8A.

The change in flow rate through the feeder however does not affect the x-ray absorption measurement of the particulate stream, as shown in Figure 3-8B. The x-ray absorption of powders with a single pass and multiple passes does predict the flow rate of the particulate stream with acceptable variation, as shown in Figure 3-8C. The RMSE for single pass and multiple pass are 0.0874 and 0.0851 g/s respectively, with R^2 of approx. 0.97 for both indicating that the sensor captures the actual flow rate through the system, irrespective of the minor changes in material properties caused by multiple passes. This observation is particularly important for pharmaceutical industry applications as the reuse of materials for calibration of PAT tools is desirable to minimize consumption of API during development.





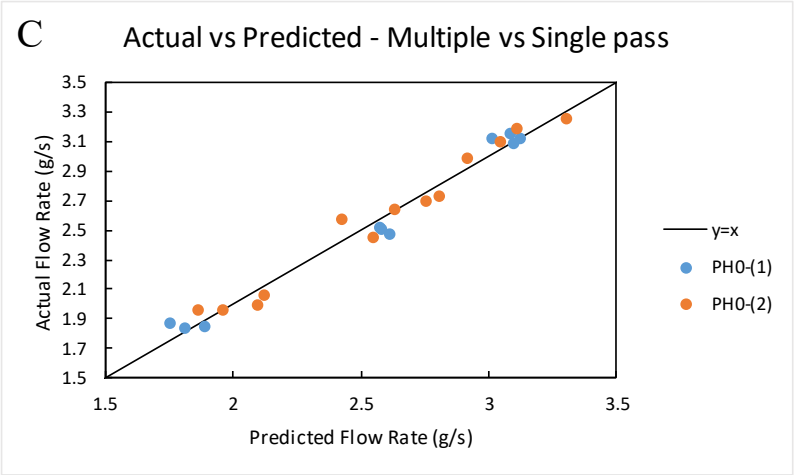


Figure 3-8: Effect of reusing material for sensor calibration

3.3.3 Composition variation

Blending of the powders fed using LIW feeders is a crucial unit operation required to achieve consistent blend uniformity. The dynamics of the LIW feeders, blender and the ratio control structure could result in variation in the composition set point of the mixing operation. APAP compositions of 0, 2, 5 and 10 wt% with MCC-200 are used to detect the dependence of the sensor performance on changes in composition. A composition change in the range considered does not significantly change the mass attenuation coefficient of the blend. In addition, as the velocity of the materials at the sensor window is similar, the system should not have a dependence on the blend composition.

Changes in the APAP composition of the blend do alter the flow properties of the blend, with reduced flowability at higher concentrations of APAP. This change in flow properties can be observed in Figure 3-9A, where the throughput of the LIW feeder at the same set point improves with better flowing material. This observed flow rate dependence on the composition emphasizes the requirement of material dependent tuning for the LIW feeders. The variation in material composition however does not affect the x-ray absorption measurement of the particulate stream, as shown in Figure 3-9B. The RMSE for sensor calibration for the blends considered individually and as a single sample is summarized in Table 3-2. Similar RMSE indicates the sensor's inability to distinguish the variation in composition of the material blend. The x-ray absorption of 0 to 10% APAP blends with multiple passes, when considered together as a single sample, predict the flow rate of the particulate stream with acceptable variation and an R^2 of approximately. 0.95, as shown in Figure 3-9C. This observation indicates the need for additional sensors to measure the composition of the stream exiting the blender unit for the implementation of a robust control system.

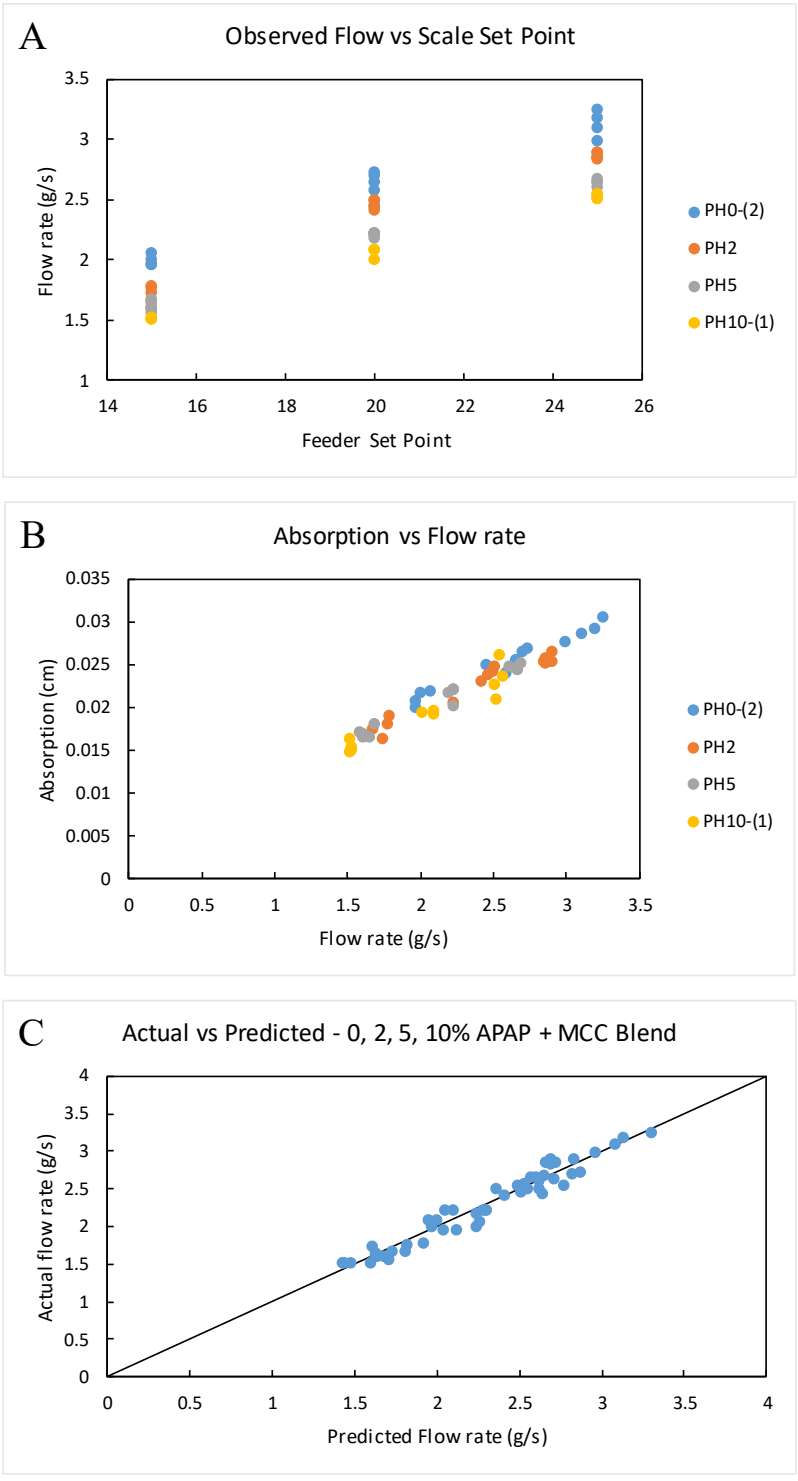


Figure 3-9: Effect on sensor performance considering operational variations in the composition

Table 3-2: RMSE for variations in composition

Material	RMSE (g/s)
PH0-(2)	0.08
PH2	0.11
PH5	0.08
PH10-(1)	0.14
All together	0.11

3.3.4 Tube diameter

The sensor measures particulate flow in dilute phase (solids loading less than 2%) by monitoring the x-ray attenuation by virtue of presence of material. A low solid loading under free falling conditions in the conduit ensures charge retention in the system for velocimetry measurements, avoids tube blockages due to particle cohesions and retains the flow properties of the particulates. A suitable tube diameter for the setup is essential to maintain the suggested conditions for radiometric sensors (Mennell et al., 2000). Material handling observations suggested use of 0.75" and 1" tube diameters for flowing materials through the x-ray sensor for the range of mass flowrates considered in this study. The measured flow rate is calibrated to the average x-ray absorption for 30 seconds of flow for 0%, 10% and 25% APAP with MCC-200. The plot comparing the actual flow rate to the predicted flow rate by considering the change in tube diameter is presented in Figure 3-10, with R^2 for each of the curves greater than 0.92. The plot confirms the expectation that where materials with similar true densities flowing at near constant velocities would have similar x-ray attenuation that does not vary with tube diameter. However, the diameter should not be too large such that the assumptions of divergent beam geometry would be violated. Moreover, the setup has to ensure that both powder materials and granules flow steadily through the conduit and do not accumulate inside the conduit given the tendency of powders to stick the walls.

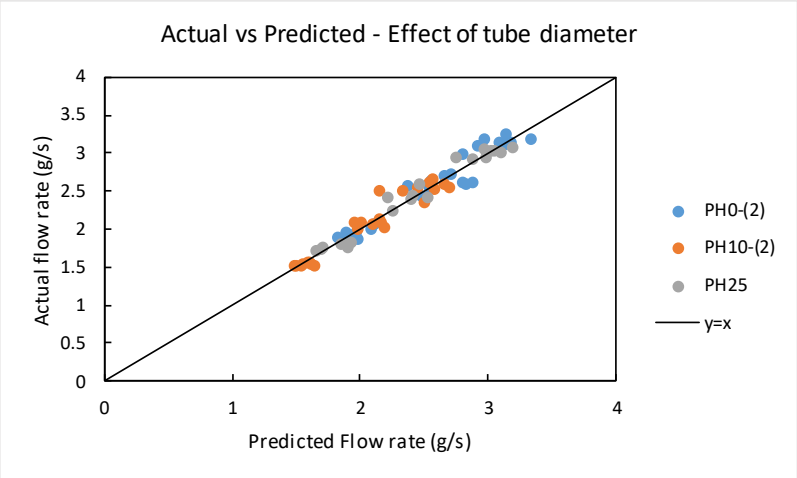


Figure 3-10: Effect on sensor calibration for change in tube diameter

3.3.5 Presence of lubricant or glidant

The addition of lubricants and glidant is often necessary in formulations to assure the manufacturability of the oral solid dose. 10% APAP with MCC-200 is used to compare the performance of the x-ray sensor in presence of such additives. An important reason to add such additives is to improve the handling and processing of the blend into tablets.

The addition of the lubricant or glidant at 0.2-0.5 wt% changes flow properties, which can be observed from the throughput from the LIW feeder, as shown in Figure 3-11A. However, the presence of the additives in the mentioned concentration does not significantly change the mass attenuation coefficient of the blend. Thus, this change in material composition does not affect the x-ray absorption measurement of the particulate stream, as shown in Figure 3-11B. The presence of lubricant or glidant can change the feeder dynamics, thus, emphasizing the need for robust particulates transport system design and careful tuning of LIW feeders. Given the insensitivity to composition, the use of additional composition sensors is necessary to implement supervisory control of the integrated tableting process.

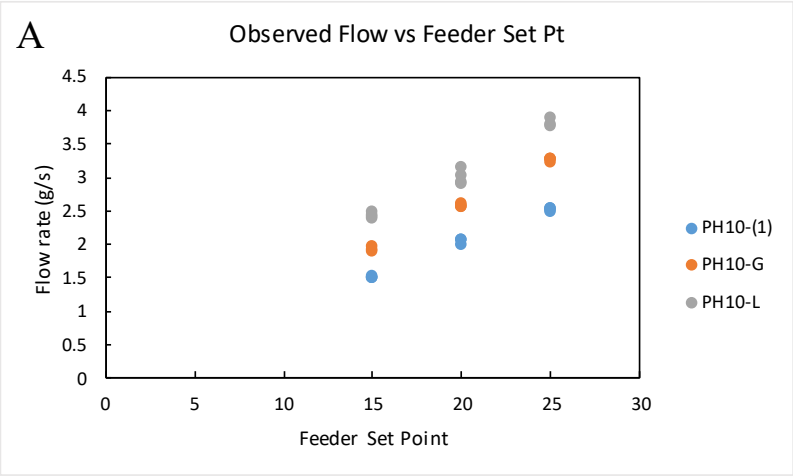


Figure 3-11: Effect of sensor measurement on addition of lubricant or glidant to a given blend

3.3.6 Measurement accuracy

Accuracy in flow prediction and the limits of detectability of mass flow rate are important factors in establishing the utility of the equipment as a sensor in the continuous tableting line. Three flow rates each of MCC-200 (blend PH0-(1)), 10% APAP blended with MCC-200 (blend PH10-(3)) and granules comprising 10% APAP and MCC-102 (G10) are calibrated to the corresponding 30 second averaged x-ray attenuation, monitored every 1 second. Additional flow rates using 1-3 different LIW feeder set-points are predicted using the 30 second averaged x-ray attenuation monitored every 1 second and the calibration equation. The predicted flow rates of these additional flow rate conditions are compared with the corresponding weighing scale measured flow rates, as shown in Figure 3-12. From the figure is evident that there is a satisfactory agreement in the flow rate monitored by the x-ray sensor, with calibration R^2 values greater than

0.92 and deviation of predicted flow rate within 5% of the actual flow rate for the materials and the conditions used in the study. The deviation in sensor monitored flow rate from the actual flow rate depends on the measurement standard deviation, the calibration curve, the accuracy of the weighing scale used for the calibration setup and the overall dynamics of the particulate flow. Materials with better flow properties and handling capabilities have a lower deviation from the actual measured flow rate.

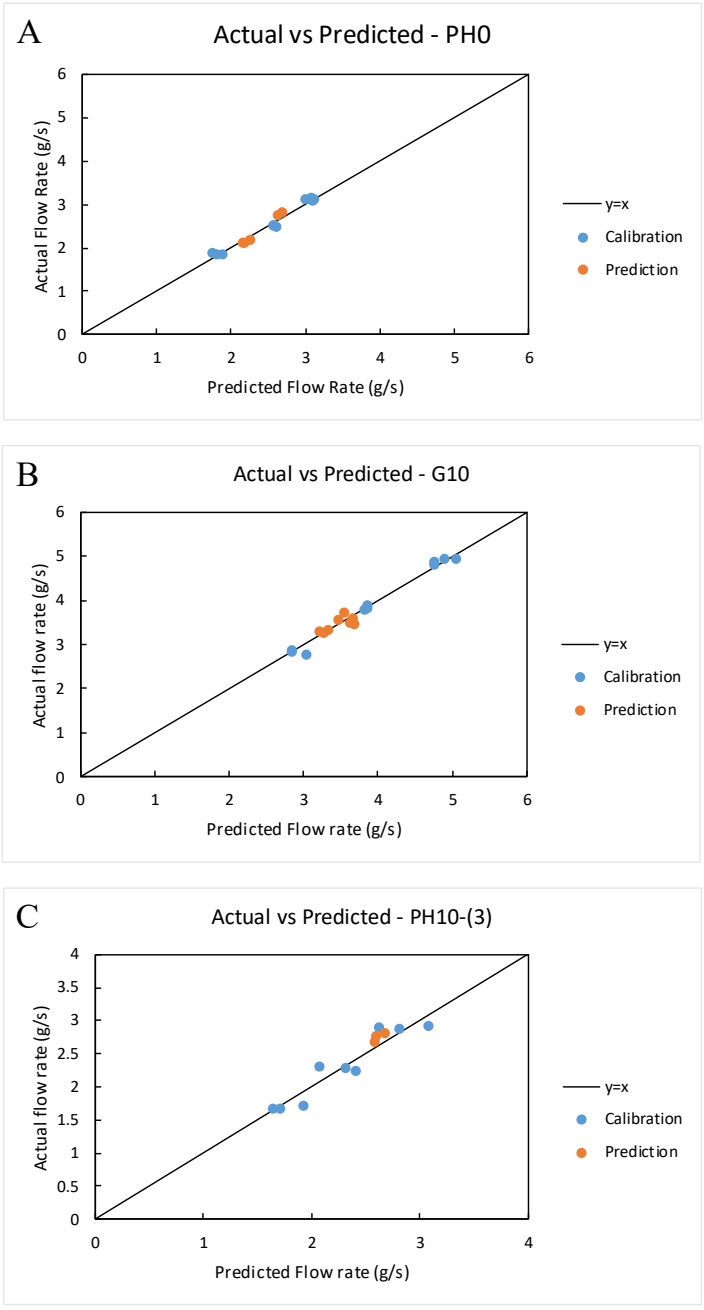


Figure 3-12: Prediction of flow rate using a calibration for a given material

The sensor measures the x-ray attenuation of the flowing material and this is calibrated to known flow rates at-line, in order to monitor the flow rate in-line. However, depending on the dynamics of particulate flow through the sensor, the ability to detect flow rate changes for a given material has to be assessed. This depends on the variation in absorption measurement, which is material dependent in addition to the averaging time of the measurements that are collected every second. Using the absorption measurements averaged over 30 seconds and the corresponding sample standard deviations, we can determine if the measurements are able to distinguish between flow rates, using a t-distribution test statistic. As the relative standard deviation at 1 second monitoring depends on the flow rate of the material as seen in Figure 7, the analysis considers the two sample variances to be not equal. This analysis shows that for 9 observations for each material, with 3 repeats at 3 different flow set points, using 30 second averaged x-ray absorption measurements collected at every 1 second, a flow rate change of approx. 0.3 kg/h can be detected for G10 granules and PH0-(1), as shown in Figure 13. However, for LP10, a lactose blend having poor flow properties than G10 or PH0, a change in flow rate of approx. 0.45 kg/h flow can be statistically detected. It is worth noting again that the difference in flow rate monitoring is at steady state flow. A detailed study of in-line mass flow monitoring including detection of changes in flow rate to observe real-time flow dynamics of particulate flow in the tableting line is the key objective of the future work associated with the sensor. Such a study would bolster the case for the integration of the sensor for supervisory control of the process.

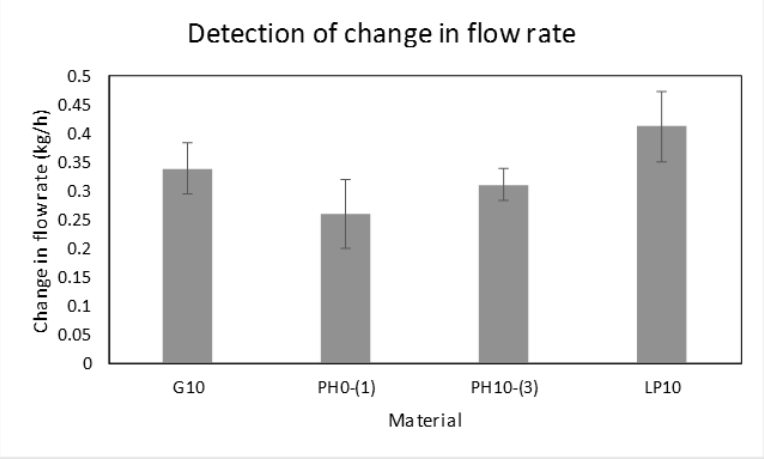


Figure 3-13: Detection of change in flow rate for a given material.

3.4 Inline Monitoring

The offline study demonstrated the ability to utilize the sensor in the integrated tableting line for future implementation of real-time process management. The important takeaways from the offline study for use in the integrated tableting line were that the measurement obtained from the mass flow sensor depends on the actual flow rate of the material, the blend flowability inside the tube passing through the sensor and the physical setup that affects the dynamics of particulate flow, in addition to the X-ray parameters. The sensor measurement captures the overall variation arising from above mentioned possibilities. Also, as spectral-based instruments are sensitive to background referencing, a fixed position of the tube is essential to ensure that the background referencing does not drift over time. The averaging time for monitoring the flow rate requires a study of the setup at the sensor location and a tradeoff between the RSD value and sacrificing information on the process dynamics. Consideration to the dynamics is recommended to be given for eventually estimating the desired hopper level to be maintained in the tablet press.

3.4.1 Sensor setup and communication to DCS

To ensure a fixed setup for the position of the tube, and to have an additional measurement of blend uniformity using a NIR sensor, a custom box was designed and fabricated collaboratively with research group members. This is shown in Figure 3-14. Safety checks for radiation leaks are conducted every year, as recommended by the Radiology and Environmental Safety Team at Purdue University. The sensor is located at the exit of the second blender, hence the measured flow rate will be able to track the dynamics induced by the two blenders.

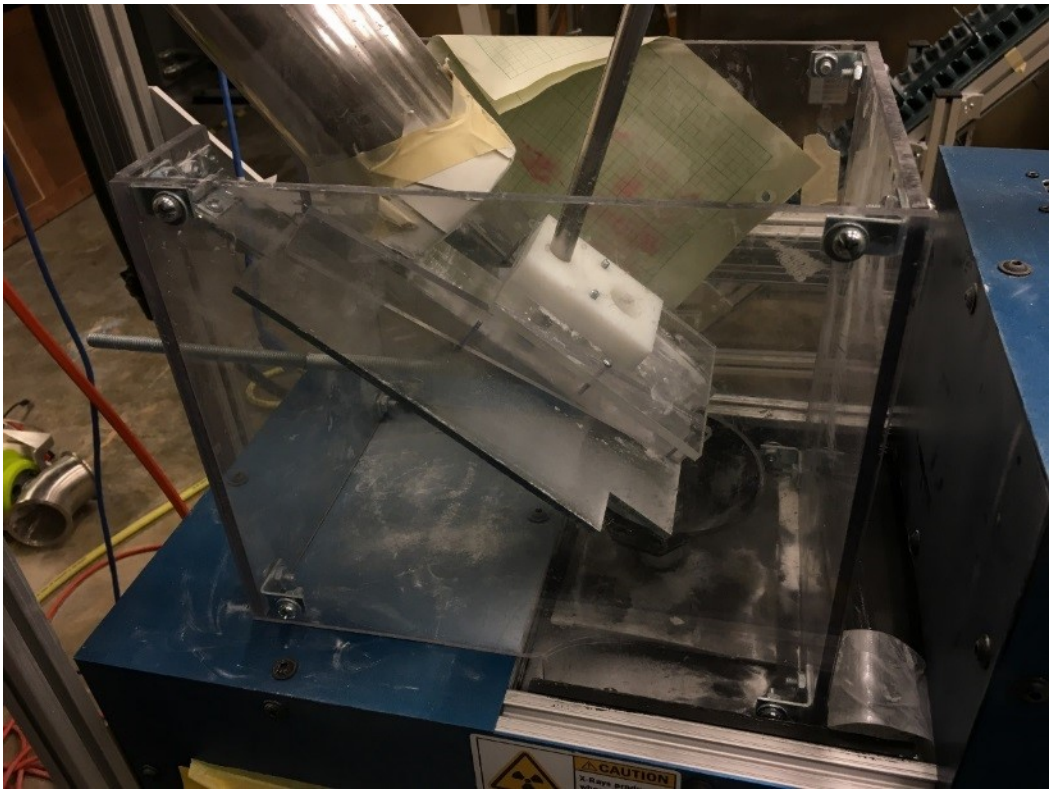


Figure 3-14: Custom physical interface for implementing the X-ray sensor in the OSD-CM process

For real-time flow monitoring, SprayQC is setup as a server En'Urga without OPC compliance. The data is routed as a TCP/IP data stream and can be interpreted using a suitable software. 'instrfind' and 'tcpip' functions of MATLAB instrument control toolbox are used for the same in the current setup. Given a TCP/IP connection, the data from the x-ray sensor can be read in any computer with MATLAB in the network, preferably the AppStation computer of the DeltaV system for a direct read/write OPC access to the controller

3.4.2 Inline Calibration

Calibration requires a known flow rate through the system and is to be done at the intended location of use. In recent end-to-end experiments in the pilot plant, frequent fouling and sensor network errors required restarting of all sensor data acquisition programs. For the x-ray sensor, this meant requirement for background referencing. While other sensors in the network (NIR or

weighing scale or AT4) do not require a shut down and can resume measurement, the background referencing requires no flow of material through the sensor. Hence, contrast to offline calibrations, the x-ray attenuation is recorded without performing a background reference, and instead a 'background referencing parameter' in used for inline monitoring, as shown in the equation below.

$$Q = (x - a) * v * b_1 \rightarrow (x - a) * b \quad \text{Eq. 3-5}$$

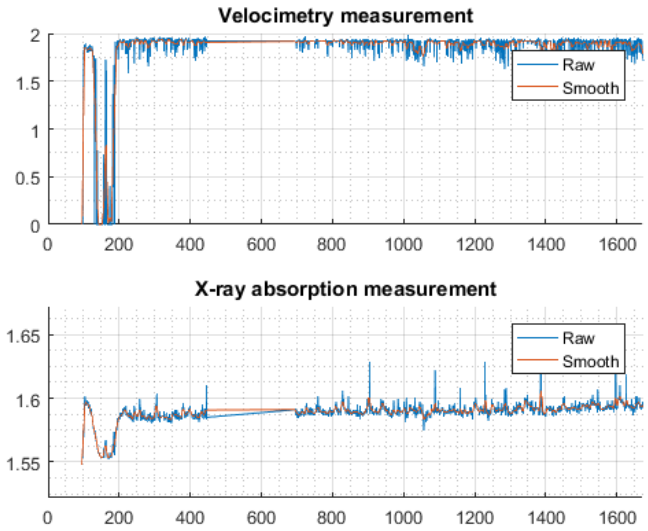
Where x and v are the measured values of x-ray attenuation and velocity from the sensor, a is the background referencing parameter, b_1 and b are respectively the proportionality constant if the velocity measurement is or is not included in the flow rate calculation.

Data from the sensor is recorded at every 1 second and is 1000 Hz averaged measurement of the x-ray absorption and velocimetry. The calibration of the x-ray sensor is performed using flow rate data from loss-in-weight feeders or by placing a weighing scale at the exit of the sensor. Accounting for time delays, each data point of filtered x-ray sensor measurements, total flow rate from the LIW feeders or the flow rate monitored using the weighing scale over the experiment time are compared in a custom MATLAB code, using 'fit' function in the curve fitting toolbox. The quality of fit is evaluated by observing the root mean square error and by comparing the total mass of powders collected at steady state conditions. The sensor measurement standard deviation is estimated using the confidence intervals of the estimated parameters.

3.4.3 Inline Monitoring Results

The sensor performance with and without including velocity measurements are analyzed. This is shown in Figure 3-15 for 10% APAP + MCC PH-200 blends, with and without SiO_2, used in recent end-to-end experiments in the pilot plant. As expected from offline understanding, addition of SiO_2 renders the utility of velocity measurements in the current system ineffective. However, it is also seen that absorption measurements are reliable; hence, the flow equation will not include velocity measurements.

a



b

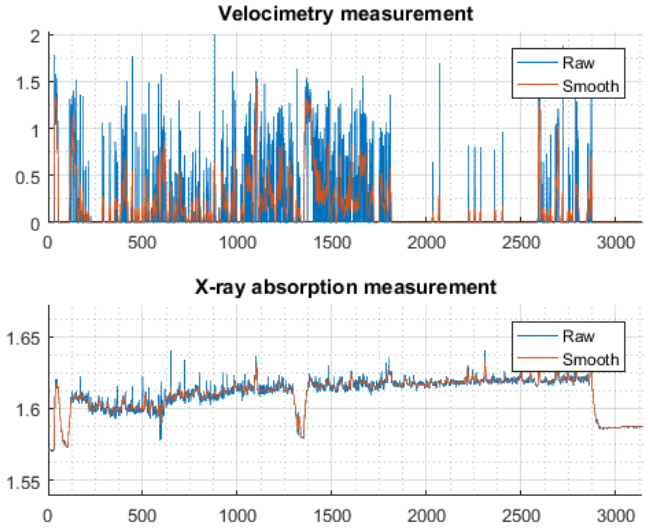


Figure 3-15: X-ray velocity and absorption measurements for 10% APAP + MCC PH-200, without (a) and with (b) SiO_2

The calibration relationship can be determined by comparing a known flow rate with the absorption measurements. The weighing scale (10 second averaging) is used to understand the tracking of the particulate flow dynamics by the sensor. The powders from LIW feeders experience two blending operations that result in the observed dynamics. The LIW feeders are observed to have an RSD of ~2% at steady state, however, the blending result in a RSD of ~5% in steady state

at the feed location of the tablet press, with a moving average time of 10 seconds. This variation is also observed using the weighing scale and is tracked by the x-ray sensor, as seen in Figure 3-16. A design decision to use the appropriate averaging time at this location for a tradeoff between the RSD and the flow dynamics is essential. This resulting flow variation is the feed to the tablet press and requires consideration for implementing the control system.

a b

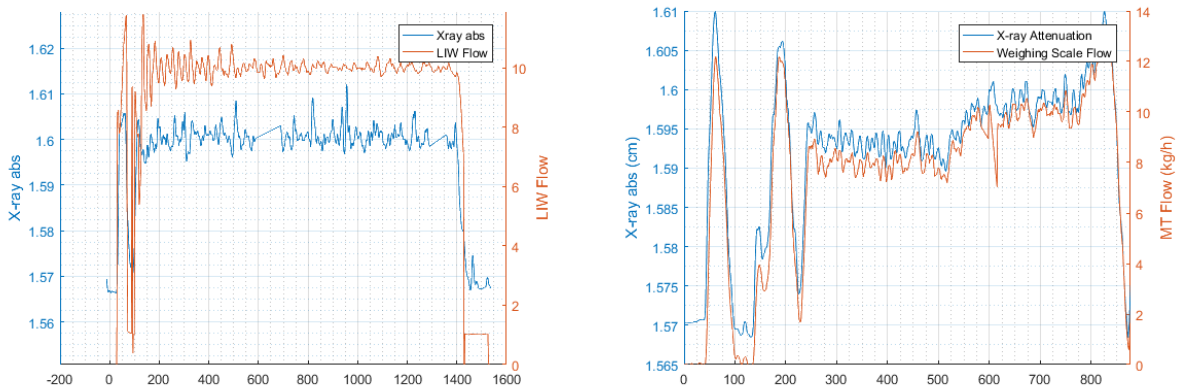


Figure 3-16: X-ray absorption tracks the flow rate at the sensor location. LIW flow rate has low RSD (a), but blender adds variations to the actual flow, as tracked by the weighing scale (b).

On calibration, the x-ray sensor accounts for all the mass collected on the weighing scale, with an error of <1g for an *unknown* flow rate when with about 10 minutes of monitoring at 10 kg/h. The RMSE at steady state is observed to be about 0.5 kg/h in the current setup. For demonstration, 3 flow rates (8, 10 and 12 kg/h) for 10% APAP blended with MCC PH-200 or PH-102 is shown in Figure 3-17. The predicted flow rate for a new 'unknown' condition was however underestimated. Observations as these where the flow is underestimated or overestimated is a constant bias and could be because of the errors in reference standards, pointing to the sensitivity of flow rate to the calibration parameters. In x-ray sensor calibration, the parameter a depends on the setup and is observed to drift by over 1%. A drift over 0.3% for the parameter affects the flow measurement by over 1 kg/h. A requirement of inline parameter correction is thereby recognized for reliable monitoring.

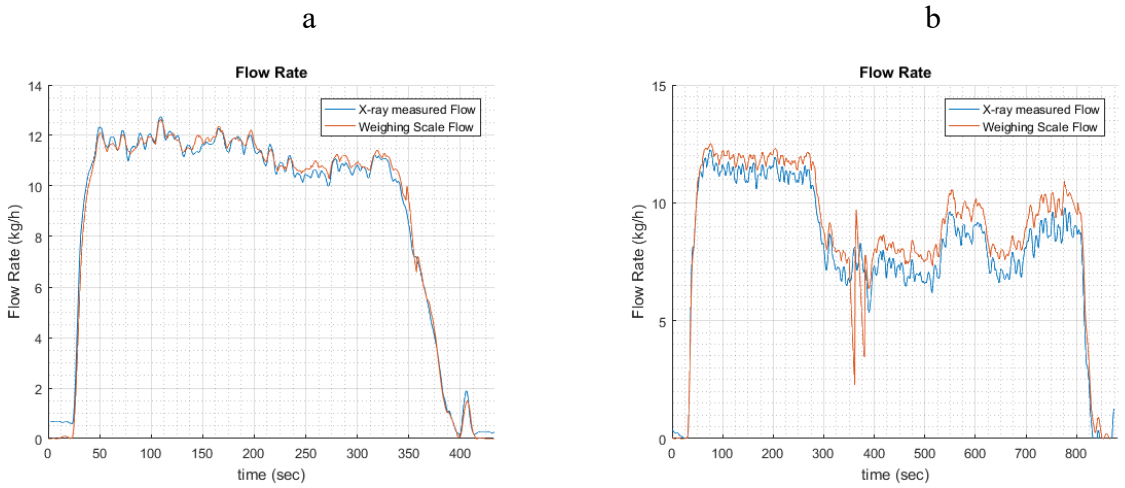


Figure 3-17: (a) Calibration of the sensor done by comparing x-ray absorption and LIW or weighing scale in the entire time interval. (b) Underestimation of 'unknown' the flow rate

3.4.4 Utility in the sensor network and limitations

The work so far in integrating the x-ray sensor to the tableting line has proved the sensor utility to effectively monitoring the mass flow rate of the material stream. However, demonstrating the added benefit for practical implementation of data reconciliation and of the control structures is critical.

Recent end-to-end experiments in the pilot plant for the same resulted in frequent fouling of sensors and sensor communication errors. Correcting the same required resetting the software or settings used for sensor data acquisition. At times, a shutdown was also required to necessitate the corrections. Moreover, physical changes after a calibration run using weighing scale to process runs has been observed to cause the tube to move rendering the calibration parameters unreliable.

Corrective maintenance for the NIR sensor placed on top of the sensor is observed to result in a constant bias for the x-ray absorption measurement. This drift in sensor measurement is shown in Figure 3-18. The boxed regions show times at which the bias is observed. Based on unorganized experimental records, the NIR sensor or the funnel for the x-ray or both was cleaned before such observations. These observations warrant equation parameters corrections on a timely basis for reliability in the measurement. This is desired to be performed without shutting down the process

and the use of reconciled estimates of flow rate. Reviewing the parameter and calibration policy is critical for reliable measurements. Such continuous improvements for calibration practices of the sensor will be investigated along with predictive maintenance practices.

a b

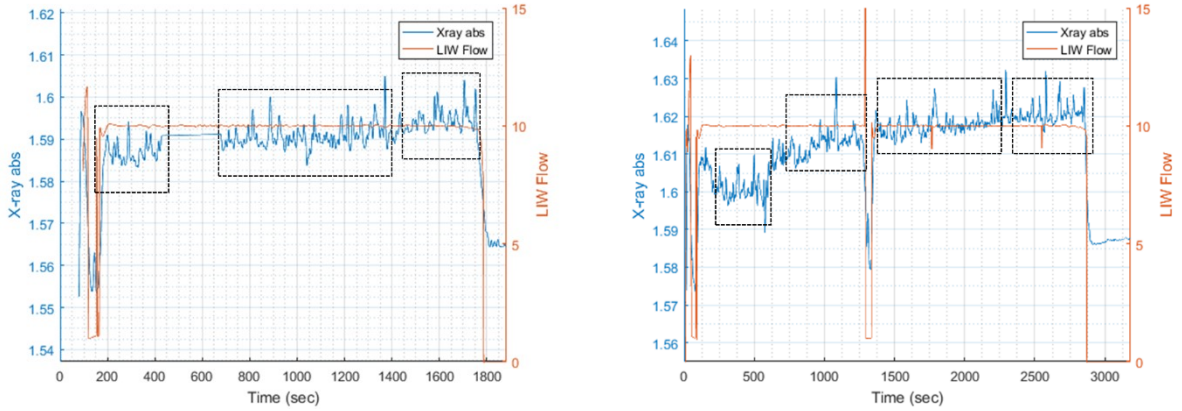


Figure 3-18: Corrective maintenance for sensor fouling causing measurement bias (constant bias)

3.5 Conclusions

The measurement obtained from the mass flow sensor depends on the material flow rate, the blend flowability inside the tube passing through the sensor and the physical setup that affects the dynamics of particulate flow, in addition to the x-ray parameters. The sensor measurement captures the overall variation arising from each of the above possibilities; however, it is beyond the scope of this work to individually distinguish these components. Recommendations from Mennel et al. (Mennell et al., 2000) for tube diameter suggests that the ratio of the distance of the tube center from the x-ray source to the tube diameter to be greater than 10, to satisfy the geometric assumptions of the equipment design. The tube material used in the study was nylon, however additional tube material bear investigation based on the adhesion of powder to the tube. The sensor evaluation also requires a LIW feeder capable of delivering particulate material continuously and consistently into the sensor, to calibrate the system for accurate measurements. Spectral based instruments are also sensitive to background referencing. A fixed position of the tube is essential to ensure background referencing does not drift over time. Intuitively, measurement variation can be reduced by averaging the x-ray attenuation measurements over a longer time. The averaging window for the measurements depends on the flowability of the material and the dynamics of

particulate flow at the sensor location, emphasizing the importance of a robust sensor network design.

The physical location of the sensor and material composition are the key for detection and determining measurement standard deviation. Operational variation in composition and presence of glidant or lubricant by small amounts does not affect the sensor for monitoring mass flow rate. Our studies demonstrate the ability of the sensor to satisfactorily monitor the particulate flow rate of powder blends and granules and thus confirm its suitability as a mass flowrate monitoring device for implementation of supervisory control in a continuous tableting line.

4 ROLLER COMPACTION IN AN INTEGRATED TABLETING LINE

4.1 Introduction

As continuous manufacturing would expand to multiple products, granulation methods could play an important role in the integrated process train. The dry granulation process, consisting of roll compaction and milling unit operations is important in pharmaceutical powder processing for size enlargement of powder materials to improve material handling and content uniformity. In dry granulation equipment, the powders are fed into a hopper and then conveyed by the feed screw between two counter-rotating rolls. By applying a compression force, the powdered materials results in a compressed ribbon. Upon exiting the rolls, the ribbon is broken up into granules in a hammer mill, generating a granular exit stream. Experimental and modeling studies have progressed the prediction and real-time monitoring of ribbon density, the CQA of the roller compaction, thereby facilitating QbD of dry granulation in drug product development (Korhonen, 2017; Nesarikar et al., 2012; Park et al., 2018; Reynolds et al., 2010). Moreover, PAT tools using NIR and microwave technologies have been demonstrated to monitor the ribbon density (Acevedo et al., 2012; Gupta et al., 2015; McAuliffe et al., 2015). A RTD study for a dry granulation integrated tableting line using multiple NIR sensors has been reported (Martinetz et al., 2018).

The objective of this chapter is to address the assessment and integration of the dry granulation process and established sensors for the implementation of data reconciliation and model-based automation of process operations pursued by the research group. This chapter discusses the process model, PAT tools, and the experimental study to enable robust real-time process monitoring systems. The chapter is organized as follows. First, a background on the roller compaction process model and the PAT tools for ribbon density is discussed. Next, the materials, formulation and the experimental and automation setup are described. The Results and Discussion section discusses the experimental observations and addresses the application of PAT tools and a mechanistic model for real-time monitoring of ribbon density. The ‘Application in the Integrated Tableting Line’ section briefly describes the use of this work in the implementation of state estimation and supervisory control system for the process. The details are beyond the scope of this chapter, and can be referred in published literature (Moreno et al., 2019).

4.2 Roller Compaction Background

4.2.1 Process Model

Roll compaction is a flow-based system, with material fed into the compaction region using screw conveyors. The ribbon density from the roller compaction process is the CQA and depends on feed material physicomechanical properties, feeding mechanism, flow rate, roll speed and roll force. A powder mechanics model relating the ribbon density to diameter and width of the rolls, the roll gap, roll surface pressures and inlet stress conditions at constant roll gap was developed by Johanson (Johanson, 1965). The model has been applied widely in pharmaceutical roller compaction for the development of finite element method models (Cunningham et al., 2010; Liu and Wassgren, 2016; Muliadi et al., 2012), discrete element method models (Mazor et al., 2017), dynamic process model (Hsu et al., 2010a), and system models (Gavi and Reynolds, 2014; Park et al., 2018). Modifications to address the limitations of Johanson's model to predict ribbon density was recently proposed using Finite Element Method (FEM) studies (Liu and Wassgren, 2016). The FEM study also recommends the release region length to be sufficiently long to ensure maximum normal stress at the minimum roll gap. A combined Discrete Element Method (DEM)-FEM study demonstrated the non-ideality in particulate flow in the roller compaction resulting from the flow of material in the hopper and screw conveyor (Mazor et al., 2017). The simulation further demonstrated the inherent variation in ribbon density along its width, resulting from the frequency of auger-based feeding.

A dynamic model was proposed using Johanson's fundamental compaction model combined with material balance based on volume change in the roll gap region and first order models for actuators viz. roll speed, feed screw speed and roll pressure (Hsu et al., 2010a). Further, the authors studied a model predictive control strategy for the process (Hsu et al., 2010b). The actual implementation of the model integrated control system could not be demonstrated owing to lack of development in inline sensors at the time. In an independent study, Reynolds et al. (Reynolds et al., 2010) incorporated the inlet and outlet mass flow rate using the screw feeder speed and roller speed and analyzed a steady state model for scale up and later in the design of a tableting system (Gavi and Reynolds, 2014). Moreover, Reynolds et al. (Reynolds et al., 2010) simplified the use of Johanson's model by using envelope density measurements of process

ribbons and not of offline compacts to obtain the material dependent parameters in the compressibility equation.

The process model for a roller compaction process consists of the material compaction equation constrained by material balance. The actuator impacts ribbon density dynamics; however, this work focuses on prediction and monitoring of ribbon density at steady state. This work uses the Johanson's model integrated with the material balance equation, as used by Reynolds et al. The model to predict ribbon density is briefly discussed below.

The Johanson model divides the compaction region into the slip region and nip region at the nip angle. The nip angle (α) is evaluated by equating the powder stress gradients in the slip and nip regions as done in Johanson's model and can be referred. The nip angle depends on the material properties, roll gap and roll diameter. A pressing force (R_f) is responsible for compacting the powders between the rolls into sheets or ribbons. The roll force can be related to the peak pressure (P_0) applied at minimum separation, as shown in Eq. 1. The roll force is applied as a hydraulic pressure in roll compaction equipment and is represented as Eq. 4-3.

$$R_F = \frac{P_0 WDF}{2} \qquad \text{Eq. 4-1}$$

$$\text{Where, } F = \int_{\theta=0}^{\theta=\alpha} \left[\frac{\frac{S}{D}}{\left(1+\frac{S}{D}-\cos\theta\right)\cos\theta} \right]^K \cos\theta \, d\theta \qquad \text{Eq. 4-2}$$

$$R_F = P_h * A \qquad \text{Eq. 4-3}$$

Here, W and D are the width and diameter of the roll respectively, and δ_E is the effective angle of internal friction. A is the area parameter relating the hydraulic pressure to roll force and is available from the equipment user manual. The roll force can also be directly measured using pressure transducers.

The ribbon relative density (γ_R) is then calculated as a function of the feed relative density (γ_0), the peak pressure (P_0) and the material compressibility (K) using a power law relationship, as shown in Equation 4.

$$\gamma_R = \gamma_0 P_0^{\frac{1}{K}} \quad \text{Eq. 4-4}$$

The material balance equation, assuming a screw feeder is integrated with the compaction mechanics. The material balance equation introduced by Hsu et al. simplifies to the equation introduced by Reynolds et al. at steady state. The steady state material balance, as shown in Eq 4-5 relates the ribbon density to the roll speed (N_R), feed screw speed (N_S), roll gap (S), roll width (W) and roll diameter (D). A fitting constant (c_S) relates the feed screw speed to the feed mass flow rate.

$$N_S c_s = \rho_{true} \gamma_R \pi D N_R W S \rightarrow \frac{S}{D} = \frac{N_S}{N_R} * \frac{c_s}{\pi \rho_{true} \gamma_R D^2 W} \quad \text{Eq. 4-5}$$

4.2.2 Roller compaction process monitoring

Modern roll compaction equipment are highly instrumented and provide robust measurements of roll speed, feed speed and roll force or the hydraulic pressure impacting roll force. A design space for the process parameters can be evaluated using material and operating condition specific experiments for a QbD approach to produce ribbons and granules. However, in continuous processing, the effect of possible disturbances in feed flow rate and operational variations in composition on the ribbon density are to be handled in real-time with a plant wide control system. Moreover, powder processing is always susceptible to material ratholing in hoppers, segregation, jamming etc. and can be detected by monitoring the CPPs and CQAs. These necessitate the requirement of an inline monitoring system, alarm system and a control system for the ribbon density for effective plant-wide control (Gupta et al., 2013).

Studies on the same roller compaction system that the current work uses have investigated the use of NIR sensor and an in-house microwave sensor (Austin et al., 2014; Gupta et al., 2015) for inline monitoring of ribbon density. These studies have indicated the utility of the sensor using PLS models for predicting ribbon density with RMSE values of approximately 0.02 g/cc. This requires sensor calibration in the actual setup, using the process conditions at normal operating conditions.

4.3 Materials and methods

4.3.1 Experimental setup and Materials

Formulations for experimental demonstration consist of blends comprising of Acetaminophen (APAP) Grade 0048 (courtesy Mallinckrodt, NC, USA) and microcrystalline cellulose (Avicel, courtesy FMC BioPolymer, PA, USA) grade PH-102. Experiments at normal operating conditions of 10% APAP with Avicel PH-102 at a target flow rate of 10 kg/h are performed by varying hydraulic pressure to capture the dependence of the ribbon density on hydraulic pressure at a fixed composition and flow rate. Hydraulic pressures set points of 30 and 55 bar are used in an Alexanderwerk WP120 system for a low pressure and a high-pressure condition. A hydraulic pressure set point of 45 bar is used additionally at target normal operating conditions. The process is operated for a period of approximately two minutes at steady state conditions for each experiment. Ribbon samples corresponding to half a circumference of the rolls are sampled around 100 seconds into the experiment and analyzed for its envelope density. The envelope density of the sampled ribbon sheet is evaluated using GeoPyc 1365 (Micromeritics) in the CP3 characterization lab at Purdue University. The samples are broken into smaller 2 cm x 2 cm squares to fit the 1" diameter measurement chamber. Density obtained using three separate analysis are averaged to be indicative of the ribbon porosity for the corresponding process conditions. The corresponding thickness of the flakes are measured using Vernier calipers.

Experiments are setup for three purposes. First, evaluating the effect of ribbon density on batch loading the hopper and continuous powder feed into the hopper of the roll compaction equipment at a target flow rate of 10 kg/h. The mass flow rate at the inlet of the rolls is evaluated by timing the mass of 10 wt% APAP by varying the screw speed from 24 to 32 rpm. Second, the effect of operational variations in composition at 90 and 110% label claim, and changing flow rates (8, 10 and 12 kg/h) at similar hydraulic pressures on model and PAT predictions are investigated. The process data from these set of experiments are used for estimating model parameters and calibrating the PAT tools for ribbon density. Lastly, the model and PAT tools are used for predicting the ribbon density with step changes to the hydraulic pressure, along with monitoring at steady state. Table 4-1 and Table 4-2 shows the material and process conditions for every experiment.

Table 4-1: Experiments for comparison of ribbon density based on feeding conditions

Experiment	Blending and Loading Conditions	RC Equipment Conditions
A	Batch blending and RC Hopper Loading	NS = 26 rpm
B	Feeding using Feeding – Blending System	NR = 6 rpm
C	Feeding using Feeding – Blending System	P_H = 30, 40, 50 bar

Table 4-2: Operating conditions for roller compactor (Alexanderwerk WP120) experiments

Exp. No.	Feed		RC Equipment Conditions		
	APAP wt%	Total Flow Rate	P_H (bar)	NR (rpm)	NS (rpm)
1	9	10	30	28	6
2	9	10	55	28	6
3	10	10	30	28	6
4	10	10	55	28	6
5	11	10	30	28	6
6	11	10	55	28	6
7	10	8	30	26	5.5
8	10	8	55	26	5.5
9	10	10	30	28	6
10	10	10	55	28	6
11	10	12	30	30	6.5
12	10	12	55	30	6.5
13	10	10	45	28	6
14	10	10	45	28	6
15	10	10	30, 45, 55	28	6

For batch loading of the mixture in the roller compactor hopper, an offline 5L Tote bin blender is used to prepare the blend. The bin blender is operated at 16 rpm for 15 minutes. In the continuous feed experiments, APAP and Avicel PH-102 are fed using separate Schenck AccuRate AP-300 loss in weight feeders into a Gericke GCM-250 continuous blender operating at 200 rpm. The blended material continuously feeds the roller compactor hopper. The flow rates from the LIW feeders are adjusted for the target throughput and composition.

4.3.2 Equipment

An Alexanderwerk WP120 roller compactor is used in a pilot plant facility. The equipment has five input variables - screw speed, roll speed, hydraulic pressure, roll gap and milling speed, of which roll compaction requires the first four variables. The equipment control system monitors and controls these variables. The roll speed and hydraulic pressure are defined by the user, while

the feed speed or the roll gap is defined depending on the use of the built-in gap control. Gap control is not used in the current work to avoid flow rate fluctuations through the process. The feed hopper agitator and vacuum de-aeration system integrated into the equipment are kept on for consistent feeding of powders into the compaction region using the screw conveyors. The setup uses 120 mm diameter and 40 mm rolls. The top roll is a smooth roll and the bottom roll is a knurled roll. During operations, the rolls and the hydraulic pressure are first turned on, followed by vacuum deaeration, the feed screw and the feed hopper agitator. Further, an acrylic cheek plate is used to observe the flow of powder into the compaction volume for ensuring complete fill of the volume between the rolls.

4.3.3 PAT tools

A reflectance NIR sensor assembled using CDI Spectrometer and Solvias probe are used in the setup. A cavity-based microwave sensor built in-house is setup for an additional measurement of the ribbon density. The physical arrangement of the roller compactor was modified to accommodate the NIR and microwave sensors. The details of the sensors used in a similar setup is available in Gupta et al (Gupta et al., 2015). To ensure robust sampling from the NIR sensor, a 3D printed part is designed as a sensor holder to maintain the position and angle of the NIR sensor, as shown in Figure 4-1.

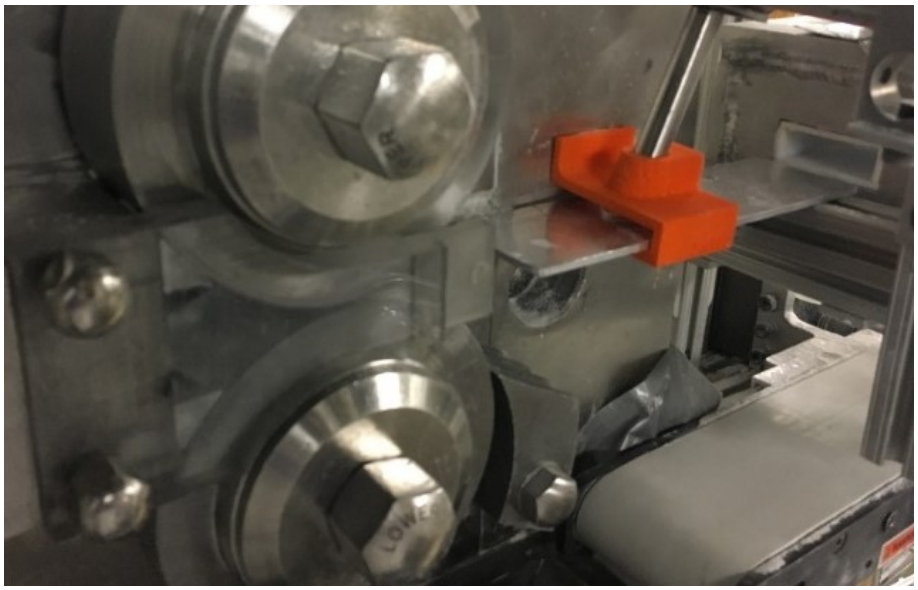


Figure 4-1: Roller Compaction setup showing the acrylic side seal, NIR sensor and sampling part, microwave sensor

The acquisition of raw spectra from the NIR is automated using Spec32 and Matlab 2017b. Two raw NIR spectra is recorded every second. A custom Matlab function, formerly developed in the research group (Austin et al., 2013), is used in Matlab 2017b for acquiring the microwave spectra. The microwave sensor reports a spectra every 7 seconds. For the calibration setup, the spectra from both the NIR and microwave sensors are analyzed using ProMV for a PLS model. The ribbon density values used in PLS model training is sampled as a uniform distribution from a normally distributed ribbon density value with the average and standard deviation corresponding to the ribbon density from GeoPyc analysis. Preprocessing reported in (Austin et al., 2014) is used to relate NIR and MW spectra to ribbon density. In the calibration step, an average of 10 raw NIR spectra is used to build the PLS model. SNV and first derivative preprocessing is used for the microwave spectra. For real-time monitoring, every spectrum acquired using the NIR is used to report a quantitative value for ribbon density.

The step change experiment is used to predict the ribbon density using the model and PAT tools and validate the measurement using the GeoPyc. Process data and spectra from the experiment are analyzed offline and reported in this manuscript. The predictions from the models are compared with ribbon density measured using GeoPyc.

4.3.4 Model parameter estimation and utilization

Equations 4-1 through 4-5 represents the roller compaction process for predicting the ribbon density. The roll speed, feed screw speed and hydraulic pressure are operating variables. Values for effective angle of internal friction and wall friction angle required for the nip angle are assumed as 40.5^{o} and 18^{o} respectively. Parameter A is retrieved from the Alexanderwerk equipment manual as 0.369 kN/bar. A custom model comprising of the compaction and material balance equations is setup in gFormulate (Process Systems Enterprise). Experimental measurements are used to estimate model parameters c_S, K and the feed bulk density. These parameters primarily depend on the material processed in the equipment. The initial guess for the three model parameters is evaluated using offline experiments. The screw conveyor constant is estimated by evaluating the flow rate at the exit of the screw conveyor without the rolls. This is performed by timing the material collected at the exit of the screw conveyor without the rolls. Initial estimates for parameters K and feed bulk density are estimated by performing punch and

die experiments in the CP3 characterization lab in a 6 mm die, with compaction forces varying from 0.3 to 4 kN. The nip angle is calculated using the parameters estimated from offline experiments. Parameter estimation for the three model parameters is performed using the Model Validation module in gFormulate. The model parameters are estimated using the envelope density and thickness measurements of the ribbons sampled during the process.

The goal is utilization of the model for real-time prediction of the ribbon density. The model with estimated parameters is setup in Matlab 2017b on the DeltaV Application Station. The roll pressure, roll speed and feed speed values are used to predict the ribbon density.

4.3.5 Control System

An Emerson DeltaV 13.3 distributed control system is used to integrate process equipment and develop the automation platform in the pilot plant facility at Purdue University. A modular network architecture is setup following ISA 95 and DeltaV Security Manual recommendations.

The spectra from NIR and Microwave sensors are acquired using Spec32 and Matlab 2017b respectively in a Dell Latitude E7470 laptop with an i7 processor and 8 GB RAM, referred as the PAT computer in this manuscript. The spectra values are recorded in Matlab in real-time and used for the PLS model development to relate the spectra to ribbon density. Relevant process data is accessed in real-time using the OPC toolbox in Matlab 2017b setup in the Application Station for automating data extraction after each experimental run. The model predictions for ribbon density using the mechanistic model is done using a Matlab function running in the Application Station. The data files from every experiment is accessed using a shared folder connected to the PAT computer via the DeltaV 2.5 network and uploaded to the knowledge management system. The spectra files for the PAT tools are uploaded to a knowledge management system from the PAT computer. The connections to the analyzers and OPC communication setup in Matlab required access to the Communication Systems Toolbox and OPC Toolbox respectively. The Matlab licenses are accessed in the PAT computer and DeltaV Application Station from the Purdue network using appropriate configurations for firewalls and IT network in the pilot plant.

4.4 Results and Discussion

4.4.1 Effect of continuous feed on ribbon density

The effect of feed on the ribbons processed at normal operating conditions of 10% APAP with MCC PH-102 at 10 kg/h are performed. Ribbons are produced by (i) pre-blending and batch loading of the feed hopper and (ii) feeding-blending using the LIW feeders and blender, at similar hydraulic pressure set points. The envelope density of ribbons sampled in experiments is analyzed to determine the feasibility of continuous feeding of the hopper. The blend and loading conditions are given in Table 4-1 and corresponding envelope densities is shown in Fig 4-2.

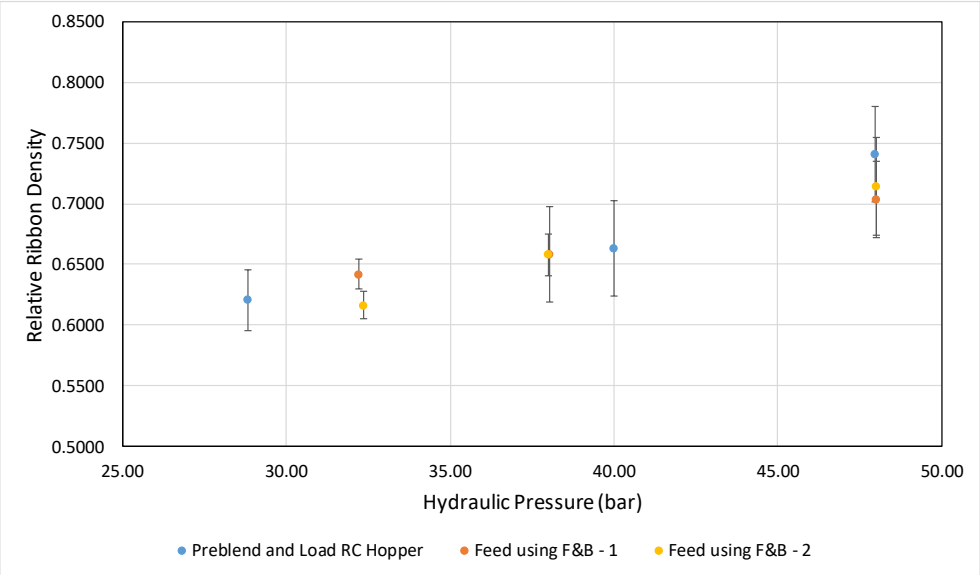


Figure 4-2: Effect of hopper loading on ribbon density

The measured ribbon densities at similar processing conditions from batch feeding and continuous feeding of the roller compactor hopper demonstrate the feasibility to operate the process in a continuous feed setup. The observed variations in the ribbon density could be attributed to variations in analytical testing on Geopyc and material bulk density based on ambient humidity.

Two further considerations for the feed into the compaction region are crucial for implementing model-based approaches for continuous roller compaction. These include the powder flow rate through the compaction region and the volume of the region filled by the powders.

The mechanistic models assume that the material in the slip region between the rolls is at the tapped density, which requires the volume between the rolls to be filled during the process. Further, if the roll speed is too low, material can compact and jam the volume between the rolls and if the roll speed is too high, the desired compaction will not take place. Hence, the operating roll speed should correspond to the feed flow rate and satisfying model assumptions for reliable process operations and model-based predictions of the ribbon density.

Feed flow rate to the compaction region is estimated by evaluating the mass flow rate dependence on the screw speed by timing the collection of material at the exit of the screw conveyor, without the rolls. Figure 4-3 shows the observed mass flow rate into the compaction region by varying the feed screw speed from 24 to 32 rpm. These experimental observations are also used to evaluate the initial guess for screw conveyor parameter (c_s). The parameter is estimated using ribbon observation. Further, experiments are performed using an acrylic cheek plate to observe the flow of powder into the compaction volume during startup and visually observe complete fill of the compaction region. Figure 4-4 shows the volume between the rolls during start up and operation.

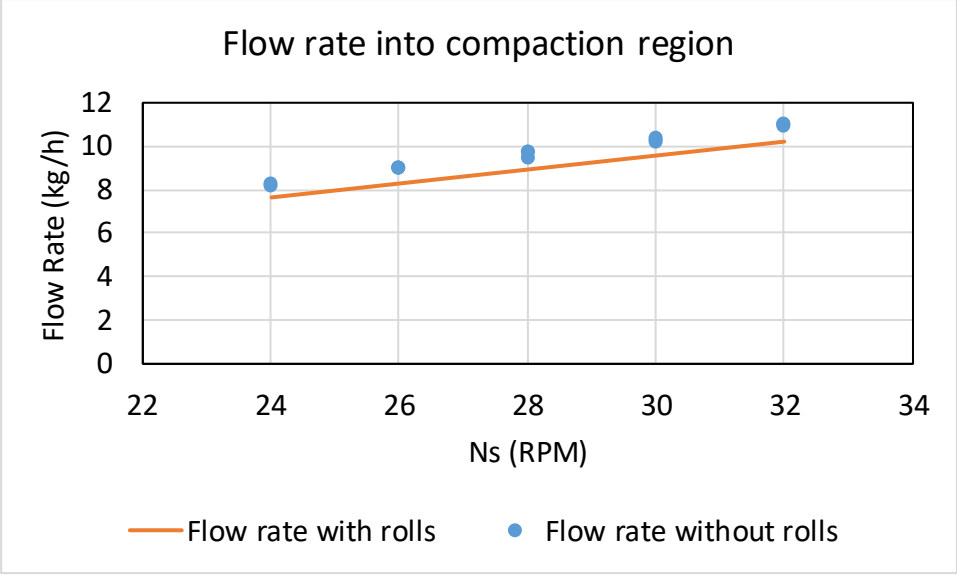


Figure 4-3: Mass throughput of screw conveyor into roll compaction region

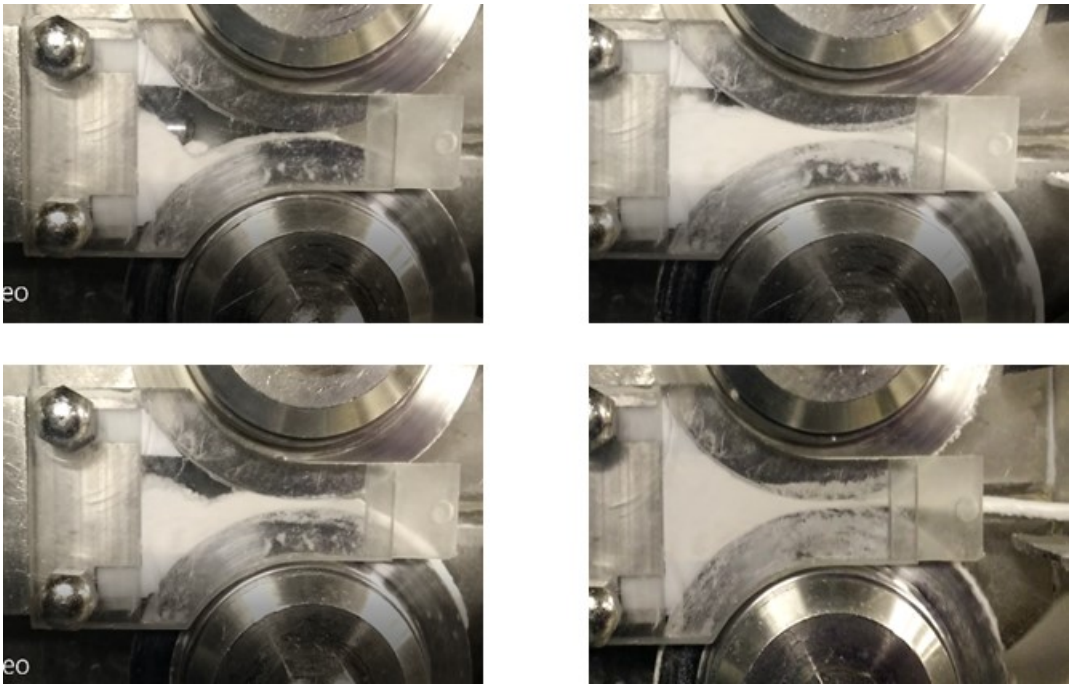


Figure 4-4: Material filling and discharge from the roller compactor

4.4.2 Effect of flow rate changes and API changes on ribbon density

In an integrated processing setup, changes to the feed flow rate from the feeding-blending system are likely to maintain quality specifications, production rates, plant wide control loops etc. (Martinetz et al., 2017). The control strategy may thus require flow rate changes in the roller compaction equipment, and its implication on ribbon density is an important consideration.

Moreover, the feeding blending process may also result in blend uniformity variations arising from output variations in the feeders and blender. The ribbon density corresponding to ±10 percent of label claim variation in feed composition at a single feed flow rate is evaluated. The continuous feeding-blending system is used to feed the roll compaction equipment hopper by varying the ratio and flow rate set points. Experiments 1 to 6 as shown in Table 4-2 is used for this study. The results indicate similar densities at similar operating conditions for the three compositions, as shown in Figure 4-5.

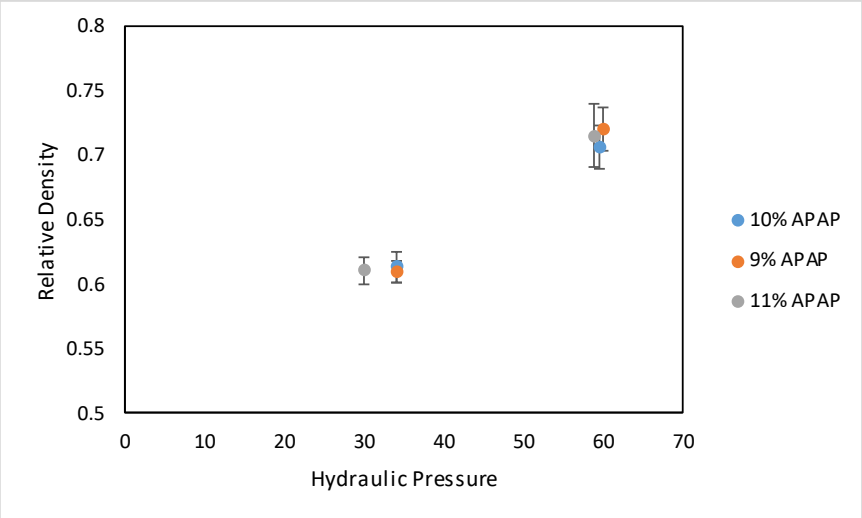


Figure 4-5: Effect of ribbon density on operational variation in composition and the hydraulic pressure

Ribbon densities corresponding to three feed flow rates are evaluated. The feed speed and roll speed are manually adjusted to heuristically match the required conditions in the compaction region. A single set point composition of 10% APAP is used for the study. The continuous feeding-blending system is used to feed the roll compaction equipment hopper by varying the ratio and flow rate set points. Experiments 7 to 12 as shown in Table 4-2 are used for this study. The results indicate similar ribbon densities at the two different hydraulic pressures for all the three flow rates, as shown in Figure 4-6. Hence, by manipulating the feed screw speed and roll speed according to the feed flow rate, the ribbon density can be controlled without changing the hydraulic pressure.

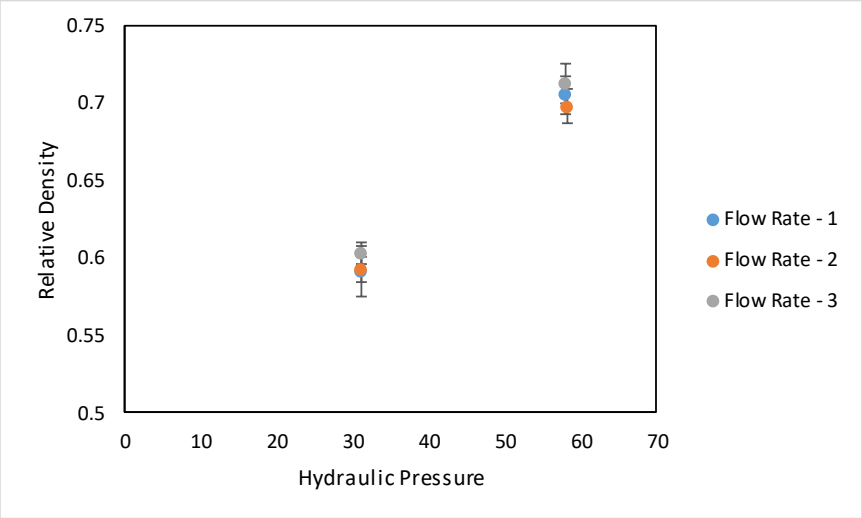


Figure 4-6: Effect of flow rate and hydraulic pressure on ribbon density

4.4.3 Ribbon density monitoring using PAT Tools

Inline sensors are essential for real-time monitoring of the CQA for implementation of feedback control and for real-time risk assessment for the product quality. The ability of the NIR and microwave sensors to monitor ribbon density at the investigated processing conditions is discussed in this section.

Since the actual ribbon density from the Geopyc measurements do not vary with the APAP variations and flow variations, as discussed in section 4.2, observations from experiments 1 through 12, along with 13 and 14 are used to calibrate the PLS model for the inline sensors. A two latent variable PLS model is fit to relate the raw NIR spectra to the ribbon density with a root mean squared error of 0.026 g/cc. A four latent variable PLS model is built to relate the 1st derivate preprocessed microwave spectra to the ribbon density with a root mean square error of 0.018 g/cc. Figures 4-7 and 4-8 show the score plot, SPE vs Hoteling's T^2 plot and the observed vs. predicted plots for the NIR and MW training data respectively.

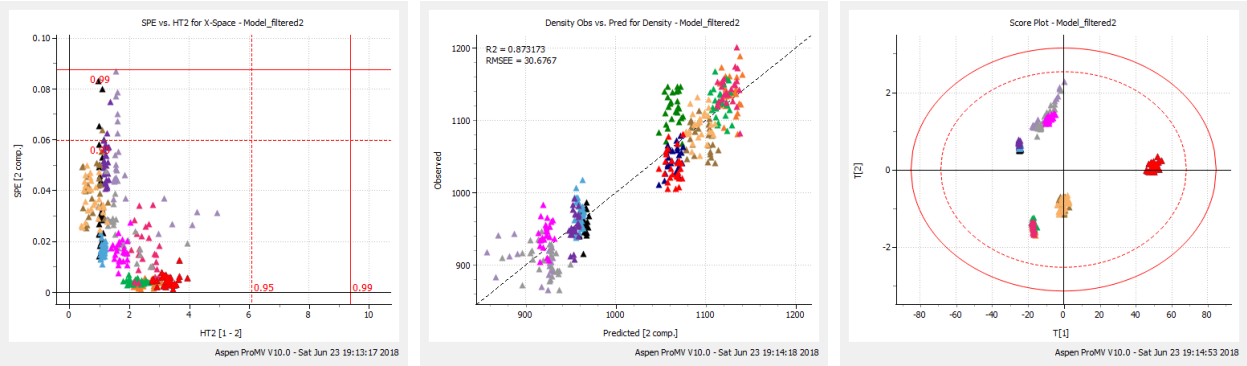


Figure 4-7: NIR PLS Model

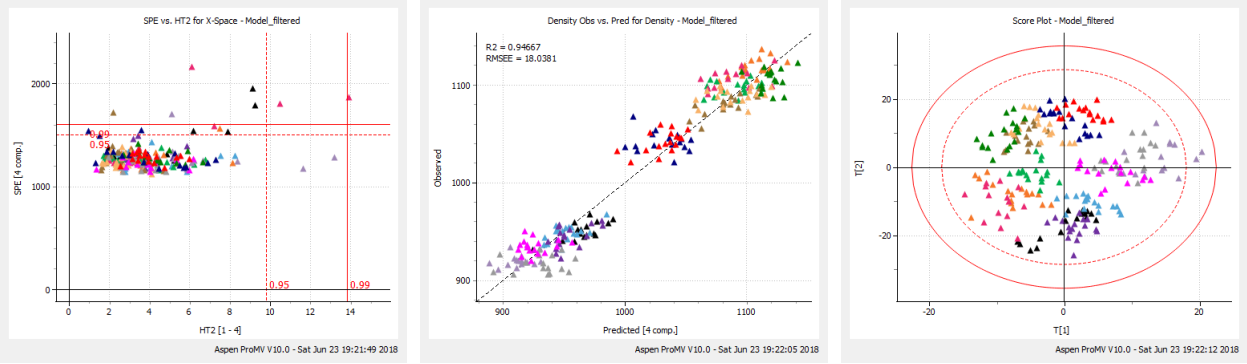


Figure 4-8: MW PLS Model

4.4.4 Mechanistic model parameter estimation and ribbon density predictions

Model parameters K, ρ_R and c_s require estimation from experimental data. The initial estimates for the three parameters are obtained from offline experiments. The compaction parameters are obtained from the compressibility experiments performed using the compaction simulator. The compact bulk density is fit as a power law function to the corresponding pressure applied while preparing the compact. The inverse of the exponent is estimated as K and the pre-exponential factor is the inlet bulk density. The compressibility curve is shown in Fig 4-9. The nip angle is calculated as 11.2^o using these values and the assumed values for the effective angle of internal friction and the wall friction angle, at 1.5 mm roll gap.

The screw conveyor constant is initially estimated from the mass flow rate dependence on the feed screw speed without the rolls. This is shown in Fig 4-3. However, with the presence of rolls the powders in the conveyors are densely packed than without the rolls and affect the flow throughput. Moreover, the process uses different roll surfaces and the compaction speeds in comparison to the compaction simulation experiments. Moreover, non-ideal powder flow in the roller compaction region is not accounted for in the offline study. Hence, estimating the parameters using ribbon measurements provide better estimates for the compaction.

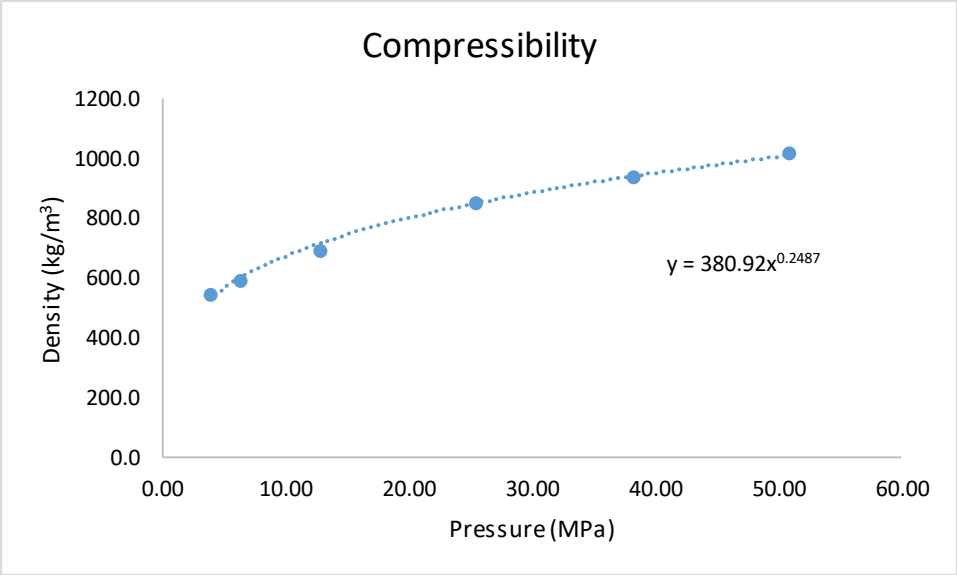


Figure 4-9: Compressibility curve for initial estimation of parameters K and ρ_0

Model parameters K, ρ_R and c_s corresponding to the process setup are estimated using ribbon density and flake thickness measurements obtained from samples of Experiments 1 to 14. The experiments are setup in Model Validation of gFormulate for parameter estimation. A constant relative variance model is used for each measurement corresponding to the measured relative standard deviation obtained from the Geopyc measurements.

Table 4-3: Initial and estimated model parameters

Parameter	Offline Experiments	RC experiments
c_s (kg/h/rpm)	0.346	0.318 ± 0.005
K	4.021	4.68 ± 0.27
ρ_R (kg/m^3)	380.9	386.9 ± 19.1

The observed vs predicted ribbon densities using the parameterized model is shown in Fig 4-10. An R^2 of 0.98 and an RMSE of 12.94 kg/m^3 is observed for the model predictions.

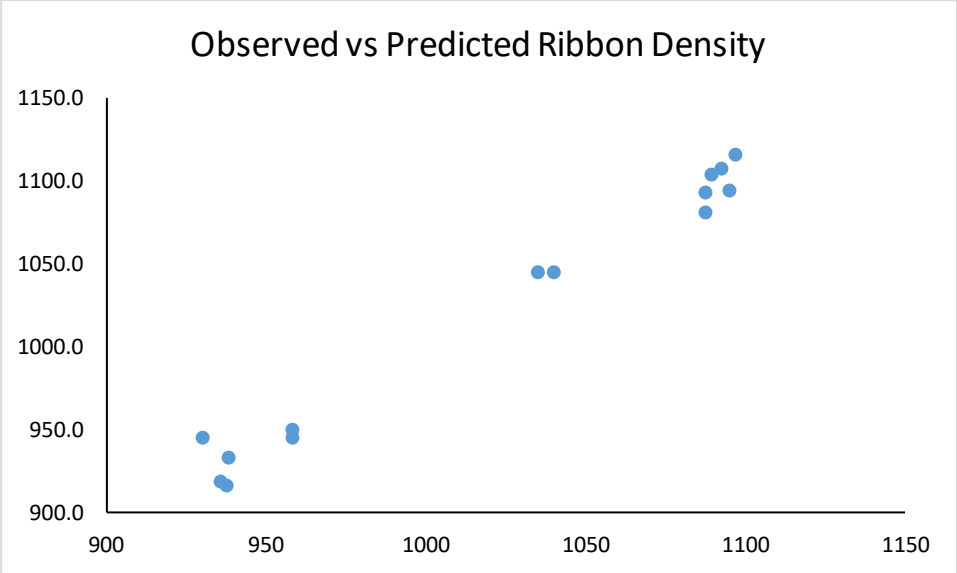


Figure 4-10: Observed vs predicted ribbon density using parameterized process model

4.4.5 Ribbon density monitoring

Inline sensors are setup using the calibrated PLS model to predict the ribbon density in step changes to the hydraulic pressure, as indicated in Experiment 15. Three hydraulic pressure conditions are used, and the corresponding ribbons are analyzed for their ribbon density offline. Experiment 15 is used to investigate the implementation of the inline sensors to monitor the ribbon density. Spectra from NIR and microwave sensors are pre-processed and the ribbon density values

are predict using ProMV. In the same experimental setup, with standard inter experiment cleaning procedures, a biased measurement is observed for both sensors, as shown in the observed vs predicted graph in Figure 4-11. The NIR sensor is seen to under predict the ribbon density and the microwave sensor over predicts the ribbon density in the observed experimental duration. However, the sensors track the ribbon density qualitatively; hence, the bias in measurement from such a sensor can be evaluated and corrected using regularly sampled and analyzed ribbons using an offline measurement technique. This bias in measurement requires to be validated before using the sensor for real-time process decisions in the control system.

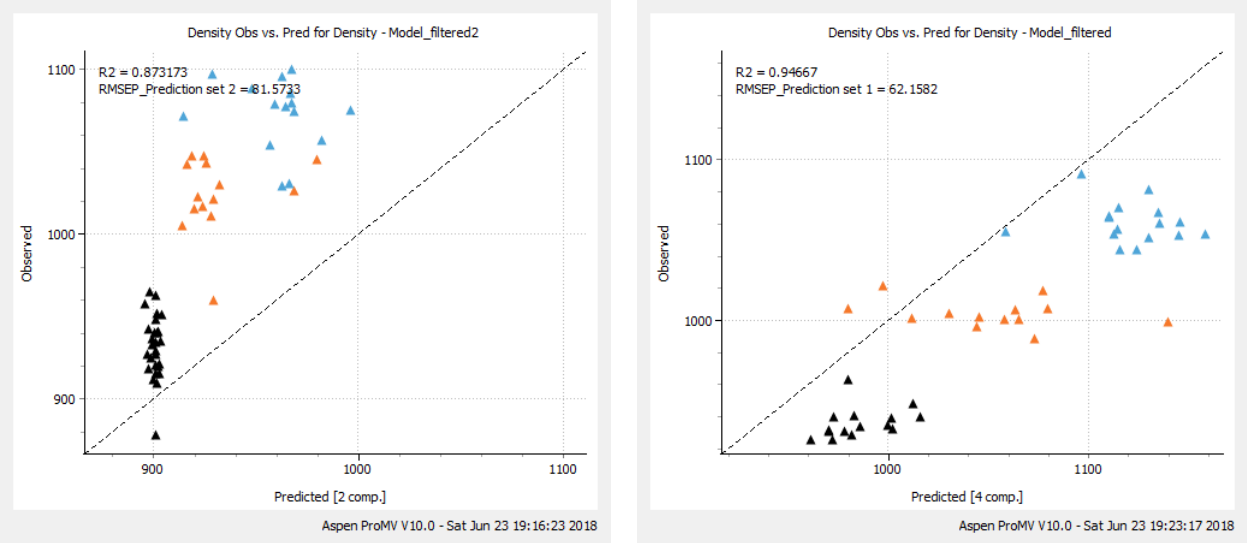


Figure 4-11: Prediction bias of inline sensors in ribbon density monitoring

The RMSE for predicting the ribbon density using the parameterized model is under 1 kg/m^3, as shown in Figure 4-12. The model validation demonstrates its potential utility to predict ribbon density in real-time, and thereby implement the same for real-time process monitoring applications. However, it is important to note that material property changes can affect the model parameters, and re-estimating the parameters is an important consideration in the real-time monitoring workflow.

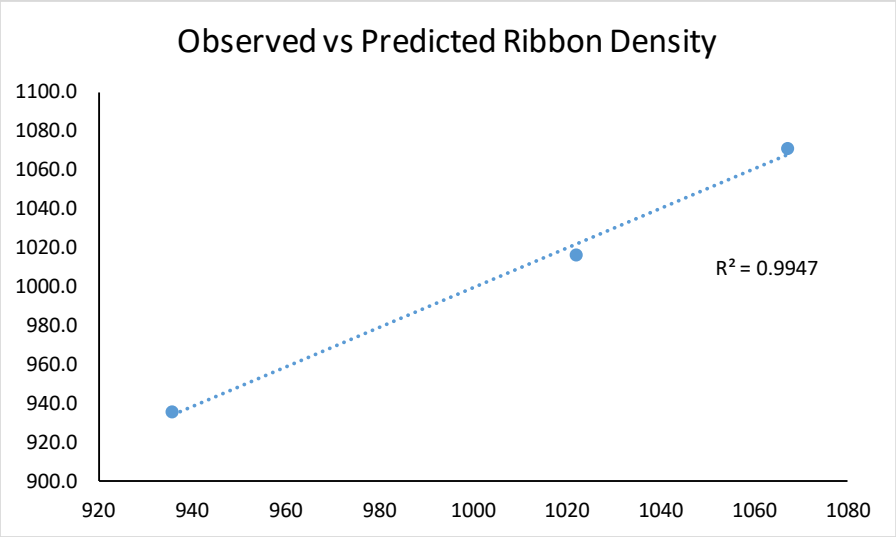


Figure 4-12: Ribbon density prediction using parameterized model

Model predictions from the mechanistic model predict the ribbon density under assumptions of unchanged or within accepted variability in material properties, complete filling of the compaction region, zero side seal leakage and unchanged equipment health conditions. Spectroscopic sensors importantly measure the CQA in real-time, thereby validating process conditions and enabling supervisory control systems. However, as observed, biases in the spectroscopic sensors is a concern during implementation for the ribbon density. Hence, an integrated framework to leverage model predictions and inline instrumentation systems with the application of process systems engineering tools is essential for reliable process monitoring.

4.5 Applications in the Integrated Tableting Line

The modeling, experimental and sensor study of this chapter were utilized for applications in robust process monitoring, and is available in published literature (Ganesh et al., 2018a; Moreno et al., 2019).

4.5.1 Sensor Network for Continuous Tablet Manufacturing

In this section, excerpts from (Ganesh et al., 2018a) is reproduced to illustrate the same. This work involved a simulated example to illustrate the use of the model in a data reconciliation and gross error detection framework for a continuous tableting line until dry granulation.

4.5.1.1 Systematic approach to measurement accuracy

Real-time release testing in continuous tableting requires accurate and reliable inline measurements. However, there exist several operational challenges. Spectroscopic sensors, such as NIR and microwave, require data pre-processing and analysis before recording in the DCS. Calibration of such sensors is material and sensor location specific. Due to a lack of well-established communication protocols in the industry, tasks such as data acquisition, filtering and processing are performed in separate software. Software issues can result in possible communication failures, rendering the measurement unavailable for specific periods during the process. Handling particulate streams can be subject to frequent fouling of sensor interfaces, leading to biased measurements. Further, tablet properties such as hardness, weight and dimension are measured at set time intervals minutes apart by destructive testing of the samples drawn. Moreover, measurements are always subject to random errors arising from sources such as power supply fluctuations, network transmission delays, changes in ambient conditions, etc.

Data reconciliation (DR), gross error detection (GED) and sensor network design (SND) have been demonstrated to address such challenges for improved measurement accuracy (Narasimhan and Jordache, 1999). DR and GED require direct simultaneous measurement of a number of variables which is larger than the process degrees of freedom to permit the estimation of all variables in the sensor network. Multiple measurements of the same process variable can improve the reliability of that measured variable; however, it does not affect the observability of the unmeasured variables. Besides, sensors using the same technology can miss certain process features which can only be seen via measurements utilizing a palette of alternative technologies. Thus, though the blend uniformity is the primary concern for a continuous tableting process, integrating available mechanistic understanding with sufficient measurements to maintain network redundancy and observability of unmeasured variables is essential for reliable continuous operations.

4.5.1.2 Case Study

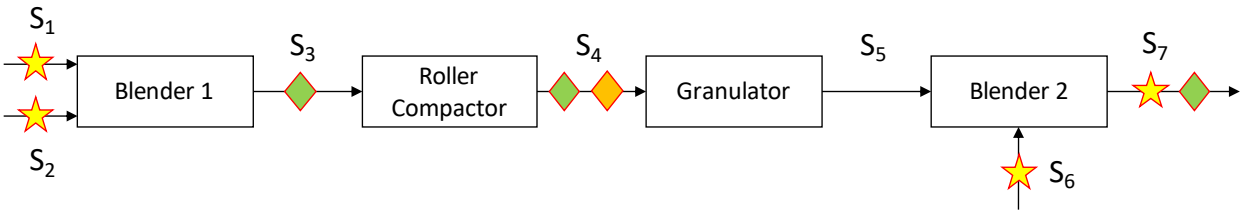


Figure 4-13: Block diagram for subsystem case study

In this study, the improvements in the accuracy of estimating the process state achieved using DR and GED for a subsystem of the continuous tableting line are demonstrated using three case studies representing situations commonly encountered in experimental implementation. We only consider the feeding, blending and granulating operations in the continuous manufacturing process, leading to the block diagram shown in Figure 4-13. There are seven material streams, and we assume there is no loss of material. The process variables are summarized in Table 4-4.

Table 4-4: Process variables with measurements, NOC mean and standard deviations

Variable		Tool	True Value (units)		RSD
F_1	API Flow	Load Cell	1.00	kg/h	2%
F_2	Excipient Flow	Load Cell	9.00	kg/h	2%
F_3	Blender1 Flow	-	-		-
x_3	Blender1 CU	NIR	10.00	wt%	6%
F_4	Ribbon Flow	-	-		-
S	Roll Gap	RC equipment	1.960	x 10^{-3} m	3%
ρ_R	Ribbon Density	NIR	0.963	kg/m^3	6%
x_4	Ribbon CU	NIR	10.00	wt%	6%
F_5	Granule Flow	-	-		-
x_5	Granule CU	-	-		-
F_6	Lubricant/Glidant Flow	LIW Load Cell	0.055	kg/h	15%
F_7	TP Inlet Flow	X-ray	10.00	kg/h	3%
x_7	TP Inlet CU	NIR	10.00	wt%	6%

The measurement technologies, if applicable, are indicated in the 'Tool' column. The corresponding expected true values, and relative standard deviations ('RSD' column) of measurements obtained from experimental data under steady-state operations are as indicated. All the unit operations are represented using overall material balances and component balance for the API across each node. Thus, there are eight material balance equations. Further, the flow rate from the roller compactor can be calculated using measured values for ribbon density and roll gap as

shown in the Eq. 4-5. Also, mechanistic understanding of the roll compaction as shown in Equation 4-1 to 4-4 can be integrated in to the framework.

The set of equations has 3 degrees of freedom for the process, which means the process has a minimum requirement of four gross error free measurements for data reconciliation. Table 4-4 shows the availability of nine inline measurements, leading to six degrees of redundancy (DoR) in the system for the GED tests. However, given the frequency of fouling, communication errors, requirement of feeder refilling, etc., consistent availability of gross error free measurements from these sensors is challenging. Moreover, LIW tuning parameters are material bulk density specific, which can vary for the raw materials. Also, calibration models for all the spectroscopic sensors are material, location and probe position specific. Hence, the redundancy is crucial to achieving robustness of this system.

Table 4-5: Measured variable estimates after data reconciliation and gross error detection

Var	**NOC**		**Case 1**		**Case 2**		**Case 3**	
	Mean	RSD	Mean	RSD	Mean	RSD	Mean	RSD
F_1	1.000	1.79	1.001	1.92	1.003	1.87	1.001	1.80
F_2	8.997	1.57	9.005	1.55	8.997	1.95	9.004	1.55
x_3	10.002	2.04	10.003	2.13	10.032	2.38	10.004	2.03
S	1.929	1.68	1.931	1.66	1.929	2.06	1.930	1.66
ρ_R	0.955	0.24	0.955	0.24	0.955	0.30	0.955	0.24
x_4	10.002	2.04	10.003	2.13	10.032	2.38	10.004	2.03
F_6	0.055	15.20	0.055	15.04	0.055	15.14	0.055	14.77
F_7	10.051	1.43	10.060	1.41	10.056	1.76	10.060	1.42
x_7	9.948	2.04	9.949	2.12	9.977	2.38	9.949	2.03

The model-based DR and GED problems are solved in MATLAB using the approach reported in Moreno et al. (2017). The GED involves solving the global test (GT) and measurement test (MT). MT requires linearization of constraints. The bilinear component balances and Equation 4-5 are linearized using Taylor series expansion. Equation 4-3 is highly nonlinear and is linearized as a linear function of roll gap at the corresponding operating conditions. A total of 1000 random normal measurements using the mean and standard deviations given in Table 4-5 are simulated. Average values of these noisy measurements are compared with the corresponding reconciled values to demonstrate the improvement in measurement accuracy and are presented in Table 4-5, with units same as those given in Table 4-4.

4.5.1.2.1 Normal operating conditions (NOC)

At NOC, all the nine measurements are expected to be active with true values and RSD as shown in Table 4-4. DR and GED for the system of equations result in improved accuracy for most process variables, particularly for the CU at all locations, as shown in Table 4-5 ('NOC' column), while ensuring material balance closure across all units and the process.

4.5.1.2.2 Case 1: Biased measurement from the NIR sensor

Suppose the NIR sensor reports the CU for x_3 as 15 wt%, while the measurements from the rest of the sensors are normal. In such situation, a bias resulting from fouling might be expected. By performing GED and DR, this faulty measurement can be rectified. The reconciled estimate for the CU at Location 3 is closer to the NOC conditions. The reconciled measurement for a shorter duration of gross errors in x_3 is shown in Fig. 4-14 (left). The results of the case study are in Table 4-5 ('Case 1' column).

4.5.1.2.3 Case 2: Biased measurement from X-ray sensor

During steady-state plant operations, the X-ray sensor at Location 3 (F_7) reports a reduced flow rate of 8 kg/h. With a granulation process, material losses or ratholing in hoppers are always a possibility. However, if both cases are dismissed, the measurement must simply be biased. For the X-ray sensor, faulty measurements arising from communication failure or calibration error resulting from corrective actions for mitigating fouling are possible. In this case, the GED and DR use the existing redundancy in the sensor network to confirm that the process state remains within bounds and thus, a shutdown of the process is avoided. The reconciled measurement for a shorter duration of gross errors in F_7 is shown in Fig. 4-14 (right) and the results are presented in Table 4-5 ('Case 2' column).

4.5.1.2.4 Case 3: Unavailability of ribbon density sensor

Calibration of sensors for providing inline measurements of physical properties such as ribbon density is challenging. Moreover, installation of such sensors within the compactor at the ribbon location may require modifications to the equipment and plant setup. The decision to avoid these complexities will result in the unavailability of a direct density measurement. In this case

study, we assume ρ_R is an unmeasured variable, reducing the DoR to five. However, an estimate of the ribbon density is important for downstream tableting. DR can accommodate sensor unavailability for estimation of CQAs using process models and measurement redundancy. DR can provide accurate state estimates as shown in Table 4-5 ('Case 3' column), confirming that the process is within bounds.

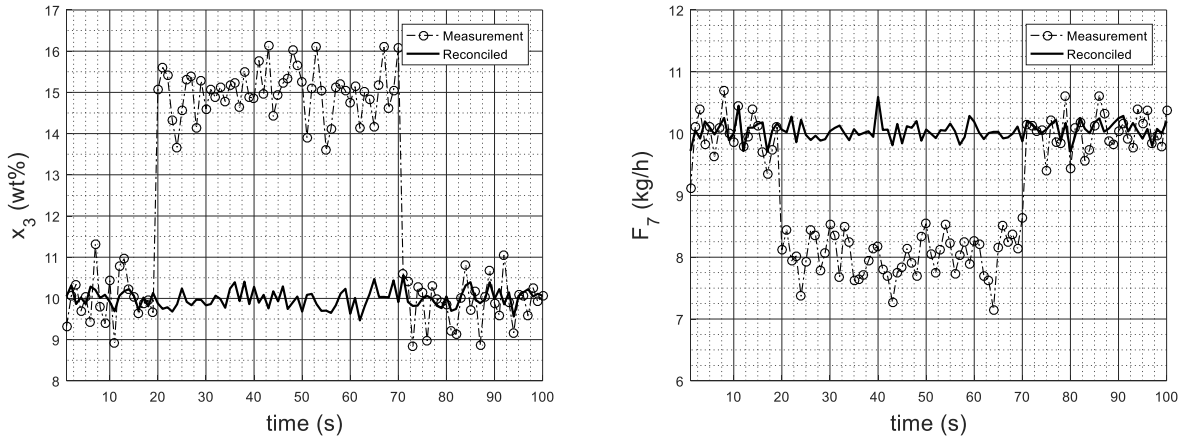


Figure 4-14: The reconciled values for measurements with gross errors. Bias in x_3 (Case 1, Left figure) and F_7 (Case 2, Right figure)

4.5.1.3 Discussion

For pharmaceutical processes, a measurement of the blend CU inline after every unit operation is essential and is typically achieved using NIR. The measurement RSD for the sensor depends on the material, location, spectra averaging, smoothing, etc. The challenge is to maintain the RSD within regulatory limits. Newer technologies for direct measurement of process variables with simplified calibration are very much desired. However, maintenance action to correct fouling of a sensor could result in bias for the measured variable which is beyond acceptable limits. It would be infeasible to pause a continuous process frequently to check for such errors. Also, ensuring material balance closure is crucial to maintain robust and profitable operations.

4.5.1.4 Conclusions

The case studies in this paper illustrate some of the practical challenges in the implementation of robust inline sensing in continuous pharmaceutical tableting. Specifically, we demonstrate the application of DR and GED to the system of unit operations and sensors using mechanistic models and material balance to obtain reliable and accurate estimates of the process

state. Expanding this framework to add the models of other unit operations and measurement technologies is a part of our current research. Moreover, in ongoing work, we show that the application of a DR framework facilitates effective implementation of process control systems (Su et al., 2017). Robust process operations using systematic sensing and control systems are essential for reliable function of a material-tracking framework, leading to real-time release testing in pharmaceutical manufacturing.

4.5.2 Sensor Network Robustness

In this section, the reader is referred to the continuous dry granulation example from (Moreno et al., 2019). The experimental, modeling and sensing contributions of this work contributed to the experimental end-end continuous tableting runs to illustrate the use of the model in a data reconciliation and gross error detection framework. In addition, the x-ray system discussed in Chapter 3 of this work, and the process level control room network architecture described in Chapter 6 were utilized for the implementation of the demonstrated experiments.

4.6 Summary

Mechanistic understanding of the roller compaction and implementation of inline sensors enable predicting the ribbon density in real-time. Implementing the sensors in real-time required significant effort in calibration, overcoming sampling challenges and yet measurement bias is observed in quantitative monitoring. As a result, for effective real-time monitoring and model-based automation, it is imperative to integrate the inline process measurements with mechanistic understanding in a systematic framework for reliable estimates of the ribbon density. Hence, the developments from this work is used in applications of model-based data reconciliation for robust process monitoring. These applications are available in published literature through the works of former research group members (Moreno, 2019).

5 A PERSPECTIVE ON QUALITY BY CONTROL IN PHARMACEUTICAL CONTINUOUS MANUFACTURING

5.1 Introduction

Developments since the 2000s following QbD, PAT, and continuous manufacturing in the pharmaceutical industry facilitated the applications of process monitoring and control methods for the critical quality attributes (CQAs) and critical process parameters (CPPs). Quality by Control (QbC) was recently introduced as a framework to bridge the implementation gap between the development and implementation of advanced process control methods for the manufacture of pharmaceutical products engineered using QbD (Nagy, 2016). These advancements towards real-time quality assurance from Quality-by-Testing (QbT), the quality control approach to test the quality attributes of in-process material or final product at the end of each batch processing step, is shown in Figure 5-1.

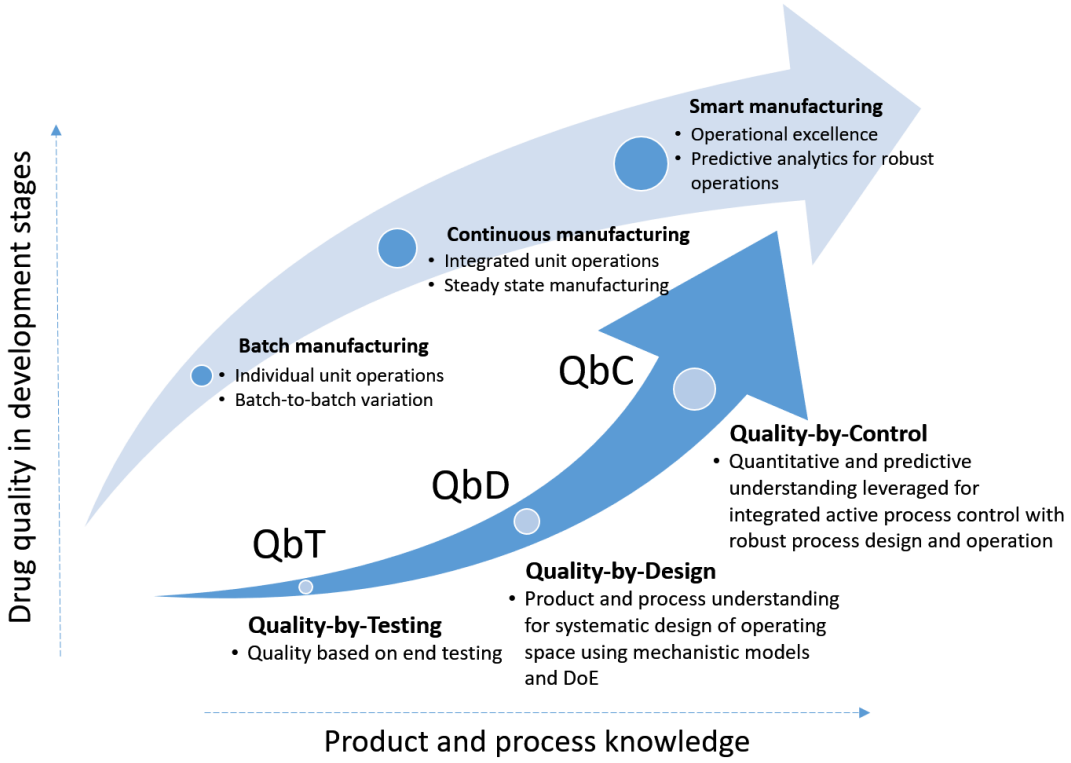


Figure 5-1: The systematic progression in quality assurance via QbT, QbD, and QbC (Su et al., 2019c).

In this chapter, an overview of the QbC framework is discussed by reprinting relevant section excerpts from the article entitled 'A perspective on Quality-by-Control (QbC) in pharmaceutical continuous manufacturing' published in 'Computers and Chemical Engineering' (Su et al., 2019c). As a second author in this article, contributions from this dissertation included developing the systems integration architecture to demonstrate the QbC framework. To succinctly discuss the same, the reprints include the sections discussing (i) the overview of the QbC concept, (ii) demonstration on a tablet press, and (iii) the challenges of QbC implementation and a summary of key learnings.

Importantly, through the implementation considerations discussed in this chapter, a need to develop systematic maintenance practices was a key lesson learned, which led to the work discussed in Chapter 6. Furthermore, the architecture discussed in this chapter also supported additional RTPM applications pursued by the research group, culminating in published works (Moreno et al., 2019; Su et al., 2019a, 2018b). Additional details of the architecture, including further improvements is addressed in Chapter 6.

5.2 Quality-by-Control

5.2.1 Background

The QbD guidance has promoted the systematic generation of the essential product and process knowledge required to implement continuous operation by identifying the critical material/quality attributes, process parameters, and the control strategies required to maintain the process operation and the quality of the product under a state of control. Recently, a three-level control strategy based on pharmaceutical QbD guidance was proposed, in which the idea of active process control was highlighted (Yu et al., 2014). This quality control strategy was then further elaborated by Lee and co-workers (Lee et al., 2015) with an emphasis on modernizing pharmaceutical manufacturing by transitioning from batch to continuous production. These developments have laid the foundations for the idea of QbC (Simone, Zhang, & Nagy, 2015; Yang, Song, & Nagy, 2015; Içten, Nagy, & Reklaitis, 2015; Nagy Z. , 2014).

A three-level quality control strategy for a continuous manufacturing process (Yu et al., 2014) was proposed to maintain the quality of the product in response to potential variations or disturbance in the process, equipment conditions, incoming raw materials, or environmental factors over time. For example, an intuitive Level-3 quality control strategy imposes tight constraints on material attributes and process parameters that affect product quality and relies on extensive end-product testing at each processing step to ensure final product quality. This level of control is commonly used in batch manufacturing, viz., the QbT, by strictly tracking a recipe during operation to ensure that those parameters are maintained within constrains. This level of control requires limited understanding, particularly at the early stage of drug development, on how raw material and process variability affects product quality. It is too conservative and is neither feasible to be effectively implemented in continuous manufacturing processes nor adaptable to achieve the benefits of continuous manufacturing (Lee et al., 2015).

The demands on end-product testing can be reduced by using a Level-2 control strategy under which variations of raw material attributes and process parameters are maintained within a design space. The design space established under the QbD guidance (CDER US FDA, 2009) requires the identification of potential sources of raw material and process variability that can impact product quality, as well the understanding of the impact that variability from these sources has on in-process materials, downstream processing, and drug product quality. Hence, drug development at the late stage or pilot manufacturing within a design space allows some flexibility in raw material and process parameters and reduces the reliance on extensive end-product testing. Intrinsically in continuous manufacturing, the process is operated in such a manner as to be consistently within the design space. As a result, Level-2 controls which employ an established design space have been implemented in most reported continuous manufacturing facilities using multivariate statistical process control methods (Almaya et al., 2017).

However, the operation within the limited design space established during product and process development can result in a lack of effectiveness in responding to process disturbances or variations that are commonly seen in continuous manufacturing process. For example, when a process disturbance leads to a departure of a CQA variable from its targeted setpoint or acceptable range, the adjustment of a CPP variable within the limited range allowed by the design space could

take a long time to bring the CQA variable back to acceptable criteria, resulting a long period of generation of non-conforming material. On the other hand, a more aggressive manipulation of the CPP variable, e.g., with an intentional overshoot, which may extend outside of the design space, is more likely to return the CQA variable within the design space much sooner. Furthermore, the concept of design space is also too rigid to adapt to mismatches in product and process understanding, e.g., material compressibility changes due to powder moisture content or particle size variations (Gupta et al., 2013).

By contrast, a Level-1 quality control strategy would feature the use of an active process control system to monitor and control the quality attributes of materials in real-time. In response to a disturbance, process parameters would be automatically and optimally adjusted to ensure these quality attributes consistently conform to the established acceptance criteria. This level of control represents a high degree of product and process understanding that can also be identified under the QbD guidance. The enhanced process understanding, which includes identification of dynamic relationships linking critical material attributes (CMAs) and CPPs to CQAs, will enable the design of an engineering control system with quantitative and predictive capabilities. As a result, the impact of upstream disturbance on downstream processing can be minimized through optimal control adjustments and any mismatches in product and process understanding can be mitigated with an adaptive and predictive control strategy. The design of such a quantitative and predictive control system at Level 1, which is based on the QbD guidance, minimizes the risk of producing off-spec product and enables real-time release, is the foundational component of QbC.

As defined by the QbD guidance, the application of the QbD framework also includes the design and implementation of a suitable control system, subsequent to the design of the operating space. However, the QbD guidance does not suggest a systematic quantitative procedure for the design of the suitable control architecture and methodology. In this context, the original QbC idea can be extended and enriched as the framework for systematic design of an active process control system that enables both the robust design and operation of the pharmaceutical manufacturing system. Thus, QbC is a logical extension of QbD which is backward compatible with the QbD guidance.

The recent progress in mechanistic understanding of processes and advancements in PAT tools can also be incorporated within this holistic QbC framework to further the adoption of model-based process automation and quality assurance in process operations (Pantelides and Renfro, 2013). Interestingly, a QbC application which highlighted the use of MPC in pharmaceutical bioprocesses was reported in. Moreover, as the pharmaceutical industry begins to adopt smart manufacturing practices, a modular approach to systems integration and process operations is crucial for optimal asset utilization and knowledge management. A systematic integration of process equipment, sensors and control systems in accordance with process automation standards enables the effective implementation of the real-time data analytics and associated knowledge management which are required to achieve RTR testing in pharmaceutical manufacturing.

5.2.2 Definition

The definition of QbC can be restated as follows: QbC consists of the design and operation of a robust manufacturing system that is achieved through an active process control system designed in accordance with hierarchical process automation principles, based on a high degree of quantitative and predictive product and process understanding. QbC in general enables reliable batch and continuous process operations, especially the real-time release in continuous manufacturing of pharmaceutical products.

5.2.3 Recent development towards QbC

Recently, with an aim towards integrating design and operations along the QbC paradigm, a systematic framework employing appropriate process systems engineering tools was proposed to develop and evaluate feasible active process control strategies (Su et al., 2017). Specifically, the hierarchical process control structure, as shown in Figure 5-2, structured according to the ISA-95 Enterprise-Control System Integration Standard, is focused more on the implementation with the levels classified according to the scale of their control objectives, not to be confused with that in for quality control strategy. For example, in a continuous direct compaction process, the Level 0 control is often implemented via the programmable logic control (PLC) system that is built into the unit operation equipment to control single/multiple CPPs. The Level 1 control relies on the use of PAT tools to measure and control CQAs and may encompass multiple unit operations. Hence,

the Level 1 control supervises the Level 0 control typically using cascaded single input and single output (SISO) control loops with the aim of achieving desired setpoints for CQAs. Level 1 control systems often span across unit operations and are designed using efficient feedback/feedforward control algorithms to reduce the impact of disturbance that otherwise may propagate downstream. A distributed control system (DCS) is employed in this regard for integrating process equipment such as the feeders and tablet press and the instrumentation for measuring material properties. The distinguishing feature of the more advanced approaches applied at Level 2 is the use of mathematical models for validating process measurements, predicting the effects of disturbances and changes in the CPPs on the CQAs, fault detection, and intensifying process operations. The functionalities provided at Level 2 may include data reconciliation (DR) and gross error detection (GED), MPC, and real-time optimization (RTO), among others.

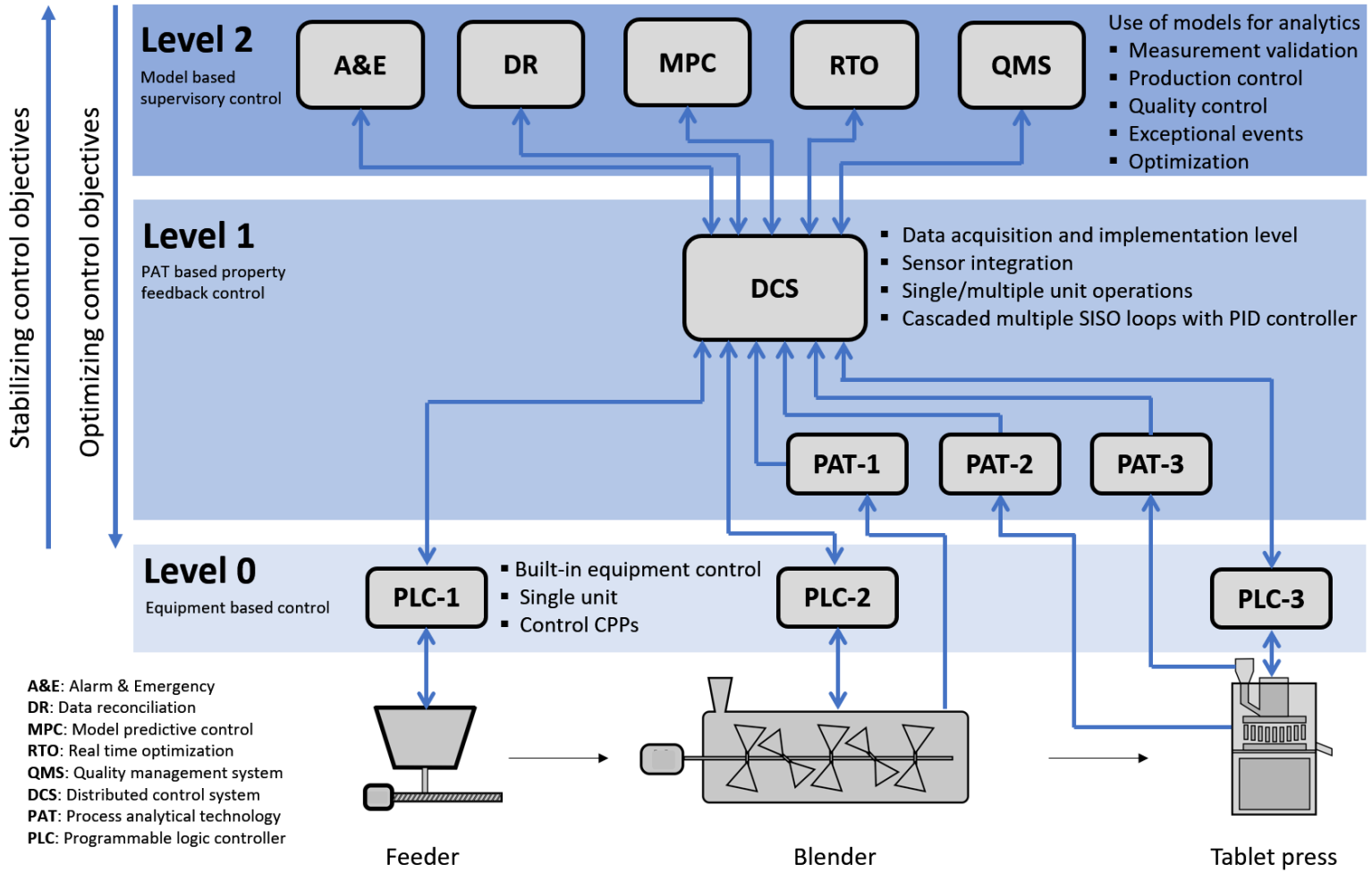


Figure 5-2: A hierarchical implementation of control systems for a continuous direct compaction process.

5.3 Case study: QbC implementation in continuous tableting

5.3.1 Continuous rotary tablet press

Tablets are the most common oral solid dosage form. They are manufactured by direct compression or by dry/wet granulation, based on material properties and formulation requirements. The processing steps involved in direct compression consist of powder feeding, blending and tableting unit operations. The case study presented in this work was performed in Continuous Solids Processing Pilot Plant at Purdue University. This integrated continuous manufacturing line begins with two Schenck AccuRate PureFeed® AP-300 loss-in-weight feeders. These feeders continuously feed the API, Acetaminophen (APAP, Grade 0048), and the excipient, Microcrystalline Cellulose Avicel PH-200 (MCC 200), into a Gericke GCM-250 continuous blender, wherein the two components are mixed. A Schenck AccuRate PureFeed® DP-4 disc feeder feeds silicon dioxide as a glidant into another Gericke GCM 250 continuous blender. The blended material is conveyed to feed a Natoli BLP-16 rotary tablet press featuring a total of 16 punch-die stations.

The tablet press is a multi-stage process, in which each station undergoes the following main steps: die filling, metering, pre-compression, main-compression, tablet ejection and take-off from lower punch. After the blend is fed into the die, the metering stage is adjusted to achieve the dosing position, i.e., the volume of powder inside the die. The powder is then locked between upper and lower punches during pre-compression and main-compression until the tablet ejection and take-off stages are reached. The pre-compression stage serves to remove air trapped in the die and to rearrange the particle packing, while the main-compression stage compacts and transforms the powder bed into a tablet. The tablet weight can be controlled by changing the dosing position subject to variations in powder bulk density, and in filling time due to changes in turret speed, or in filling efficacy due to changes in powder flow properties. The in-die tablet thickness is determined by the punch displacement which is manually set before the tableting operation for the tablet press used in this study. Hence, the maximum main-compression force dependents on the amount of powder in the die or, equivalently, on the tablet weight.

5.3.2 QbC implementation

The continuous direct compaction process was integrated with PAT sensors to monitor the process operation within the design-space and process control strategies to maintain consistent product quality. For example, the API mass fraction was measured *in situ* using a Near-Infrared spectrometer (Control Development, Inc.) at the exit of the first continuous blender. The powder flow rate was measured using an X-ray based mass flow meter (SETXvue XP-300, En'Urga, Inc.) (Ganesh et al., 2017).

An Emerson DeltaV 13.3 distributed control system is used to integrate process equipment and develop the automation system in this pilot-plant-scale facility. A modular and hierarchical network architecture has been implemented following ISA 95 and DeltaV Security Manual recommendations for systematic implementation of QbC. The network diagram of the pilot plant is shown in Figure 5-3. Relevant firewalls are set up based on DeltaV Area Control Network, DeltaV and non-DeltaV machine interfacing and access to Purdue's Network for software licenses. The DeltaV workstations are set up as virtual workstations using VMWare Type 1 hypervisor. The loss in weight feeders and blender communicate using a Profibus network, while the Yasakawa controller on the Natoli BLP-16 tablet press equipment communicates with DeltaV via a VIM2 card, configured using VIMNet explorer in the Engineering Station. Control modules for the process equipment are implemented using DeltaV Control Studio in the DeltaV ProPlus Workstation. Relevant process variables are recorded in the DeltaV historian. The DeltaV data access server and historian are accessed using the Application Station. The data from PAT Tools that are interfaced with the process are acquired in laptop computers consisting of the PAT specific hardware and software. Execution of the data reconciliation algorithm is performed in the PAT-Main laptop. Tools such as KepServerEX, LinkMaster (both Kepware, PTC Inc.) and Matlab's Instrument Control Toolbox (MathWorks Inc.) are used to interface the PATs, the laptops and the control system.

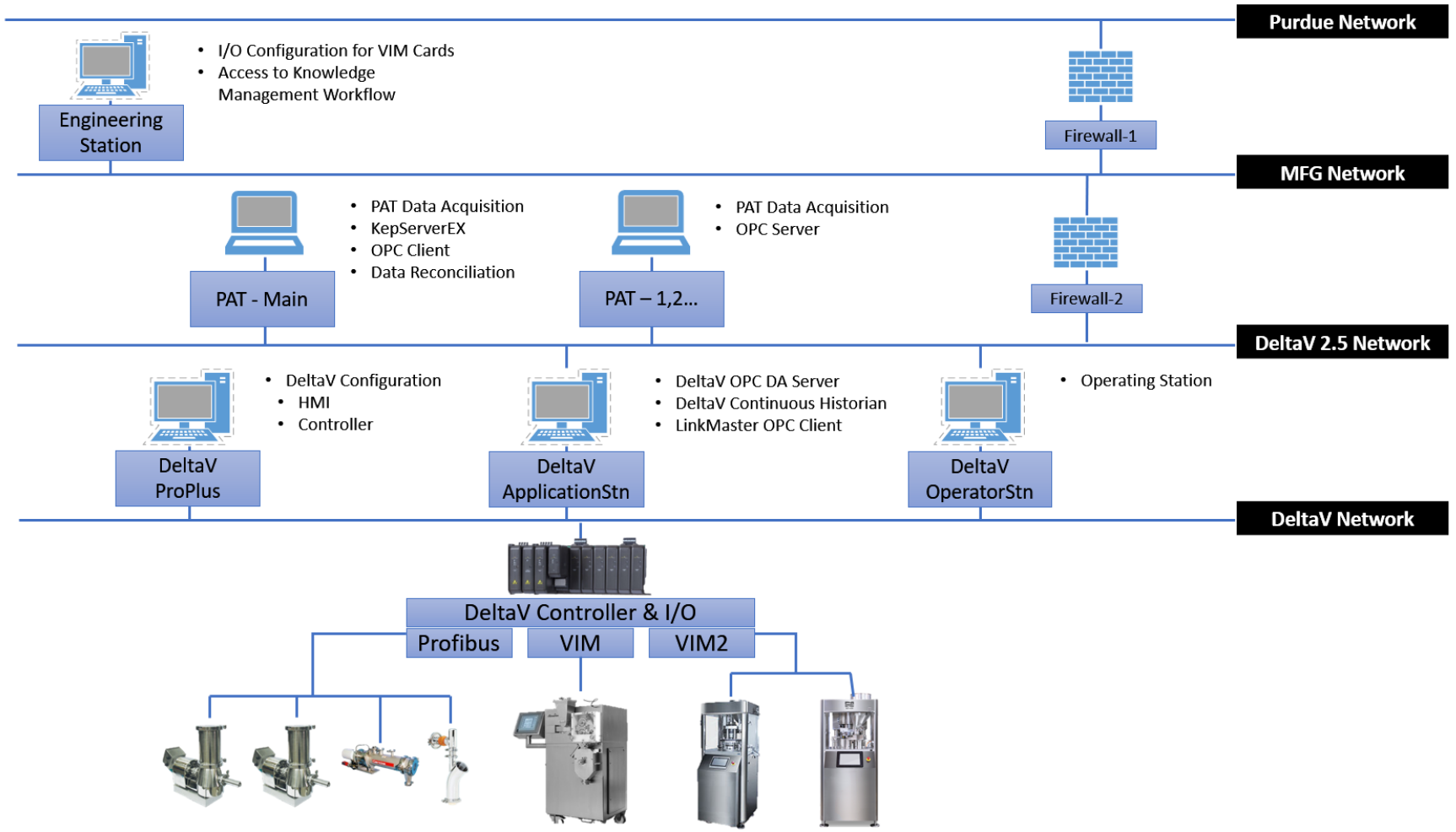


Figure 5-3: Network setup in continuous tablet manufacturing pilot plant at Purdue University.

Specifically, the critical-to-quality variables in the tablet press were identified as tablet weight, relative density, tensile strength and main compression force. The weight of the tablet ultimately determines the API potency within a dose. It also determines the main compression force at the pre-set punch displacement, or in-die tablet height, and thus the relative density and tensile strength of the tablet, which in turn affect the final product attributes such as tablet dissolution behavior. Commercial at-line instruments, such as Sotax AutoTest 4 tablet tester, are often employed to measure the tablet weight, as well as tensile strength and dimensions, at a frequency of several minutes. However, destructive and time-consuming measurements cannot be efficiently integrated with existing process control system to maintain consistent quality production in real time. Therefore, an in-house design for real-time tablet weight measurement based on a Mettler Toledo ME 4001E balance was employed in this study, as discussed in the next subsection. Though a similar design was also used in a recent work for tablet weight control, neither the tablet weight measurement reliability and accuracy were thoroughly verified therein, nor its validity in enhancing the real-time tablet weight control was confirmed. For example, the effect of introducing extra variations due to measurement data imperfection or process control into the tablet quality attributes compared to the conventional open-loop or the Level 0 control operation was not demonstrated. Another drawback of a sampling time of 20 s in their tablet press data acquisition system was also found, which may impede capturing process dynamics and thus downgrade the expected process control performance. Hence, in the following sections, a QbD understanding of the material properties and tablet press performance is combined with a data reconciliation strategy for tablet weight measurement to enhance the QbC implementation for the continuous rotary tablet press.

5.3.3 Active process control of continuous tablet press

The Natoli BLP-16 tablet press has a built-in PLC panel to manipulate process parameters of dosing position and turret speed, which is regarded as a Level 0 control in this context. A Level 1 control with decoupled PID control loops was designed for a cascaded control of tablet weight, tablet production rate, and main compression force by manipulating the setpoints of dosing position and turret speed at the Level 0 control. A Level 2 MPC was also designed, in which the main compression force was constrained and monitored as it is closely related to the tablet CQAs of hardness, tensile strength, and dissolution rate. Emerson DeltaV Control Studio and DeltaV

Predict toolbox were utilized for Level 1 and 2 control development and implementation, respectively, details of the control loops can be found in Figure 5-4. Note here that both Level 1 PID control and Level 2 MPC control used the reconciled tablet weight measurement from Level 2 data reconciliation. Details of system dynamic responses under step changes in dosing position, turret speed, and system interactions under Level 1 and Level 2 closed-loop control of the studied tablet press can be found elsewhere (Su et al., 2018a). For QbC demonstration purpose in this case study, continuous tableting experiments were performed in three different scenarios: (i) Level 0 control, (ii) Level 1 control, and (iii) Level 2 control to validate the online data reconciliation, as well to compare the control system performances, as shown in Figure 5-5. The at-line Sotax AT4 tester was implemented to sample the tablets during the run to independently verify the final tablet quality.

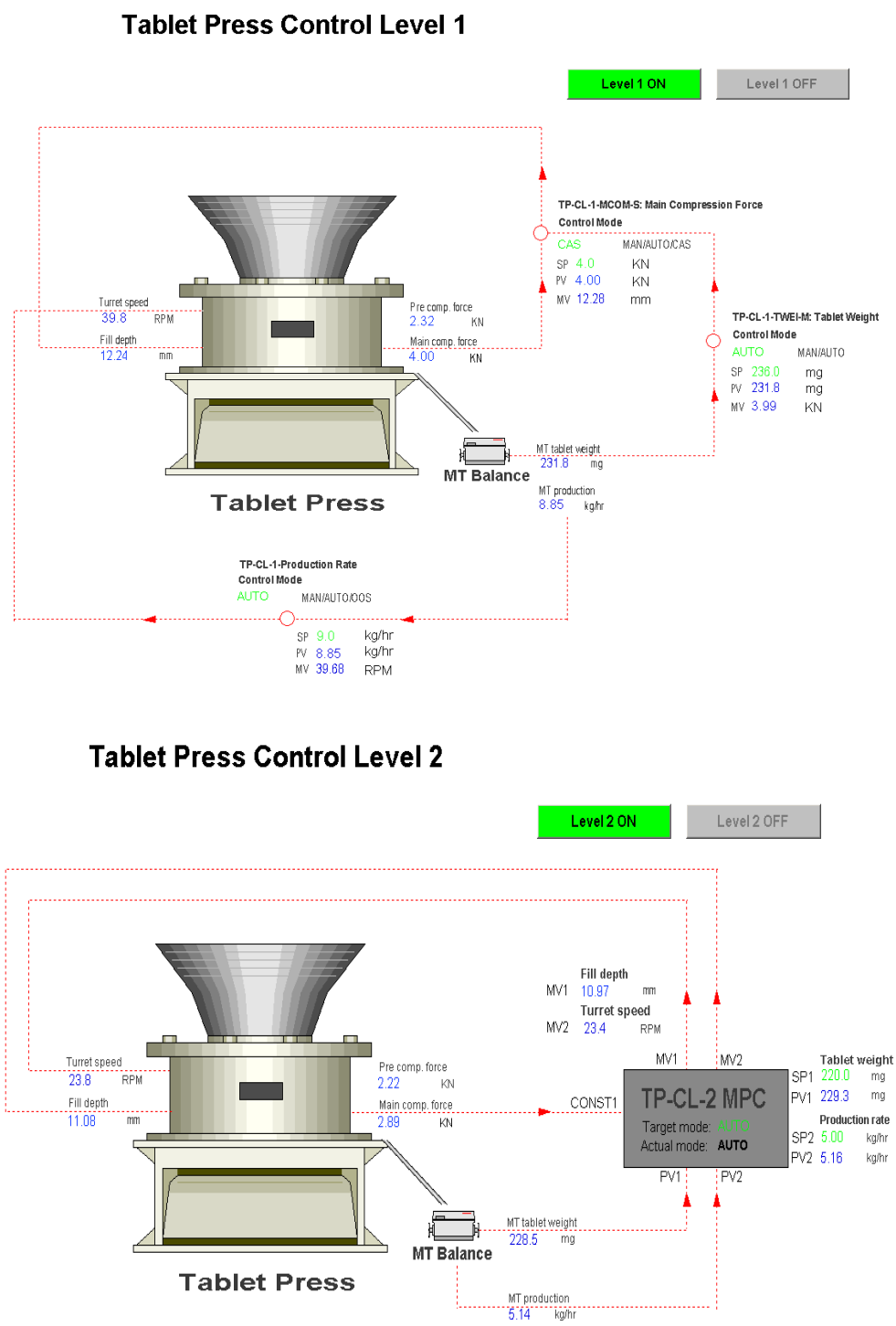


Figure 5-4: The hierarchical Level 1 PID (top) and Level 2 MPC (bottom) control for continuous tablet press at DeltaV DCS system.

A total of 16 tablets were analyzed at each sampling instant with the Sotax AT4 tester, viz., by collecting all the tablets produced in one rotation of the turret. In such a way, variation among punch stations and variation with processing time can both be characterized, (see the box plot of sampling data points and the zoomed-in inset in Figure 5-5(a). The Level 0 control operation at the beginning of the tablet press run in Figure 5-5(a) was to confirm that the reconciled tablet weight measurement agreed well with the at-line measurement or to allow the data reconciliation to automatically update the critical relative density in order to reduce possible model-plant mismatch due to material variation. Note that the reconciled tablet weight measurement started to match the Sotax AT4 measurement at the third sample and the updated critical relative density at the beginning of the operation in Figure 5-5(c). Furthermore, during the control closed-loop operation, the data reconciliation continued updating the model parameter and reached a plateau under Level 1 and Level 2 control set-point changes. Even after a reinitialization of data reconciliation at time 3600s in Figure 5-5(c) by setting the Kawakita model parameter of critical density ρ_c to its initial value of 0.250, offset between reconciled tablet weight measurement and at-line Sotax AT4 measurement was observed but was then gradually reduced with the update of critical relative density. Hence, the proposed data reconciliation demonstrated an important feature of on-line automatic calibration for tablet weight measurement and was not interfering with the control system design.

The control performance of the tablet press was good using both the Level 1 and Level 2 strategies, viz., the tablet weight reached the setpoints steadily under both control strategies except that the Level 2 MPC control showed a more aggressive and promising control performance. During the setpoint changes of tablet weight, the tablet production rate was maintained the same to adjust to the campaign production or processing capability upstream, *e.g.*, the feeding and blending, see Figure 5-5(b). More importantly, variations of the tablet weight among 16 stations at steady-state remained the same as the control open-loop operation with current experiment runs, (see the box plots of each sampling point in Figure 5-5(a)). Moreover, these variations along the processing time were also well preserved and verified under steady-state operation, see the at-line tablet weight measurements at setpoint of 234 and 260 mg, except during the time when data reconciliation was deliberately reinitialized. Overall, the control system design was shown capable of achieving the process automation to reach the targeted tablet weight setpoint automatically and

steadily, which is important during process startup or product switch. Another benefit of the active process control system is to maintain the tablet weight under common risk of process disturbances or material property variations, thus attaining a real-time release strategy. Specifically, the performance improvement by the Level 2 MPC is significant in shortening the period of diversion of off-spec product during setpoint changes or process disturbance.

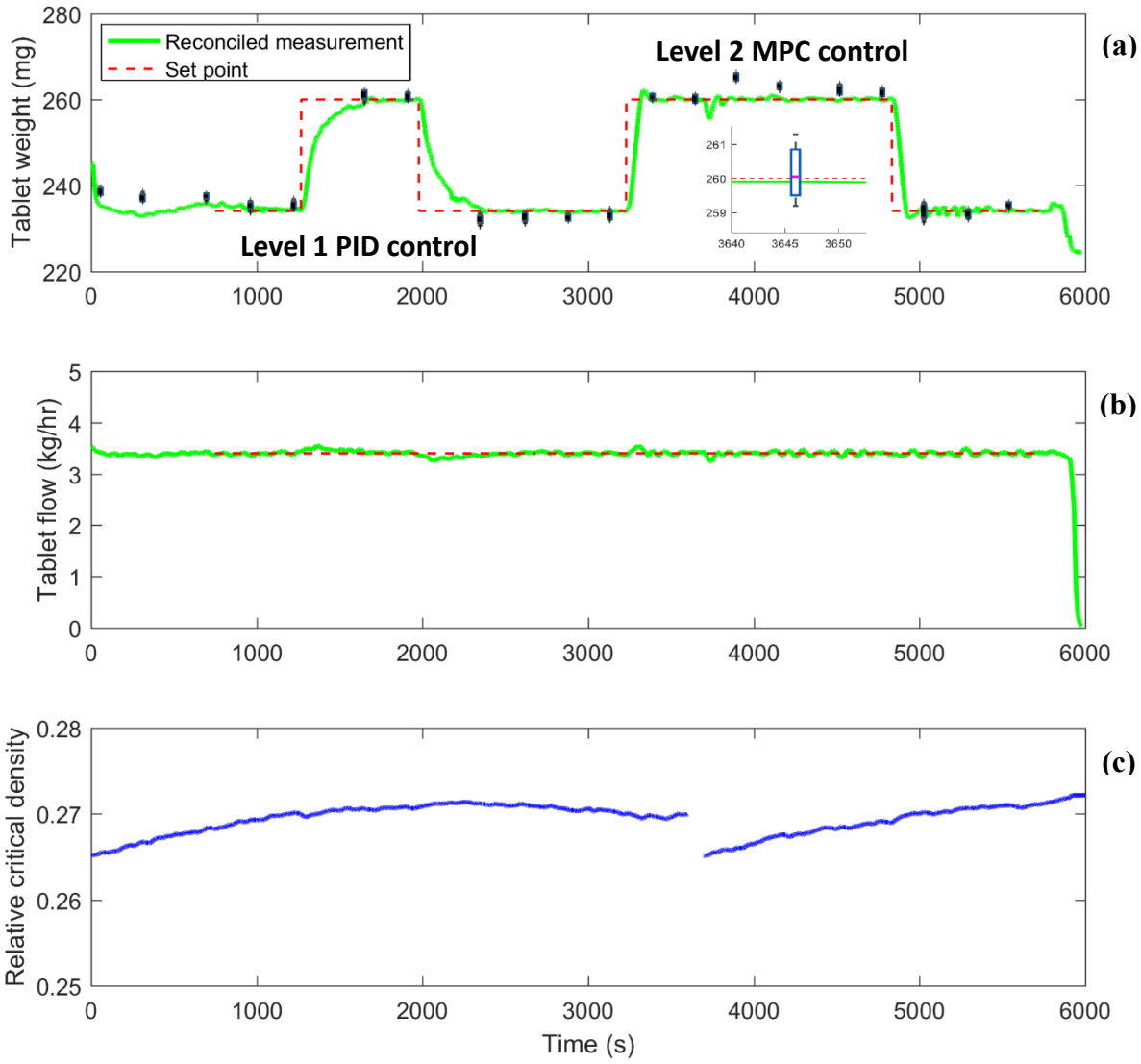


Figure 5-5: Online integrated data reconciliation and process control of Level 1 and 2 for continuous tablet press.

5.4 Challenges of QbC in continuous pharmaceutical manufacturing

First, systematic frameworks based on sound control engineering theories for process control development in continuous pharmaceutical manufacturing have not yet achieved a common understanding and wider application in the industry. Classical process control engineering theory has matured and been extensively employed in continuous fluid-based petroleum and chemical industries. In these applications, process dynamics is often driven by chemical reaction or mass transport, which have response times measured in minutes to hours. Thus, this process control experience may or may not be directly transferable to the more challenging solid-based unit operations typically employed in pharmaceutical secondary manufacturing, where physical changes usually occur within seconds or minutes and therefore faster response may be required of the control system. Furthermore, in pharmaceutical continuous manufacturing there may be limited hold-up in each unit operation to mitigate segregation and thus the buffering provided by material inventory is limited. Additionally, stream recycling or substantial back mixing in the process must be avoided in highly-regulated pharmaceutical secondary manufacturing due to the necessities of maintaining lot identity for material tracking purposes. Thus, variability in raw materials upstream has a rapid and direct impact on downstream processes, which affect the in-process materials and final drug product qualities. In this regard, control system with QbC design should be able to respond to the disturbance rapidly in a predictive or combined feedback and feedforward manner, rather than the classical feedback control design, making the consistent production of quality solid dosage challenging.

Secondly, deployment of PAT tools in real-time remains challenging given the complexity of sensor calibration, and model validations. The sensor positioning, sampling concerns and fouling result in measurement drifts and bias, thereby affecting real-time process data accuracy. Sensor network design and maintenance for reliable CQA measurements have not been systematically studied in continuous manufacturing in pharma industry. It is worth noting that the robust mechanical design of traditional manufacturing equipment (such as rotary tablet press, roller compactor, etc.) has resulted in minimum variation of CPPs and/or CQAs during operation and thus allowed batch pharmaceutical manufacturing to assess quality using post-batch statistical quality control (SQC) methods. A QbC active process control system, by contrast, is challenged to use possibly noisy and biased CQA measurements to effectively supervise the control of CPPs

and minimize the need for batch-end SQC. These issues impose the need for some degree of redundancy in sensor network so as to allow application of methodology such as data reconciliation and gross error detection. The data reconciliation strategy has been recently shown to be able reduce the measurement noise in a continuous feeding-blending system and to detect measurement errors in CQA variables. Further studies on using data reconciliation combined with joint state and parameter estimation are needed for QbC implementation to address issues associated with the uncertain measurements of CQA's provided by some spectroscopy-based PAT tools. An important aspect to investigate is the extent to which this integration imposes additional dynamics on the process, and how this could potentially amplify variations in CPPs and thus in CQAs.

Thirdly, process performance monitoring and continuous improvement in continuous manufacturing are seldom reported in the pharma industry. Continuous improvement is pursued in most manufacturing sectors to exploit the deeper understanding of the manufacturing system and its components, which naturally develop as manufacturing experience with a product and process is accumulated, as also identified in QbD guidance. Despite its potential, continuous improvement has not been pursued aggressively in pharmaceutical manufacturing, given the real and perceived regulatory burden of approvals required for changes. Hence, the advent of continuous pharmaceutical manufacturing with the proposed QbC paradigm opens the door to continuous improvement at multiple levels, including predictive maintenance, control performance monitoring, control structure re-organizing, etc., since such improvements can be targeted to achieve tighter tracking of CQA and more robust plant wide control, which will maintain the process within its designed operating space. The direct impact is to allow longer continuous runs without forced interruption, reduced frequency and duration of periods during which nonconforming materials are generated, and reduced risk that a product lot released may include nonconforming material. Herein, three research challenges to be addressed under QbC are centered on the use of high frequency sampled data, reduction of process-plant mismatch and closed loop model identification, which are captured in Figure 5-6. For example, process model identification is one of the important steps in systematically accounting for process uncertainties or model-plant mismatch in model-based control strategies in pharmaceutical continuous manufacturing.

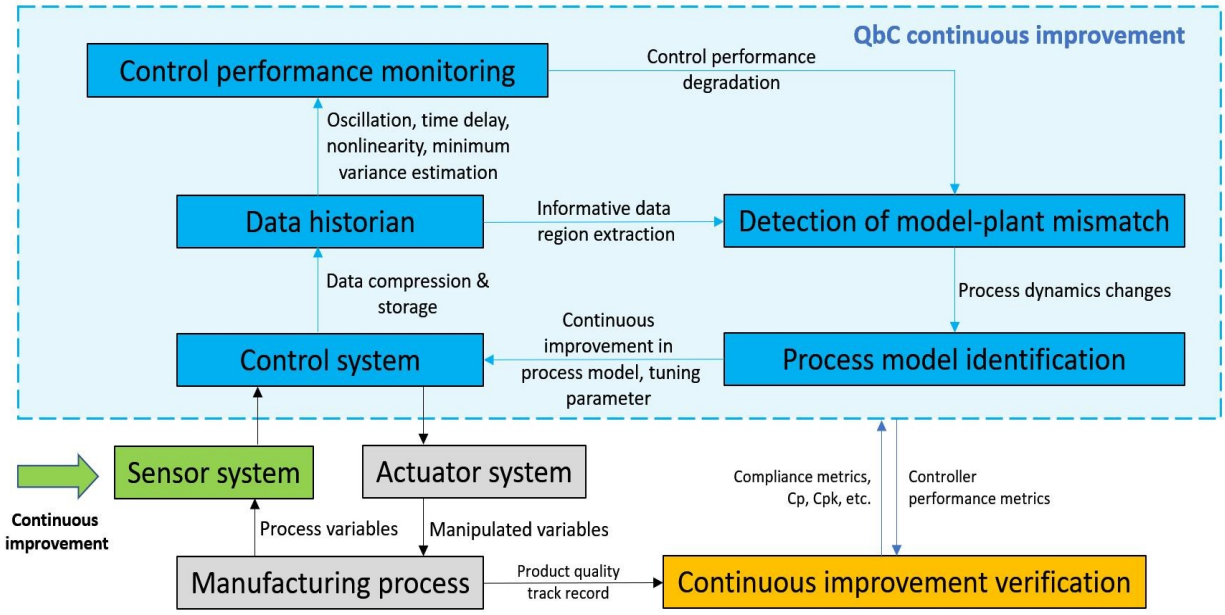


Figure 5-6: Continuous improvement in QbC system in pharmaceutical continuous manufacturing.

6 CONDITION-BASED MAINTENANCE FOR PROCESS OPERATIONS MANAGEMENT IN CONTINUOUS TABLET MANUFACTURING

6.1 Introduction

Manufacturing innovations in the pharmaceutical industry have proliferated since the mid-2000s following the initiatives on Quality by Design (QbD) and Process Analytical Technology (PAT) of the United States Food and Drug Administration (FDA) (FDA, 2004a; Ierapetritou et al., 2016; Troup and Georgakis, 2013; Yu et al., 2019). One such set of manufacturing innovations that are helping industry progress towards operational excellence are the design and operations of integrated continuous processes (Yu and Kopcha, 2017). The ultimate goal of such integrated systems is to ensure that the individual elements function collectively as a whole and satisfy the design properties or characteristics of the overall system (SEBoK, 2019a). The implementation challenges and fault scenarios of the subsystems do impact the operations of the integrated system, notably, a failure or unplanned downtime in one of the subsystems could result in a downtime of the entire process. Failures in advanced pharmaceutical manufacturing systems could lead to uncertain quality, resulting in the requirement for increased offline quality testing or issuing recalls, hence impacting time to market and consumer reach. Hence, the complexities of the individual components and their integration into a larger system warrant comprehensive safety and reliability efforts for ensuring the functioning of every component , thus, preventing systemic failures (Venkatasubramanian, 2011). This work is, hence, an attempt to introduce Condition-Based Maintenance (CBM) as a strategy for continued verification and sustainment of process operations. The continuous manufacture of oral solid doses (OSD-CM) is used as a case study to illustrate CBM. Six drug products produced via OSD-CM have been approved by the FDA in recent years, yet, there has been limited discussion on the management of abnormal conditions during operations, preventing unplanned deviations and downtime, and system sustainment (Gupta et al., 2013; Hamdan et al., 2012, 2010).

OSD-CM involves a systematized integration of solids processing unit operations, process analyzer, and information technology systems (CDER US FDA, 2019; Giridhar et al., 2014; Singh et al., 2014; Su et al., 2019c). Research efforts since the 2000s have resulted in data-driven and mechanistic models as well as heuristics for the design and operations of the process (Ierapetritou

et al., 2016). The real-time process management (RTPM) applications that enable process automation, such as process control, material tracking, fault management, and knowledge management, rely on process data from direct measurements as well as a combination of methods and models for soft-sensing. The sensor network, an integrated system for process monitoring encompassing the data sources built into the unit operations equipment, field devices and process analyzers, and the data architectures and infrastructure, enables the data flow required for managing the process and facility operations. Risk assessment is vital to ensure reliable operation of the sensor network for effective supervisory control of critical process parameters (CPPs) and critical quality attributes (CQAs) (Su et al., 2017). Although PAT tools and the data management infrastructure and system architectures have been developed for the implementation of OSD-CM (Brodbeck, 2018; Cao et al., 2018; Laske et al., 2017; Su et al., 2019c); there has been limited discussion on continued verification and robustness of the sensing infrastructure (Liu et al., 2018; Moreno et al., 2019, 2018; Su et al., 2019a). Hence, this work builds on the advances in RTPM for OSD-CM and aims to emphasize the system integration and maintenance aspects required to assure sensor network robustness.

Maintenance management is an integration of technical, administrative, and managerial actions during a system's life cycle to ensure the functional utility of an asset. Maintenance activities can be broadly classified as reactive or proactive. Reactive maintenance involves corrective or emergency maintenance, which is to correct a problem once an imminent risk has been manifested as a failure. Proactive strategies aim to manage the failure modes and the ensuing consequences before they occur using measures such as time-based or age-based inspection and replacement of components, or on detection using prognostic information of a condition that may lead to failure or degradation of the functionality of the system (Kothamasu et al., 2006). Maintenance activities for life cycle management of assets are not new to pharmaceutical manufacturing facilities, and both calendar-based and inter-batch preventive maintenance are generally employed (De Felice et al., 2014; Friedli et al., 2010). However, product dependent modular integration of unit operations and applicable monitoring technologies, potential increased run times as a scale-up strategy, and risks associated with material handling require additional considerations for qualification, maintenance, and cleaning of individual physical assets and the overall continuous manufacturing system (ASTM Committee E55, 2014; CDER US FDA, 2019).

The advances towards Smart Manufacturing or Industry 4.0 for the digitalization of process operations management (Davis et al., 2012; Isaksson et al., 2018) are enabling the availability and accessibility of real-time process data for proactive practices in fault monitoring, diagnosis and maintenance (Anand et al., 2019; Baur and Wee, 2015; Moyne and Iskandar, 2017; Venkatasubramanian, 2019). With increasing digitalization of process operations in the pharmaceutical industry, strategies for system reliability and proactive maintenance such as CBM offer numerous benefits for continuous process improvements through systematized management of assets and manufacturing operations (BioPhorum Operations Group, 2019; Herwig et al., 2017; Romero-Torres et al., 2017; Vann et al., 2018).

CBM is a proactive maintenance strategy for critical assets or those assets that have significant repair and replacement costs or cause significant impact on the process when they fail as identified through reliability centered maintenance analysis (Márquez, 2007). While the maintenance tasks can be performed following organizational philosophies such as total productive maintenance, CBM involves the methods for continuous or periodic assessment of system condition to trigger a fault condition based on a measured parameter limit, and further respond to the fault with a subsequent maintenance activity (Ahmad and Kamaruddin, 2012; Bengtsson and Lundström, 2018; Moubray, 1999; Shin and Jun, 2015). The awareness of system condition in order to trigger maintenance action enables reducing the failure risks in the initial stages of operation introduced from frequent preventive maintenance. Furthermore, the real-time assessment of process and maintenance data leads to lean operations of the manufacturing process by reducing the time required to perform a root cause analysis and the ensuing restoration activity. CBM has evolved since the mid-1900s with the growth in sensing and communication technologies as a key asset optimization and reliability improvement tool and is an enabler for predictive maintenance (Center for Chemical Process Safety, 2007; Márquez, 2007; Moubray, 1999; Moyne et al., 2012; OSIsoft LLC, 2018). It is worth highlighting that CBM, under the name of CBM Plus, is the maintenance policy of the United States Department of Defense for the assessment, sustainment and operations of defense systems (Office of the Assistant Secretary of Defense for Sustainment, 2008) and is recognized as an efficient and effective method of maintenance by the International Society of Automation (ISA) Technical Report 108 for Intelligent Device Management (ISA, 2015a).

The remainder of this article is organized as follows. First, Section 2 discusses the CBM framework by providing an overview of the data flow. This is followed by a proposed systems architecture for the implementation of CBM for supporting OSD-CM. Section 3 discusses the sensor network risks for OSD-CM and the developments in implementation of the systems architecture for CBM. A pilot-scale advanced manufacturing testbed for tablet processing is utilized for this illustration. The enterprise-control system integration is emphasized, while briefly discussing sample faults that may require continued verification during process operations. Concluding remarks are provided in Section 4. CBM is a mature maintenance management strategy, which could utilize a wide variety of analysis techniques, methods, and tools within the diagnosis, prognosis, and decision support systems. However, a detailed review and investigation of all of this methodology is beyond the scope of this work. We restrict our focus to those methods and tools we find to be most relevant to OSD-CM.

6.2 Development of a CBM Framework for OSD-CM

6.2.1 Data Flow

The data flow for CBM is comprised of three main steps and is illustrated in Figure 6-1. This data flow adopts the general workflows for fault detection and digitalization of process operations from the published literature (ISA, 2015a; Márquez, 2007; United States Department of Defense, 2008; Venkatasubramanian et al., 2003c). These three steps are briefly described in this subsection, which also highlights relevant contemporary developments in RTPM for OSD-CM. The supporting infrastructure for implementation of manufacturing operations functions could often be geographically distributed across a site and require considerations for an enterprise architecture for system integration. Standardizing the architecture and procedures could allow for the adoption of a common approach to integrate the various components of OSD-CM into a manufacturing facility for commercial operations, as well as support maintenance, repair and operations of the systems. A systems architecture to facilitate the implementation of data flow for CBM and additional manufacturing operations functionalities is addressed subsequently.

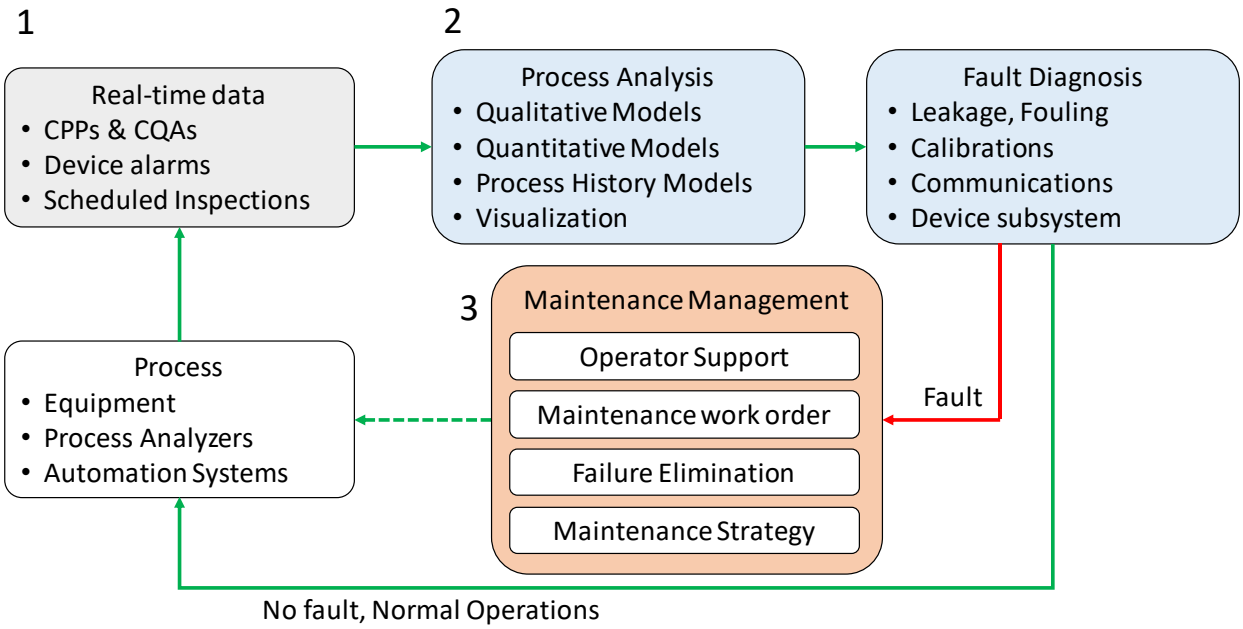


Figure 6-1: Data flow for continued verification and condition-based maintenance

6.2.1.1 Real-time data: Sensors, Communications and Data Management

The first step is to ensure the ability to source the data and expand the communication network and databases for the collection and contextualization of real-time process data (Romero-Torres et al., 2018). Advances in sensing systems for OSD-CM processes (Laske et al., 2017), and the use of data management and networked communications facilitate this step (Anand et al., 2019; Cao et al., 2018; Ganesh and Hausner, 2019; Su et al., 2019c).

To this end, while active process control strategies for product quality assurance require CPP and CQA data, proactive maintenance additionally requires leveraging the asset condition data for diagnostics. Process operating condition data, such as device running status and alarms, run hours, motor speeds, individual tablet punch forces and standard deviations, device temperature and vibrations, oil levels, greasing frequency, spectroscopic instrument device temperatures and light intensities may already be configured by equipment vendors as performance and safety indicators for system health monitoring, troubleshooting and preventive maintenance. Real-time diagnostics from all the individual assets, along with the operational knowledge of the integrated system, provides a pathway to continued process verification and proactive maintenance planning. Furthermore, monitoring of material flow rate across the system using inline mass flow

sensors such as discussed in (Ganesh et al., 2017) enable the evaluation of process yield in real-time and consequently enable the detection of flow leakage or process variations. Asset condition data, along with the CPPs and CQAs, facilitate the integrated process and asset monitoring at multiple hierarchical levels such as plant operators, plant managers, control room engineers and research and development personnel for continued process verification and further process improvements. It is important to note that integrating the data sources for proactive maintenance policies in OSD-CM would require active collaboration between the technology vendors and users for identifying the failure modes of the assets and enabling additional sensors and communications links.

6.2.1.2 Process analysis and fault diagnosis

The second step is the qualitative and quantitative analyses for the assessment of potential failure modes in real-time. The maturity in process knowledge enables the extension of the diagnostic indicators to prognostic monitoring, thereby facilitating predictive maintenance. While a detailed review of the specific methods for fault detection is beyond the scope of this work, the Guidance for Industry documents provided by the FDA such as PAT (FDA, 2004a) and Q9 Quality Risk Management (FDA, 2006) highlight multiple tools for risk management in the development and implementation of pharmaceutical manufacturing processes.

Recent developments in OSD-CM include frameworks such as the exceptional events management (EEM) and intelligent alarm system (IAS) to address the issues of fault detection, diagnosis and mitigation of abnormal events (Giridhar et al., 2014; Gupta et al., 2013; Hamdan et al., 2012, 2010). Herein, qualitative model-based methods such as signed directed graphs, and process history-based qualitative trend analysis and quantitative methods such as wavelet analysis and principal component analysis were demonstrated to diagnose faults caused primarily by material blockage and buildup in OSD-CM subsystems. Methods to monitor sensor failures such as robust state estimation, data reconciliation and gross error detection were recently introduced and further demonstrated for OSD-CM applications (Moreno et al., 2019, 2018; Su et al., 2019a). Statistical process and quality control methods (Montgomery, 2012) have further enabled detecting deviations in the process and product (Almaya et al., 2017; Laske et al., 2017).

Fault monitoring methods, along with the ability to diagnose the associated root cause, provide the required capability to prescribe a maintenance activity or point to the need for additional condition assessment to support the prediction of specific downtime event types. Fault diagnosis is vital in proactively managing the consequences of a fault, such as the need for maintenance actions or emergency responses, instead of reactively responding to unsafe conditions and unplanned downtime. The reader may also refer to published literature (Venkatasubramanian et al., 2003c, 2003a, 2003b) for a detailed review of qualitative and quantitative methods for fault detection and diagnosis in the chemical processing industries.

6.2.1.3 Maintenance management

The third step encompasses the feedback path for continued assurance of system conditions or the triggering of appropriate notifications such as an alert, an alarm, or a prompt for corrective or preventive actions for restoring normal operations based on evidence. This maintenance management step involves using the diagnostic checks to verify continued satisfactory operation of the system or to trigger operator and supervisor alerts or alarms for abnormal conditions and to further schedule a maintenance activity as corrective or preventive task. Notably, these triggers enable the CBM framework to respond to alerts or alarms from measurements of the system rather than as a reaction to unplanned downtime events (Kothamasu et al., 2006).

Maintenance tasks rely on the identified conditions and subsequent corrective actions provided by the technology vendors as well as on the reliability assessments performed during process engineering. An automated system could execute these tasks, or may require the assistance of supporting technical operations teams (ISA, 2015a). Maintenance activities may require verifying the compliance of a subsystem, performing routine tasks such as tightening of connections, checking liquid levels and lubrication, or performing an overhauling or rebuilding of an asset (Márquez, 2007). Performing these tasks may require spare parts, calibration references, and tooling as well as a work order to perform and record the tasks. Moreover, a possible shutdown of the process may be required, including updates to manufacturing schedules for performing the maintenance action to restore the asset to its required level of operation. Further, real-time risk mapping, such as recently introduced for OSD-CM in (Su et al., 2017) can be used to prioritize the conditions for maintenance activity.

Importantly, maintenance actions only restore the system to its initial functionality. Hence, in addition to proactive use of data and maintenance records for continued verification of current system conditions, the assessment of potential system improvements to eliminate the root causes leading to failures, as well as to update maintenance strategies for effective use of the assets and resources is vital for improving system capabilities. Computerized Maintenance Management Systems (CMMS) and knowledge management systems aid in managing and optimizing these activities (Andrews and Nahas, 2018; Center for Chemical Process Safety, 2007; Joglekar et al., 2017; Márquez, 2007).

6.2.2 System Architecture

6.2.2.1 Approach

Many hardware and software components together enable the required data flow of the CBM framework. To that end, a credible and comprehensive system architecture is essential for the interoperability of the component pieces in the overall process, and facilitates the implementation by providing guidance for structuring, classifying and organizing information (SEBoK, 2019b). Notably, the specific considerations associated with the maintenance of machinery and enterprise architectures are captured in multiple industry standards, provided by the International Standards Organization (ISO), International Electrotechnical Commission (IEC), Society of Automotive Engineers (SAE), Machinery Information Management Open Systems Alliance (MIMOSA), Department of Defense Architecture Framework (DoDAF), ISA, User Association of Automation Technology in Process Industries (NAMUR) and other industry specific standards. While a detailed review of these standards is beyond the scope of this work, some ISA standards are outlined to highlight the considerations of communication and network architectures, human-machine interfaces, equipment modes, and intelligent device configurations required in the systems integration for CBM applications.

A high-level operational concept graphic for the data and information flow required for systems integration, highlighting select ISA standards, is shown in Figure 6-2 and is briefly described below. The concepts from the ‘functional hierarchy’ and ‘manufacturing operations management’ models of the ISA-95 Standard on Enterprise-Control System Integration (ISA, 2010a) are primarily adopted for this architecture. The functional hierarchy model of ISA-95

suggests the hierarchical classification of a manufacturing facility into three main domains, namely, process control (levels 0-2), manufacturing operations management (Level 3) and business planning and logistics (Level 4). The process control domain involves the considerations of physical assets and the monitoring and control of the production process, while activities such as maintenance are a Level 3 function, in addition to production, quality and inventory management. Information exchange must take place between the hierarchical levels for executing operations in the manufacturing facility. Recent architectures continue to expand on the basic idea of ISA-95 mainly through advances in sensing and information technology systems that facilitate the secure integration of Levels 2 and 3 for real-time information exchange. Such synthesis advances RTPM implementation towards the Industry 4.0 paradigm (Isaksson et al., 2018; Lopez et al., 2018). For example, architectures are increasingly referred to as edge (Levels 0-2 comprising the physical location of manufacturing assets and additional measurement devices such as the at-line and off-line sensors) and the cloud (Levels 2-4 comprising the network of tools used for implementation of the analyses required for advanced process control, manufacturing operations management and enterprise resource planning). The integration of multiple automation and information technology tools addressing these hierarchical levels enables the overall operations management of the system of interest.

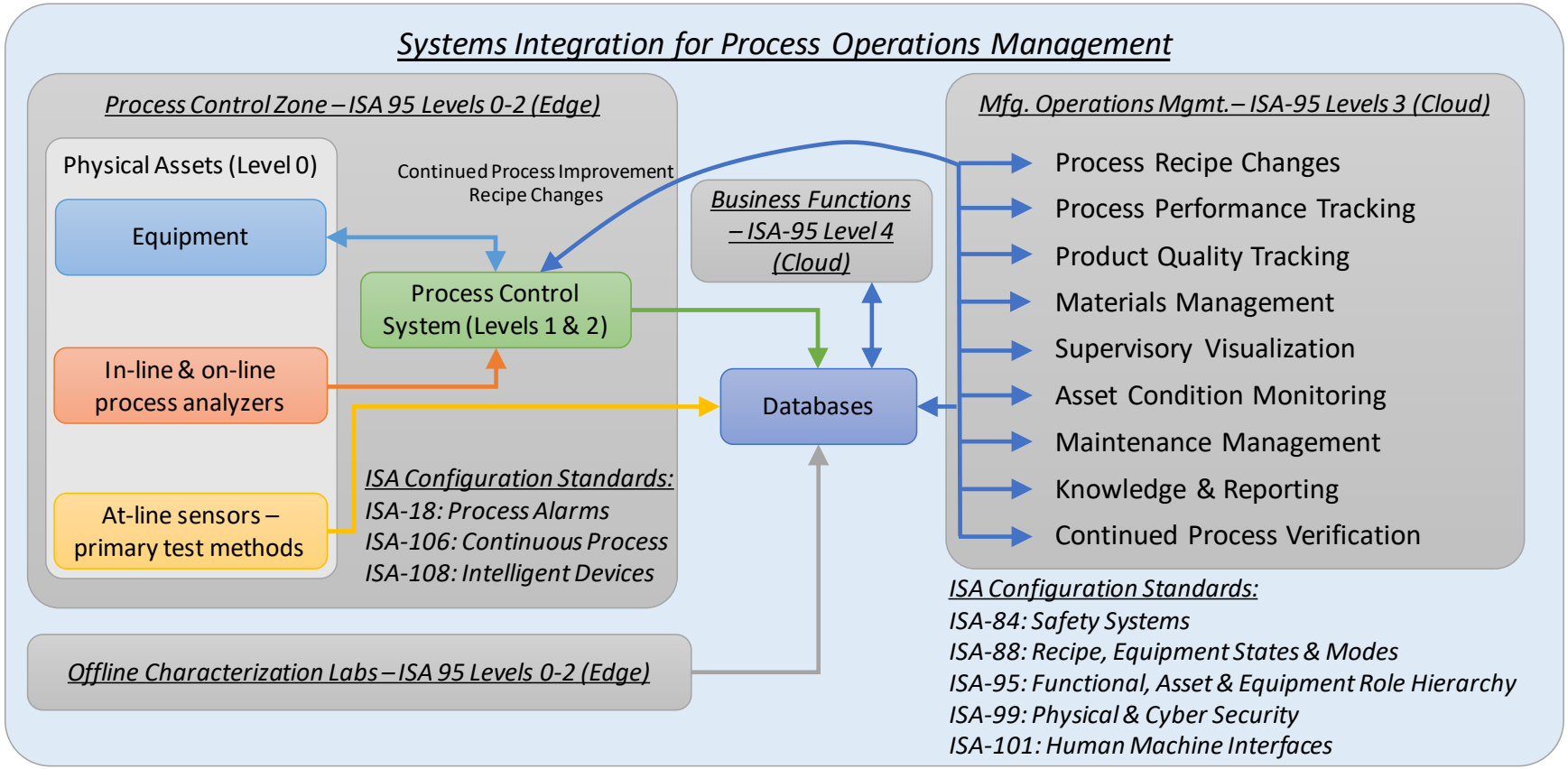


Figure 6-2: Systems Integration for Process Operations Management highlighting ISA Standards for standardizing the implementation of an integrated continuous manufacturing system

Maintenance management may often require vendor assistance and the use of product manuals with the support of specialists connected remotely from widely distributed geographical sites. Hence, in addition to the hierarchical ISA-95 models, the 'zone and conduit model' of ISA-99 Standard on Security for Industrial Automation and Control Systems (ISA, 2007) is leveraged to guide the network configurations, enabling connectivity between functions while ensuring cybersecurity. Furthermore, the aspects of functional areas, intelligent devices and maintenance processes in ISA-108 Technical Report for Intelligent Device Management (ISA, 2015a) are leveraged. As defined in ISA-108, an intelligent device has digital communication and supplementary functions such as diagnostics in addition to its basic functionality. Herein, diagnostics is defined as an automated function to detect faults, malfunctions, deviations and variations of hardware or software components of the device. Hence, the goal for OSD-CM is to emphasize the use of diagnostics from built-in systems in the equipment, sensors and automation tools to guide operators and control rooms on infrastructure faults. Furthermore, with the rise of intelligent sensing technologies as 'Internet of Things' devices, the above considerations from ISA-95, ISA-99 and ISA-108 enable hierarchical integration into the system architecture.

Additional ISA standards facilitate implementation of the architecture; however, they are not employed in this work given its focus on proactive maintenance management. The equipment state models defined in the ISA-88 Standard for Batch Control (ISA, 2010b) and the ISA-106 Technical Report on Procedure Automation for Continuous Process Operations (ISA, 2013) can assist defining the current asset operating scenario. The ISA-101 Standard on Human Machine Interfaces for Process Automation Systems (ISA, 2015b) can be leveraged in the context of human-machine interface. The ISA-18 Standard on Alarm Management in the Process Industries (ISA, 2016), and the ISA-84 Standard on Identification of Mechanical Integrity of Safety Controls, Alarms and Interlocks in the Process Industry (ISA, 2012) further benefit in standardizing the engineering and implementation of sensors and methods for fault detection, configuring process alarms and operator notifications of abnormal process conditions or equipment malfunctions using measurements of process conditions and logic.

Notably, some recent works in OSD-CM have proposed adopting such ISA standards. Frameworks adopting the ISA-88 Standard for Batch Control (ISA, 2010b) in defining equipment

operation modes for managing recipes and supervising device states were recently addressed (Brodbeck, 2018; Cao et al., 2018). Previous work from our research group proposed adopting the Process Condition Model from ISA-18 for intelligent alarm management in OSD-CM (Gupta et al., 2013), as well as Quality by Control, a hierarchical framework following ISA-95 for QbD implementation (Su et al., 2019c, 2017).

6.2.2.2 A CBM Architecture for OSD-CM

With the approach to systems integration described above, a proposed high-level view following the CBM+ OV-1 architecture (Office of the Assistant Secretary of Defense for Sustainment, 2008) for the data and information flow required in implementing CBM in OSD-CM is shown in Figure 6-3 and described below. The architecture is a general representation and can be applied to both batch and continuous manufacturing processes. Specific details of this application depend on the system of interest. They are the subject of ongoing research but are not addressed in this work.

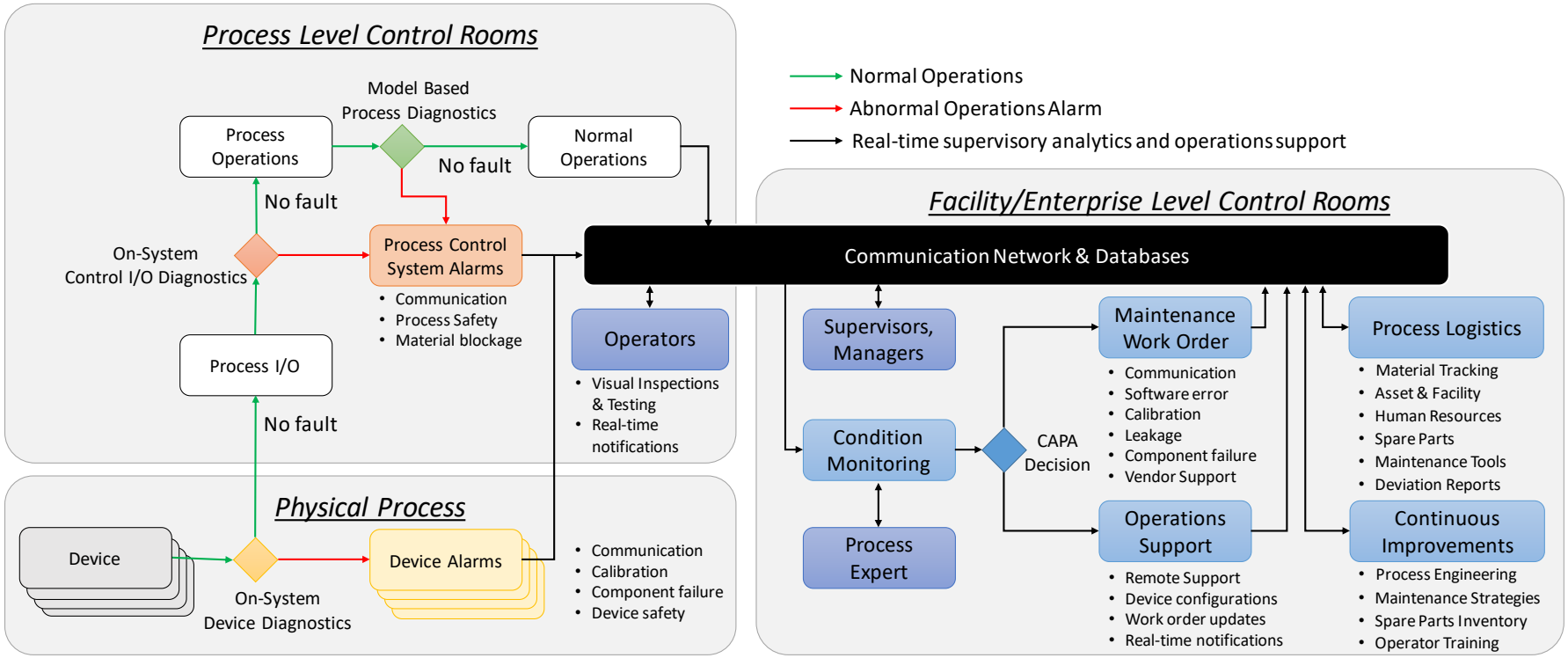


Figure 6-3: Data Architecture for Proactive Maintenance Management in CM

An OSD-CM process operation comprises multiple physical devices at the Level 0 of ISA-95, such as equipment and sensors constituting the 'Physical Process'; and the incorporation of these physical devices at Levels 1 and 2 of ISA-95 enables the integrated OSD-CM process, shown as 'Process Level Control Rooms.' Systematic frameworks for supervisory control of pharmaceutical processes at Levels 0-2, referred to as Quality by Control, was recently presented (Su et al., 2019c). For functional use in the integrated OSD-CM process, the individual equipment and sensors usually require configuration with capabilities for digital communications and supplementary functions, such as diagnostics, in addition to the basic material processing or sensing function. These device-level diagnostics are essential in ensuring effective functioning and the identification of abnormalities, such as communication errors, calibration expiration, subsystems or component failures, or breach of device safety in the subsystems. Further, diagnostics for control systems input and output communications (I/O) and of the overall process are crucial for continued verification of normal operations in the integrated system. Alarms in response to disruptions in process conditions such as those related to safety, material blockage and communication failures are reported to the process level operator stations or control rooms, which consequently require steps for intervention to return the process to normal operations.

'Facility or Enterprise-level Control Rooms' or technical operations command centers at ISA-95 Levels 3-4, enable procedures for managing the consequences of failures for CAPA. These include activities such as composing deviation reports, issuing maintenance work orders, providing operator support, updating process logistics, tracking inventory of spare parts and maintenance aids, and executing process reengineering for continuous improvements. The 'Communication Network and Databases' facilitate the automation of Level 3 applications for improved operations support at Levels 0-2 in real-time. Notably, this integration enables access to real-time data from the physical process for enterprise transactions, thereby exposing the process to cybersecurity concerns. Thus, a reliable infrastructure for communications and data management to bridge the two domains is vital. Recent developments in industrial automation resulting in the availability of capable and reliable information technology systems to bridge these two domains is one of the major enablers of CBM and additional RTPM applications following Industry 4.0 practices.

6.3 Implementation in an OSD-CM Testbed

6.3.1 Sensor Network Risks for OSD-CM Operations

Structural malfunctions that occur due to wear in the individual equipment could result in a change in the information flow between various variables (Venkatasubramanian et al., 2003c). Hence, the operational risks in the sensor network components, as well as the impacts of material handling on the sensing infrastructure, such as those summarized in Figure 6-4, and others, if not adequately addressed, may render advanced process control and strategies for real-time product quality assurance ineffective. Since these failures can degrade the utility of the integrated system, it is essential to take steps that would ensure robustness during operations, such as system performance monitoring, calibration verifications, and device maintenance (Su et al., 2019c). Some of these risk considerations affecting the components of the sensor network are briefly outlined next.

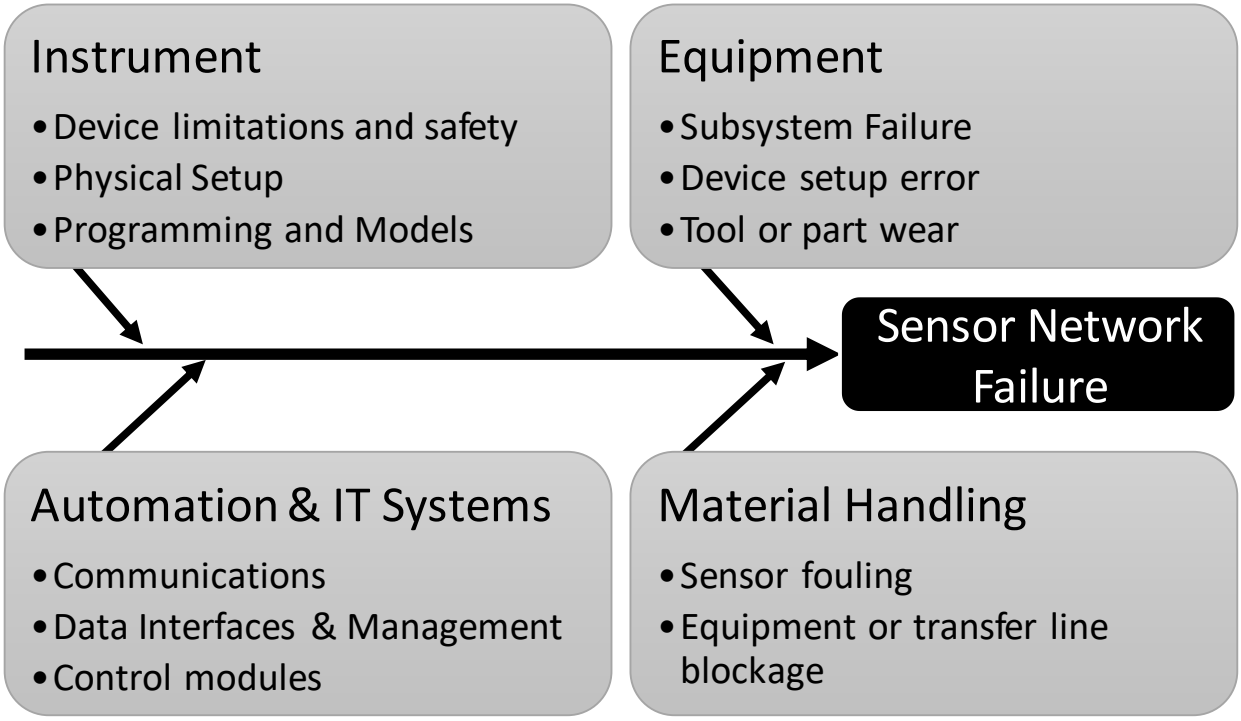


Figure 6-4: Failure root causes in the sensor network components requiring robust design and diagnostics for continued verification in process operations

6.3.1.1 Equipment

Process equipment, such as feeders, granulators, and tablet presses, used in OSD-CM are critical not only for material processing, but also for enabling plantwide control and providing data for process diagnostics and additional operations management functions. The equipment rely on efficient functioning of their corresponding subsystems and components, such as load cells, solenoids, wear strips, gaskets, retainers, motors, bearings, lubrication systems, electrical connections, and internal controllers among others. However, the assurance that these components are functioning as desired is not always easy to attain and the sheer number of these subsystems and components in an integrated OSD-CM system increase system complexity. Process operations are further challenged by the risks associated with handling of particulates, such as fouling, caking, segregation, and rat-holing. In addition, wear in machinery tooling could result in unacceptable product quality, cause product leakage and thus affect process performance and the information flow for quality assurance. Furthermore, the subsystems for device level control of CPPs may fail due to poor equipment handling or safety design. The subsystems for lubrication and temperature control of the moving parts may further experience leakage, which could affect the product quality. Consequently, the verification of equipment performance during operations as well as between runs after cleaning cycles is imperative to ensure reliable conditions of the equipment and avoid the need for unplanned shutdowns.

6.3.1.2 Instruments

Process analyzers or PAT tools are critical for OSD-CM operations, as these provide direct or inferential measurements of CPPs and CQAs. The data from these tools facilitate aspects of real-time quality assurance, advanced process control and additional manufacturing operations management functions. Importantly, these instruments are comprised of electronic and mechanical components, light sources, optic cables, measurement probes and interfaces, and further, the analysis methods and software to acquire and analyze the data in real-time. Device age such as reaching the limit of the average rated life of the light source, damages to the optic fibers, calibration models and certifications, device safety and exposure limits and others require considerations for proactive asset management. For example, for a fault in the inline near-infrared (NIR) sensors, the mitigation could require cleaning the sensing window and routine verification of the calibration model as well as further updating the sensor design to manage and mitigate the fouling conditions. However, if a light source is nearing rated average life, corrective or preventive

actions may require providing inventory of critical components and scheduling the corresponding PAT experts for recalibrations to facilitate short downtimes. These events are generally manageable during operations through device start-up and shut-down procedures, and through configuration of real-time diagnostic indicators in the programs running the analytics for continued verification. Moreover, managing the parametric changes in the models of these analytical system that could affect the decisions of the supervisory control strategies requires effective model maintenance (García-Muñoz et al., 2017; Miyano et al., 2015). A discussion on the maintenance of analytical models is an important area of concern for the OSD-CM community, however it is beyond the scope of this work which is focused on the holistic architecture for system integration.

In addition to the instrument degradation and chemometric model management, process measurements from field devices include random errors arising from sources such as power supply fluctuations, network transmission and signal conversion noise, analog input filtering, and changes in ambient conditions which increase overall complexity (Narasimhan and Jordache, 1999). Furthermore, material handling of powders is an inherent challenge in all solid processing facilities. Non-stationary events or gross errors such as frequent sensor fouling arising from particulate processing affect the measurement accuracy. These events could result in a sensor network that is no longer observable, thereby affecting real-time process monitoring systems and subsequent data driven applications (Bagajewicz, 2010) and necessitate continued verification of the real-time process data sources during operations.

6.3.1.3 Integrated System

Although an individual item of equipment or PAT tool may be configured satisfactorily in standalone mode, OSD-CM necessitates communications between the individual components and a suite of information technologies for the continuous flow and processing of material and data. Automation systems and the information technology infrastructure, including hardware, software, and network devices, require reliable communication architectures and systematized implementation. Real-time data analytics and decision making at multiple hierarchical levels and functional roles for quality assurance further require additional considerations for systematic data management such as configurations of data connectors and cybersecurity on automation network, transient faults, buffer/memory, or data packet loss in the network and handling multiple databases. Further, the underlying hardware and software associated with automation systems could have abrupt unpredictable failures, hence raising consideration of network and component redundancy,

as well as proactive strategies for ensuring effective functioning. Also, the implementation of control strategies in supervisory control systems require engineering updates and maintenance of software programs, or control modules, for reliable operations. These modules may rely on tuning parameters that are also affected by equipment age and operating conditions. Failures of the control system are addressed as one of the main challenges for Quality by Control (QbC), thereby necessitating considerations for system robustness such as control performance monitoring, control structure re-organizing and overall system maintenance for targeted improvements to achieve tighter tracking of CQA and more robust plant-wide control (Su et al., 2019c).

6.3.2 Testbed description

The case study discussed in this work uses the advanced manufacturing testbed of the Center for Particulate Products and Processes at Purdue University (Purdue CP3). As discussed in Section 2, a system architecture enables the use of real-time process data for proactive fault analysis and maintenance management, hence CBM. An implementation example of the enterprise-control system integration architecture is discussed in the case study. Subsequently, example fault scenarios in equipment and process analyzers that may require continued verification during process operations and proactive maintenance considerations are discussed. As noted earlier, this work aims to emphasize the system integration and maintenance aspects for sensor network robustness. Additional ongoing research on failure modes of the process, and the corresponding condition monitoring and maintenance considerations will be reported in subsequent publications.

The conceptual schematic of the process for OSD-CM in the Purdue CP3 facility, incorporating the direct compaction and dry granulation processing alternatives is shown in Figure 6-5 (Ganesh et al., 2018a). The testbed is comprised of assets from multiple vendors, therefore requires a modular and vendor-agnostic integration of the unit operations, PAT tools and supervisory control systems for the continuous flow and processing of material and data (Ganesh et al., 2018a; Moreno et al., 2019; Su et al., 2019a, 2019c, 2019b).

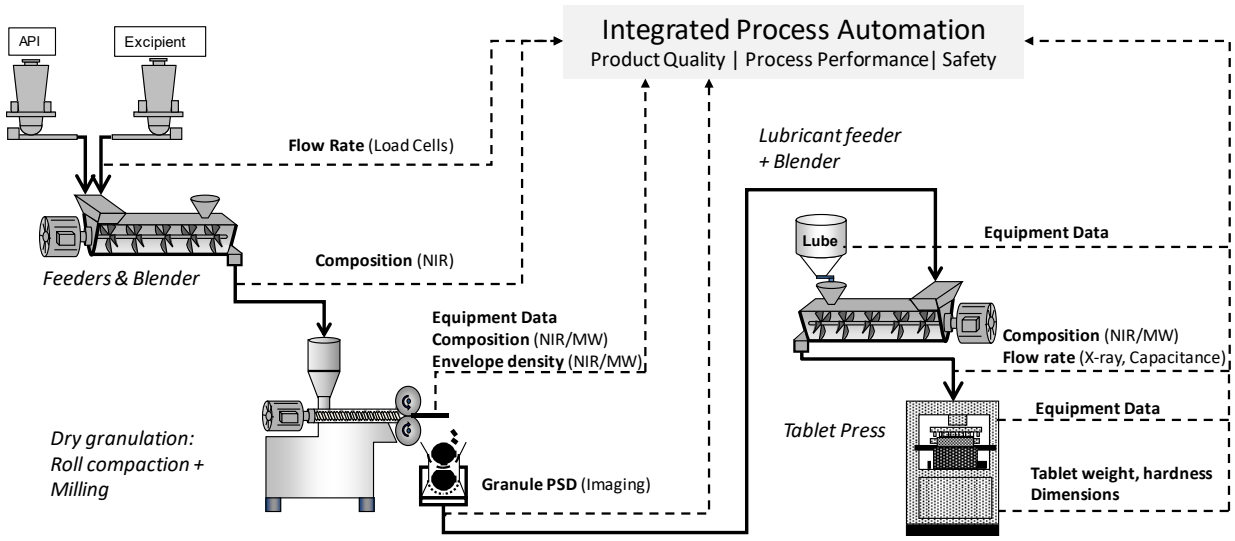


Figure 6-5: Schematic of CM with direct compaction and dry granulation processing routes (Ganesh et al., 2018a)

The case study explores a subset of the process to illustrate the systems architecture for CBM. The physical setup is shown in Figure 6-6. Specifically, a Natoli NP-400 22 station rotary tablet press is utilized for direct compaction of the blend fed continuously using a K-Tron KT-20 loss-in-weight feeder. An in-house design for real-time tablet weight measurement based on a Mettler Toledo ME 4001E balance, and the Innopharma Multieye2 NIR sensor were used as representative inline PAT tools. The exit of the tablet press is also connected to a Sotax AT-4 for at-line sampling of tablets to provide weight, thickness and hardness measurements to the supervisory control system.

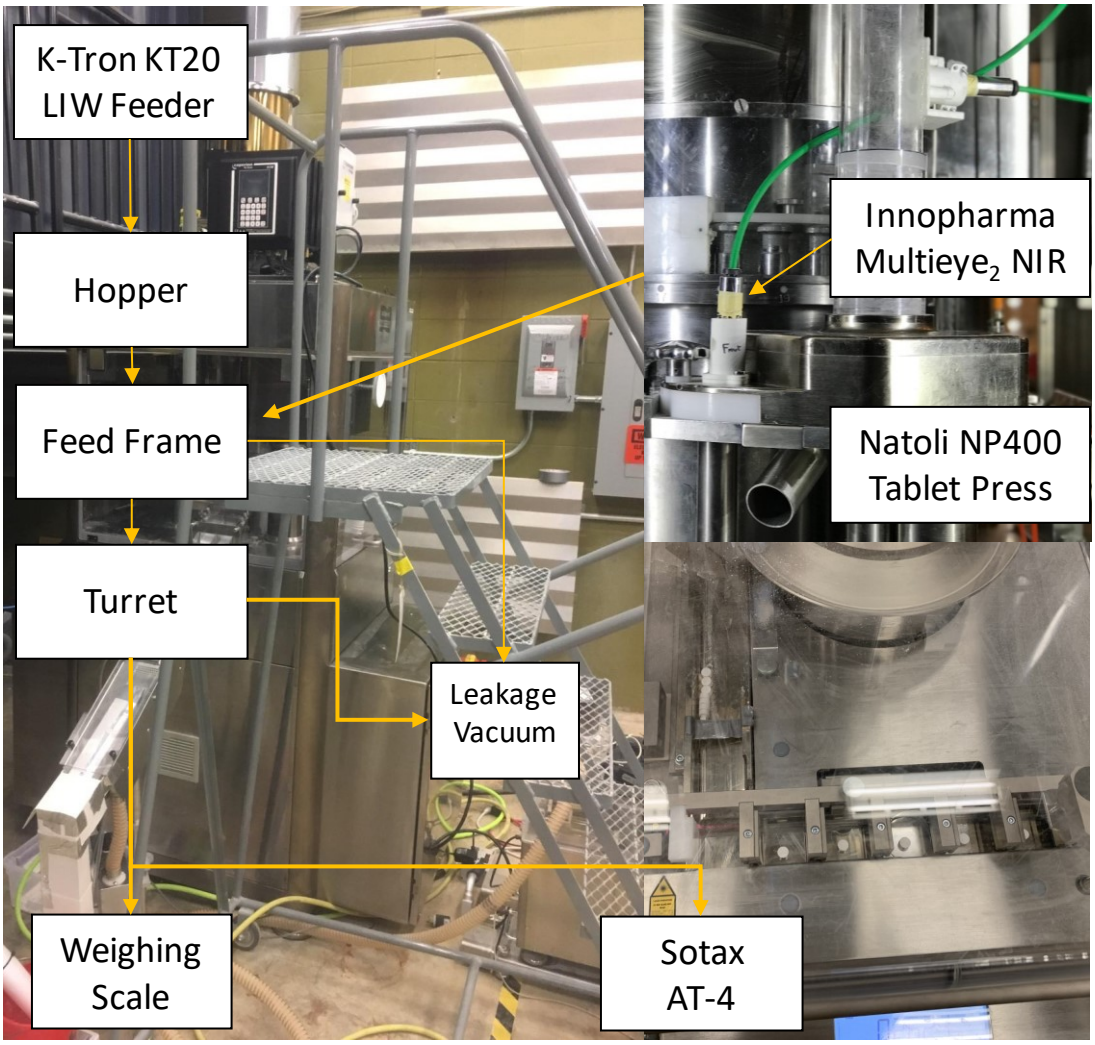


Figure 6-6: Subset of the OSD-CM process to illustrate CBM systems architecture

6.3.3 Enterprise-Control System Integration

6.3.3.1 Architecture Overview

The implementation of the systems architecture proposed and illustrated in Figures 6-2 and 6-3 requires three vital infrastructural considerations. The first involves the integration of the equipment and the sensors at the process control domain at Levels 0-2; second, the integration of the process into the manufacturing operations management domain at Level 3; and, third, the implementation of Level 3 functions. To this end, DeltaV 13.3 (Emerson) is used for the data management and plant-wide automation through the 'Process Level Control Room', while OSIsoft PI System (OSIsoft, LLC) and SmartFactoryRx (Applied Materials, Inc.) are employed for the setup of the 'Facility/Enterprise Level Control Room'. An overview of the data flow is shown in Figure 6-7 and Figure 6-8, with the 'zone and conduit' diagram for the network connections shown in Figure 6-9. While each of these tools has multiple capabilities, they are implemented for specific purposes in the testbed to leverage the existing control systems in the testbed, which are described subsequently. It is to be noted from these figures that (i) the functional data flow follows ISA-95 to integrate process equipment that are configured as (ii) intelligent devices as defined in ISA-108 for material processing and sensing, while (iii) network architectures to host the machines and enable machine to machine communications follow ISA-99.

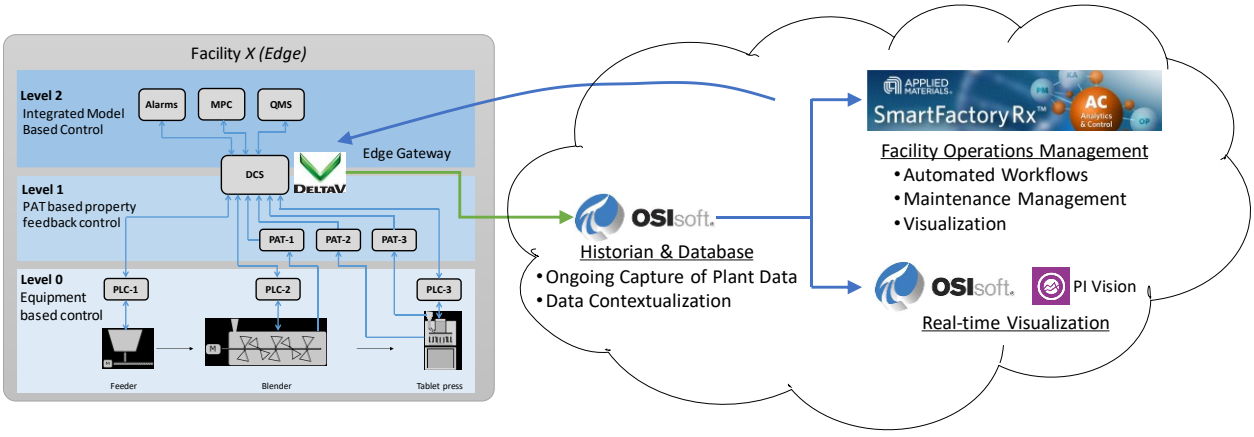


Figure 6-7: Enterprise-Control System Integration in the CP3 OSD-CM Testbed

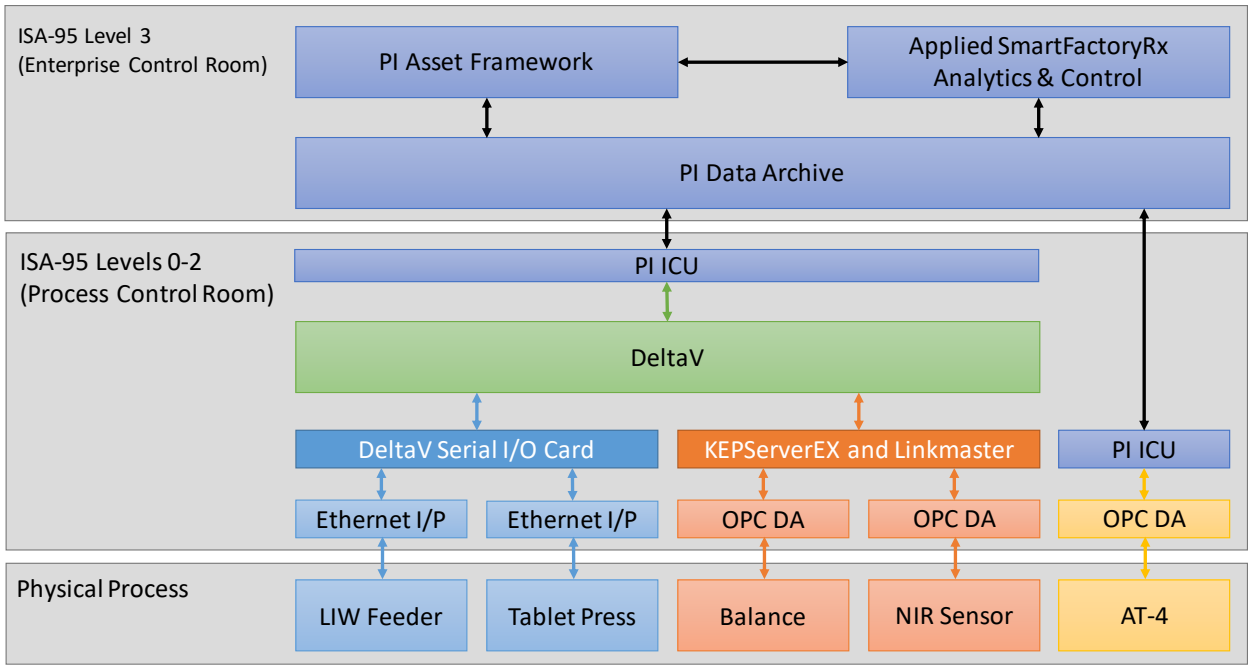


Figure 6-8: An overview of the data flow from Assets to Control Platforms in the Testbed

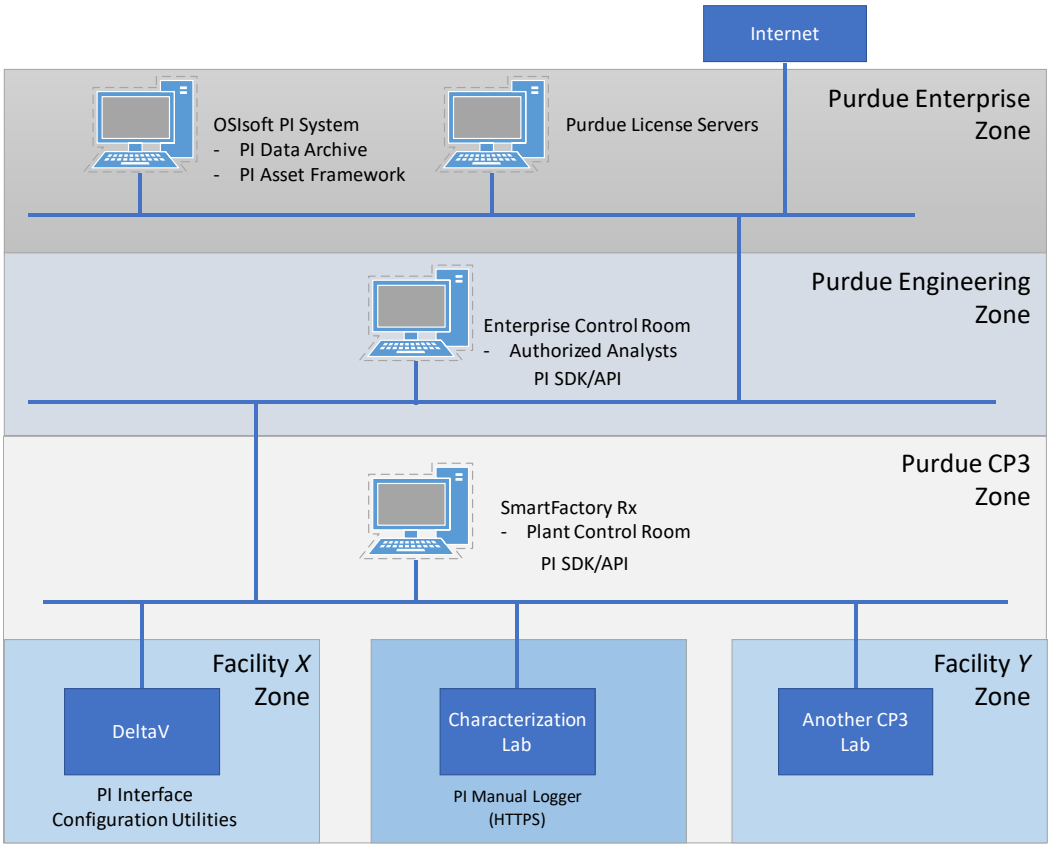


Figure 6-9: Network connectivity of the OSD-CM Process Facility as part of an Enterprise

6.3.3.2 Process/Site Level Control Room

Architectures to systematically implement Levels 0-2 using equipment level and supervisory controllers for maintaining the normal operating conditions and product quality specifications were recently introduced by the research group and established as the Quality by Control (QbC) framework. To this end, a DeltaV 13.3 distributed control system (DCS) provided by Emerson is used for the modular integration of the individual units to result in an integrated OSD-CM process for the implementation of QbC. The DCS is configured to facilitate the integration of equipment and PAT tools with the controller for plant-wide process control. The DeltaV controller is physically installed in the pilot plant facility, and the workstations are deployed using virtualization technologies. The control modules and operator interfaces for plant-wide control applications are configured using DeltaV Control Studio in the DeltaV ProPlus Workstation, while the data access server and the continuous historian are accessed using the DeltaV Application Station. The KT-20 loss-in-weight feeder and Natoli NP-400 tablet press equipment communicate with DeltaV via ethernet I/P, while the object linking and embedding for process control (OPC) data access (DA) protocol is used for communications with the PAT tools, as shown in Figure 6-9. The different colored arrows representing data flow are intended to indicate the different communication protocols required to establish the integrated system. As shown, the communications must be harmonized as the data flow progresses from the physical process to the DCS. Establishing these connections usually requires physical communication cards based on the protocol or access to the OPC DA server of the system. While the physical I/O cards used to connect the equipment are stable communications links, direct access of the OPC servers to connect PAT tools raises cybersecurity considerations. Connecting PAT tools to the DeltaV OPC server thus required the application of data transfer adapters using tools such as KepServerEX, LinkMaster (both Kepware, PTC Inc.) and Matlab's Instrument Control Toolbox (MathWorks Inc.). Product guidance documents such as DeltaV Security Manual are utilized to manage the complexity in the systematized integration of the devices with the DCS. More detailed descriptions of the network architecture at Levels 0-2 for active process control applications are reported in our previous works (Moreno et al., 2019; Su et al., 2019c, 2019a).

6.3.3.3 Facility/Enterprise Level Control Room

While the integration at Levels 0-2 of ISA-95 enables the supervisory control of OSD-CM, applications such as CBM involve the integration of the process with the manufacturing operations

management domain corresponding to Level 3 of ISA-95. The integration of Levels 0-2 with Level 3-4 for the implementation of this work required an expansion of the infrastructure. To this end, the DeltaV system is implemented as the edge control system of 'Facility X', and the PI System provided by OSIsoft is used to bridge the process control domain and manufacturing operations domain. This 'Facility X' houses the OSD-CM process and forms a part of the 'Purdue CP3' facility zone, as shown in Figure 6-9. The SmartFactoryRx platform provided by Applied Materials is then implemented to make use of data from the PI System for ISA-95 Level 3 applications. The SFRx platform enables the development and systematized implementation of data-driven and mechanistic analyses in a drag-and-drop workflow-based strategy engine for asset and facility management functions. Applications such as process performance monitoring, maintenance management, and knowledge management can be implemented using its built-in functionalities, interfaces with external proprietary and open source programs, and web service interfaces (Moyne et al., 2012; Vann et al., 2018). The data flow for Level 3 systems is harmonized using the PI System, as shown with the data flow colors in Figure 6-9.

The PI System and SmartFactoryRx workstations configured using virtualization technologies are hosted in Purdue's Enterprise Network, and the lab managed 'Purdue CP3' Zone respectively to replicate a cloud environment for data aggregation, and analyses as shown in Figure 6-9. The zoning of networks facilitates configuring network security protocols. Moreover, the layering of the control zones enables leveraging resources provided by Purdue in the form of software licenses for tools such as MATLAB that may be required for developing the data driven applications. Studies on the use of the integrated infrastructure for applications in the testbed is an ongoing research activity; while in this work, the PI System is used in subsequent illustrations as a representative process visualization tool at the facility control room level.

The PI System is comprised primarily of the PI Data Archive, the time-series historian and PI Asset Framework, a repository for asset-centric models, hierarchies, objects, and equipment (OSIsoft LLC, 2018). The PI Interface Configuration Utilities (PI-ICU) enable the data connection between data sources and the PI Data Archive. The data tags are configured as PI Points in the Data Archive. Additionally, the Data Archive is an essential security layer between the edge and the systems for Level 3 applications. The corresponding PI Points are accessed using the PI Asset

Framework in real-time. The PI Asset Framework is used to contextualize the PI Points as Asset Models and define user access to the databases to facilitate cybersecurity and enable further analysis. PI Vision, a PI System tool is used for visualization and to interface with external software such as SFRx using System Development Kits (SDKs). As the integration layer of data sources from the process domain for manufacturing operations management, the PI Data Archive is configured to harmonize tag naming for systematizing the access, security and use of the data.

6.3.4 Fault Scenarios in Data Flow

The development of process automation systems for OSD-CM necessitates data exchange at multiple hierarchical levels. Moreover, to connect to the different communication protocols in each of the unit systems, multiple hardware and software components are required. Some fault scenarios arising in the IT infrastructure and automation systems experienced in the testbed are summarized in Table 6-1. It is the possible occurrences of these types of scenarios that require the continued verification of data quality for assurance of the usability of real-time data from the field sources for the supervisory applications.

Table 6-1: Sample Fault Scenarios that occur in the IT infrastructure and automation systems

Failure Root Causes		Diagnostic Sources	Maintenance Actions
Data adapters	Communication Failure Cybersecurity Network Configuration	Infrastructure software flags	Inspect I/O Card Inspect Cables Inspect security settings and network configurations Verify architecture
Control Modules	Control Module Error Model and Tuning Error	Control Module Flags Model Flags	Update Software Model Maintenance

For example, a fault in the data adapters could have root causes such as communication failure, network settings causing cybersecurity concerns and network mapping conflicts. Fortunately, the automation systems enable the configuration of flags to monitor these faults and to trigger alerts. These flags can then be integrated into fault trees for root cause identification. However, failures in the components of automation systems usually require offline updates to the

respective modules, replacement of the associated hardware, and also potentially a complete reconfiguration of the system that may result in downtime. Aspects such as robust and secure network architectures, redundancy, time-based inspection of the hardware components, and proactive maintenance of IT systems can aid in preventing or reducing such downtimes. Similar considerations for the control modules require control performance monitoring (Su et al., 2019c). For CBM, the components of the OSD-CM process are configured considering the data flow diagnostics, however, it is also important to consider the devices that are not available as off-the-shelf intelligent devices. Following Figure 6-9, the tablet press is used to illustrate the data flow from equipment in the physical process at Level 0 to the facility level control room at Level 3, while the NIR sensor is used to illustrate the same for a PAT tool.

The NP-400 is equipped by Natoli with an Allen Bradley ControlLogix PLC that controls the subsystems of the tablet press. Indeed, the tablet press itself is an amalgamation of multiple subsystems configured as an intelligent device by the vendor to provide diagnostic data in addition to performing its tablet processing functionality. The PLC is connected to the DeltaV DCS using Ethernet I/P. Establishing this connection requires an ethernet cable, a communication network with the VIM2 I/O card and corresponding data adapters. The VIM2 card requires its own set of communication adapters with the DCS that are configured using the DeltaV ProPlus workstation to map the process variables from the tablet press into the DCS. In addition to their use in developing plant-wide control strategies, the DCS data tags are accessible from the OPC DA server through the DeltaV Application Station. This data flow enables the implementation of Levels 0-2 functions. Similarly, the Multieye2 NIR provided by InnopharmaLabs is configured with Quanta, proprietary software which controls the spectrometer, records spectral data and enables CQA predictions using suitable models. The OPC DA3 server provided with the Quanta software enables real-time communication of the data to the DeltaV DCS. Therein, data adapters using KEPServerEX and LinkMaster are used to establish the communication between the Quanta OPC DA 3 server and DeltaV OPC DA 2 server. For secure connections between the workstations, an OPC unified architecture (OPC UA) adapter through KEPServerEX is used. Limitations in KEPServerEX require LinkMaster to write data into the DeltaV OPC server for process control purposes. For Level 3 applications, a PI-ICU to directly read from KEPServerEX in the Application Station is implemented.

As evident from the above description, the communication variety among the component equipment and analyzers results in a complicated data flow to the DCS. Standardization of the interfaces for this data by the PAT tool and DCS vendors could simplify the maintenance requirements of these interfaces. However, in a modular setup such as the testbed used in this case study, software flags at each of these interfaces allow for continued verification of the data flow. These software flags, such as a time stamp or connection status tags from the equipment and automation systems, are used in abstraction hierarchies, a qualitative model-based fault detection method, to configure triggers for abnormal conditions and the corresponding prescriptive actions to minimize the resources required for corrective action. Furthermore, proactive monitoring of this data flow will involve regular time-based inspection of the cables and communication hardware as well as collaboration with Purdue Engineering Computers Network for IT Securities. At present, unfortunately, failures in the data flow can be detected only after a component itself fails but the condition triggers at the data interfaces enable quick resolution of the root cause for maintenance purposes.

The data integration in the DeltaV DCS enables the development of automation modules for the supervisory control of the integrated process, facilitating the implementation of a 'Process Level Control Room.' To integrate the process into a technical operations command center or the 'Facility Level Control Room' for Level 3-4 functions, a PI-ICU is configured to access the OPC servers hosted in the DeltaV Application Station. The PI-ICU enables the collection and storage of data into the PI Data Archive following appropriate considerations of security and data compression. The data tags from the PI Server are then used in the PI Asset Framework to create the facility and equipment hierarchies. A screenshot of the PI Asset Framework is shown in Figure 6-10. PI Asset Analytics and PI Vision are then utilized to configure triggers on the real-time data for continued verification of the data flow and visualization of operator alerts in the facility using a traffic light system.

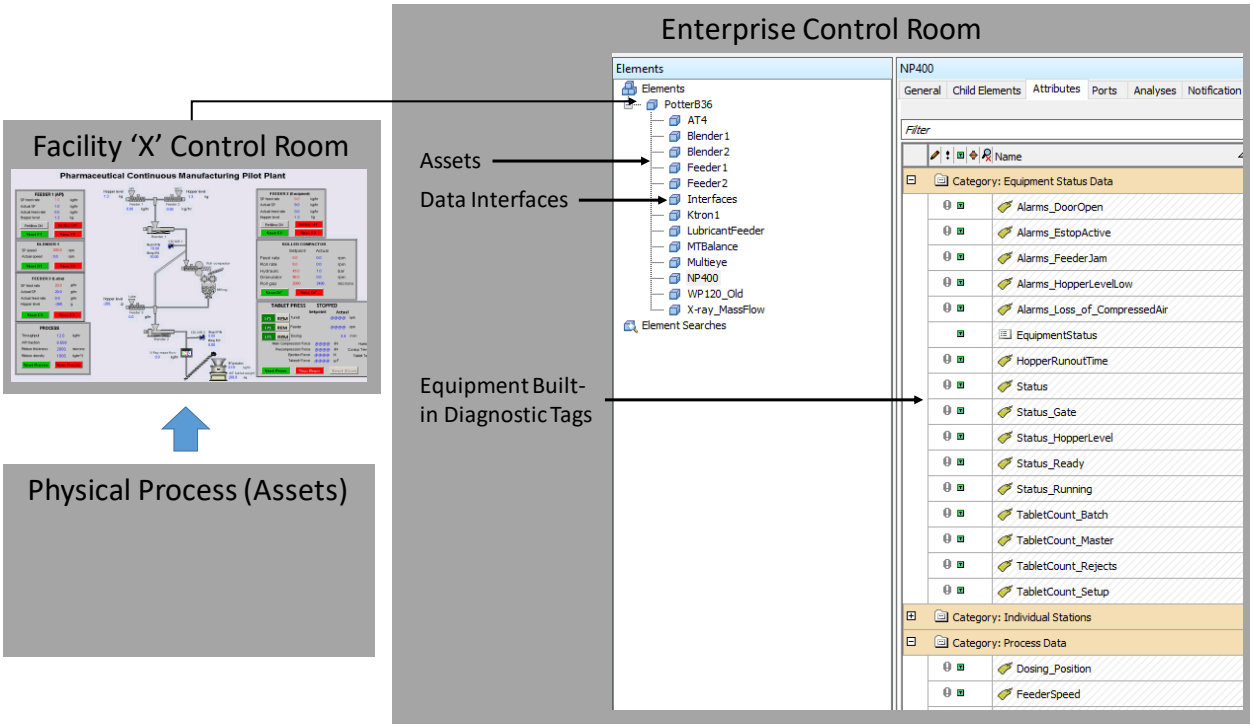


Figure 6-10: Data from assets of Facility 'X' for Level 3 applications

The operations dashboard for the entire process is shown in Figure 6-11, which is simultaneous accessible on the process floor as well as the enterprise control rooms. As shown, a green status indicates a working condition, while the red indicates a system shutdown or fault status. The gray color indicates stand-by status. In this illustration, the testbed researcher uses the traffic lights as alerts for the required corrective or preventive action. The ongoing configuration of SmartFactoryRx system is designed to automate a workflow to utilize the triggers to not only alert the operator, but to further initiate corresponding maintenance actions.

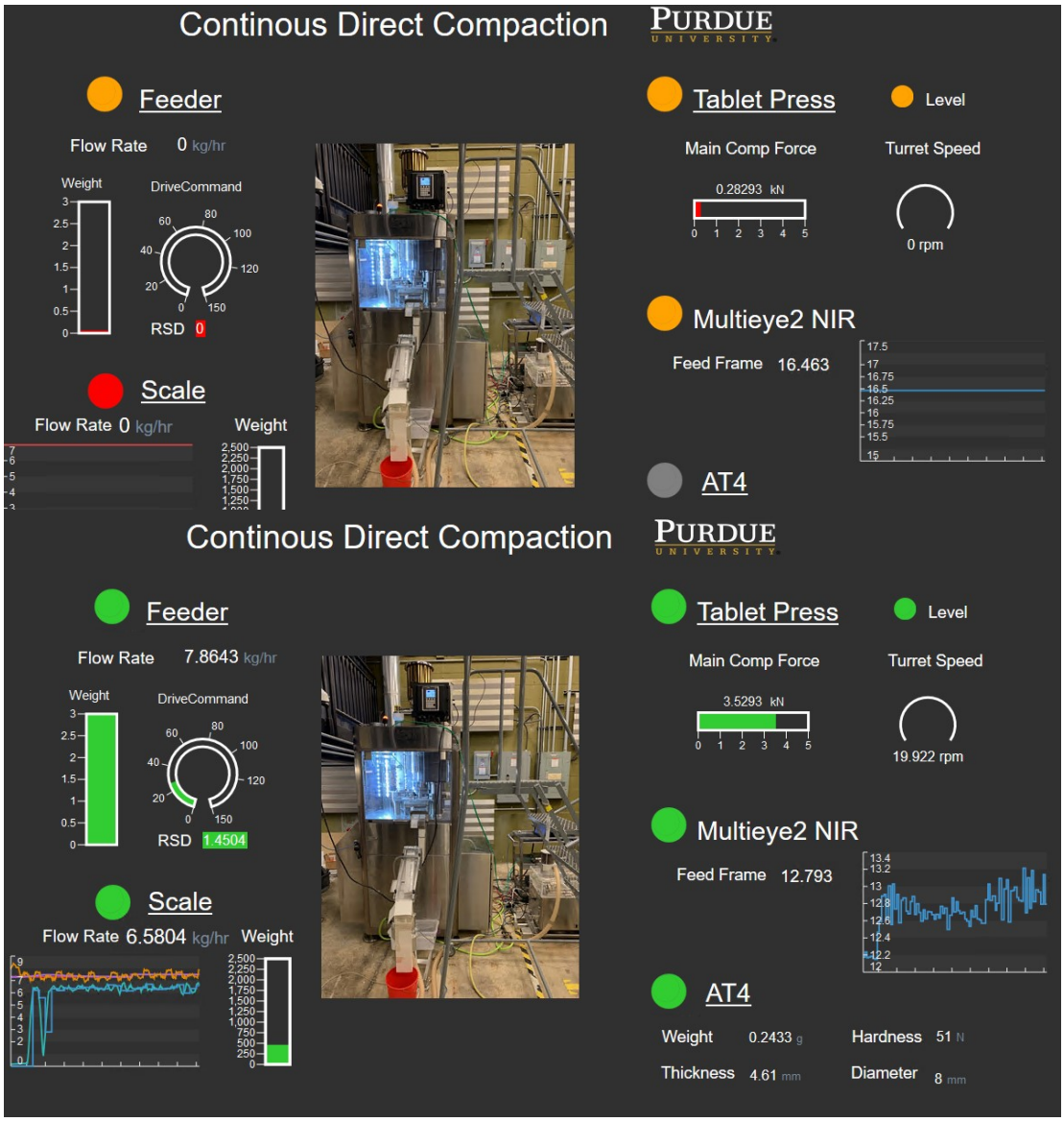


Figure 6-11: Dashboard of the Process in the 'Facility Level Control Room'. Top: Inactive or connection requiring a maintenance action. Bottom: Continued Verification of Data Flow.

6.3.5 Fault Scenarios in Process Instrumentation

Individual PAT tools used for inline and at-line monitoring of CPP or CQA usually consist of three components, namely, the sensing device, a program to control the instrument and analyze the data, and the cables connecting the sensor to the computer. For the measurement to be useful for real-time quality assurance and advanced process control of the integrated process, the measurements must be communicated to a supervisory control system and require additional considerations for data transfer. Each of these components has failure modes that may render the

data unreliable or unavailable, hence requiring device diagnostics to identify abnormal conditions and their corresponding root causes. Some example faults in the process instrumentation and potential data sources for fault diagnostics and maintenance actions are summarized in Table 6-2. The failure scenarios are illustrated with a weighing balance and the AT-4. The simple weighing scale is used to collect tablets exiting the tablet press chute and to record the cumulative weight of the tablets produced, while the AT-4 is used as the at-line tablet property measurement tool, as shown in Figure 6-12. The balance is configured in-house for this application and resembles a 'non-intelligent' device in its setup, while the AT-4 system is an intelligent device provided by Sotax with its diagnostics and data exchange servers.

Table 6-2: Sample Fault Scenarios that occur in individual PAT Tools

Failure Root Causes		Diagnostic Sources	Maintenance Actions
Device Limitation	Maximum Capacity Average Rated Life Temperature	Device Data	Calibrate Sensors Change Parts
Physical Setup	Sensor Holder Design Blockage Communication Failure	Visual Inspection Device Software Flags	Change device setup Change cables
Programming and Models	Device Software Issue Model Failure	Device Software Flags Model Flags	Update Software Model Maintenance

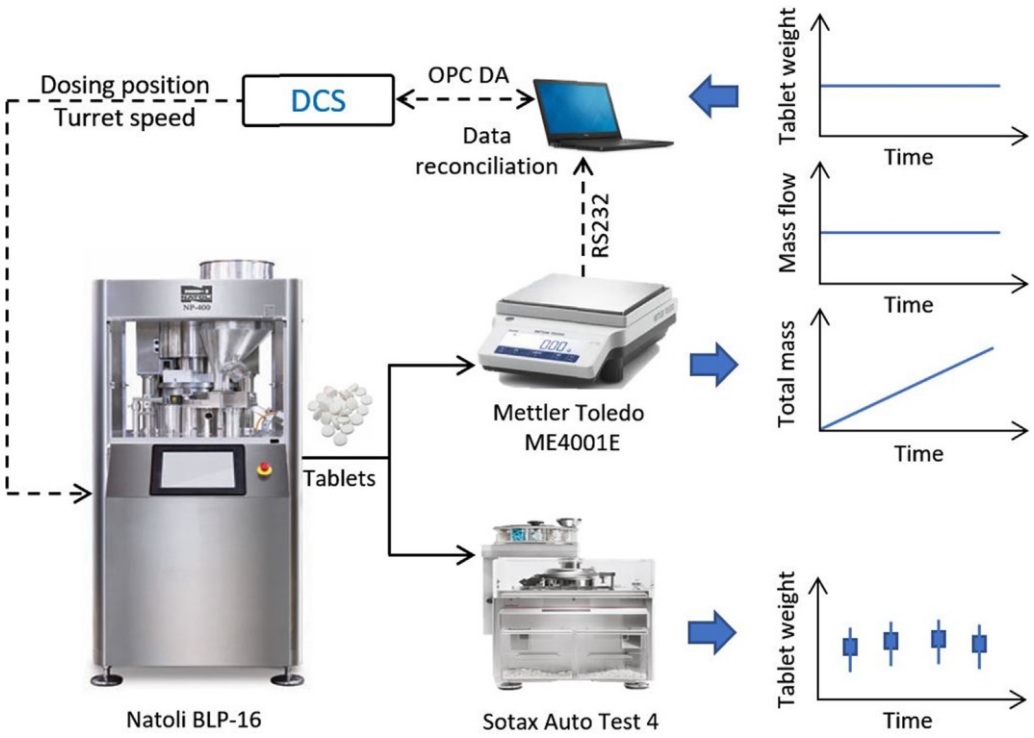


Figure 6-12: Tablet weight measurement for real-time monitoring and control (Su et al., 2019c)

The balance serves as a non-redundant mass flow rate measurement for the integrated sensor network; hence, a reliable measurement from this sensor is imperative for robust monitoring and control (Moreno et al., 2019; Su et al., 2019a). To record the flowrate measurement, the balance is connected to a laptop computer via RS232 cable to collect the measurement data of total weight on the scale, then processed for the flow rate measurement using MATLAB (MathWorks Inc.) Instrument Control Toolbox. For a reliable raw measurement from the sensor, from an asset setup point of view, first the total weight on the scale must be below the load cell's rated limits, and to obtain the flow rate measurement, the cables from the sensor have to be securely connected to the computer, and the program that collects and analyzes the data must be robust. Importantly, some of the analyses performed on the raw measurements of the sensor may require access to software licenses. Continued verification of the sensor's reliable functioning requires visibility of the total weight on the scale and an assurance that the physical connections and software enabling data acquisition data and processing are active. Triggers are configured for these device limitations to alert an operator for corrective action, such as a required change of the collection bucket during process operations to safeguard the load cell. While the operator can manage the total weight on

the scale and thus such a change is not a maintenance action, similar triggers can be configured to identify some safety concerns, preventing an unscheduled process downtime.

The AT-4 is used to sample tablets for at-line analysis, and these primary test method analyses provide vital data for quality assurance and model maintenance. However, while the collection and measurement of samples are automated through the device, the physical setup and transfer chutes could result in a blockage. Such blockage results in a failed measurement from the process, thereby requiring operator alerts and further considerations to improve the physical setup. The AT-4 system is provided as an intelligent device by the vendor, and the diagnostic data is accessed using the OPC DA2 server on the device. Furthermore, for potential additional 'Internet of Things' devices, the AT-4 is setup to illustrate the data flow and fault considerations for such intelligent devices, as shown in Figure 9. Data tags corresponding to device alerts and alarms are identified and used in the alerts to prevent an unplanned shutdown of the process. The operator dashboard at the control room employing the device diagnostics is shown in Figure 6-13.

Figure 6-13: Alert indicating material blockage and measurement failure in the at-line sensor

While the above illustrations can be managed by the operator to ensure timely measurements from the analyzers, damage to the cable and physical connections, software, and calibrations require additional support or spare parts and subsequent maintenance considerations. Additionally, measurements provided by the load cells require periodic verifications using reference weights. For proactive maintenance, although damage to the cables or software failure cannot be predicted, a record of load cell recertification and license expiration dates provide information to schedule the corresponding activities during a planned downtime proactively. In addition, with a record of the frequency of occurrence of failure root causes, software maintenance to update the data transformation workflow or cable replacements may be desired.

6.3.6 Fault Scenarios in Process Equipment

The tablet press, a critical asset in the integrated CM process, is, by itself, a multi-stage process and is treated as such in this illustration. The equipment is comprised of multiple stations for tablet compaction, during which material in each station undergoes the following major steps: die filling, metering, pre-compression, main-compression, tablet ejection and take-off from the lower punch, as shown in Figure 6-14. The setpoints for the operating condition at each of these stages are implemented by a subsystem comprised of mechanical and electrical components, with alarms or system diagnostics built into the equipment control system to provide notice of abnormal conditions. Some faults scenarios in equipment that could affect the functionality of the integrated process, and potential diagnostic and maintenance actions are summarized in Table 6-3.

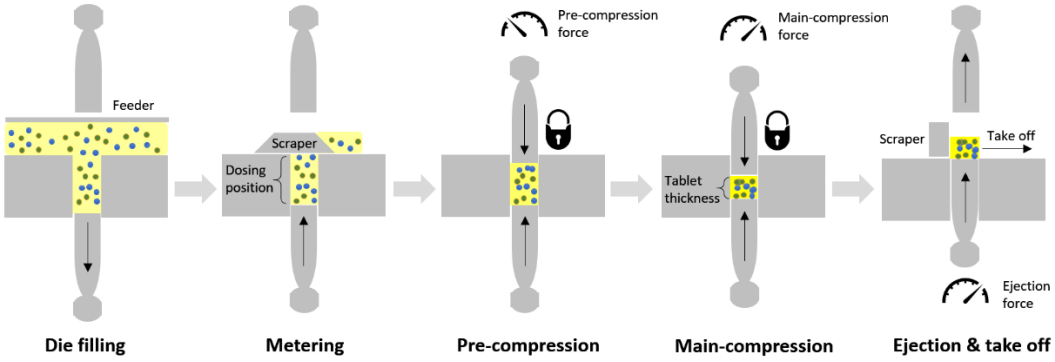


Figure 6-14: Major steps in a rotary tablet press (Su et al., 2019c)

Table 6-3: Sample Fault Scenarios that occur in the tablet press

Failure Root Causes		Diagnostic Sources	Maintenance Actions
Subsystem Failure	Subsystem Safety Design PLC & HMI Error Communication Failure	Device Data and Alarms Process Models	Inspect Subsystems Update Software Verify device settings
Physical Setup & Operating Conditions	Tool installation Equipment Leveling Punch penetration	Visual Inspection Condition monitoring Process Models	Verify device settings, subsystem calibrations, setup
Consumables	Grease or Lubricant Levels Dust Handling	Device Data and Alarms Visual Inspection Vacuum system inspection	Replenish consumables
Tool or part wear	Wear strip Tablet Punch Assembly Turret Balancing	Device Data and Alarms Visual Inspection Process Models	Maintain tools Change parts

Wear in the tablet press tooling such as punches, subsystems, scrapers or dosing cams; alignment changes of the turret; consumption of grease and barrel oil require regular equipment maintenance for effective operations (Bundenthal, 2017; Natoli Engineering Company Inc, 2019). Further, the PLCs used for the integration and control of these multiple subsystems require regular software updates. The risk considerations for these subsystems are generally managed through equipment start-up and shut-down procedures, operator training and device maintenance. Furthermore, the equipment is configured as an intelligent device to provide alarms. Nevertheless, unanticipated downtime in the tablet press could result in an unplanned shutdown of the entire process and thus continued verification of performance and operator support for troubleshooting of the failure modes is important for quick turnaround. Moreover, gradual wear in the equipment could result in a change in the information flow between various variables (Venkatasubramanian et al., 2003c). To illustrate this possibility, a main compression force subsystem failure and wear of the turret assembly are discussed further.

A recent malfunction of the main compression thickness control loop was encountered but did not trigger an alarm in the device PLC. As the process was in operation under active process control, the process model or digital twin, also used in model predictive control, detected this

malfunction. The details of the process model were discussed in previous works (Su et al., 2019a, 2019b, 2018a). An early stage use of the digital twin for condition monitoring of this fault is illustrated in Figure 6-15. The digital twin predicts the tablet weight (Twei), pre-compression force (Pcom), main compression force (Mcom), and tablet production rate (Prod) over a receding prediction horizon. The model prediction errors were calculated based on the real-time measurements of these controlled variables, were populated in a moving-window time, and were compared to the historical error distributions model prediction error distributions. The unflagged main compression thickness control failure could be identified from a shift in the error distribution for main compression force, as seen in Figure 6-15 b, and used for root cause analysis of the main compression stage.

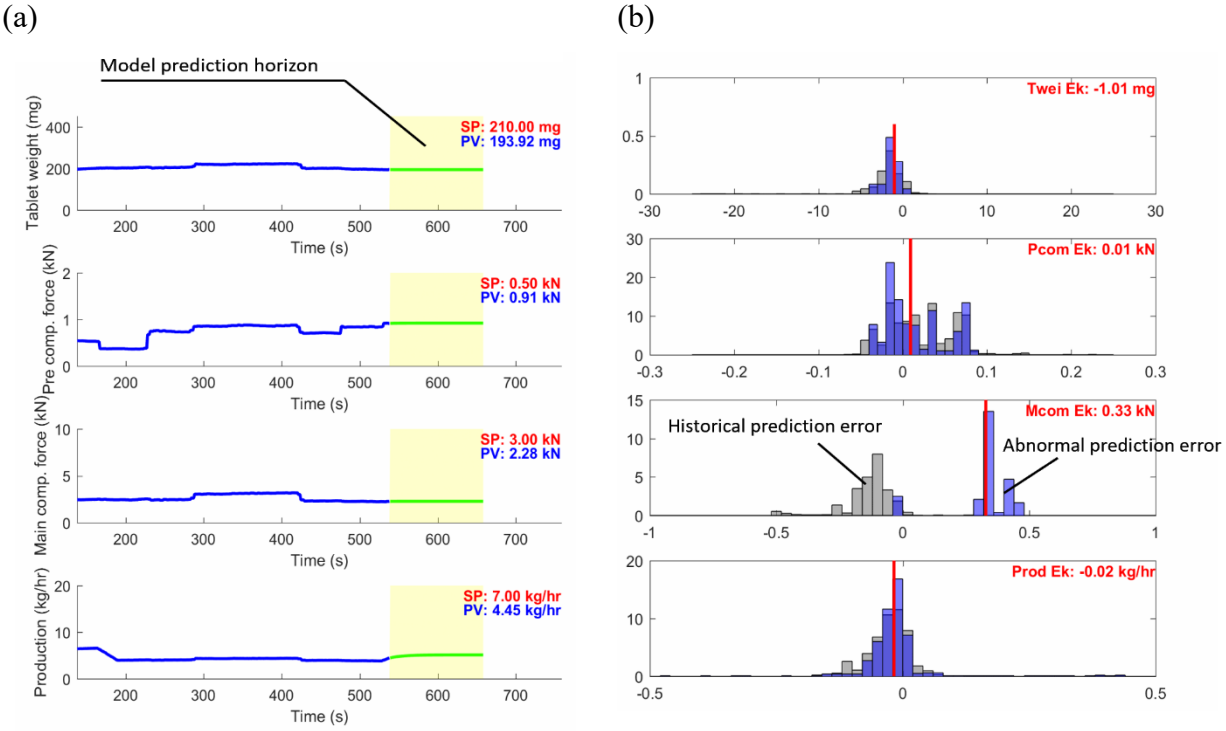


Figure 6-15: Model prediction error distribution based on a digital twin as a fault monitoring strategy

Equipment troubleshooting supported remotely by the tablet press vendor recognized the above subsystem failure as a safety design for the main compression thickness assembly, which was caused by a previous improper equipment shutdown. As the gap between the punches was not accurately available after a thickness encoder failure, no set-point changes were allowed to prevent crashing the lower punch into the upper punch. The immediate corrective action required

disassembling the tablet punches and further, verifying the calibrations for the thickness at the main compression station, usually performed as a maintenance activity. Additionally, the preventive action required updating the standard operating procedures for startup to ensure that the subsystem is operational before loading the material and performing a shutdown of the system. It should be noted that troubleshooting with the vendors was performed remotely, which required a reliable and secure network to connect over the internet.

The physical setup between the feed frame and the turret of the tablet press uses a wear strip. The wear strip prevents the contact between moving parts and is subject to deterioration. Moreover, the turret assembly is supported by the main frame assembly, and regular operations necessitate rebalancing the inspections of these parts to prolong the life of the equipment and importantly ensure the functionality of the subsystems for the process. Wear in these parts eventually is manifested as powder leakage in the tablet press, as shown in Figure 16. While these faults can be identified by the vendor and experienced user of the tablet press, such leakage reduces the overall yield of the process. Such leakage can be detected using level sensors in the hopper or by monitoring the material balance across the equipment in real-time. The dashboard in Figure 6-16 shows the mass flow rates that are used as a trigger criterion in the testbed. Once the necessity of maintenance is established, spare parts, tools and maintenance procedures must be available to enable the maintenance activities.

Figure 6-16: Leakage arising from wear in the tablet press, with utilization of mass balance for condition monitoring

6.4 Concluding Remarks

OSD-CM processes enable the continuous flow and processing of material and information through the systematic integration of solids processing unit operations, supported by analytical systems, process knowledge, and automation methods. Some of the failure modes arising in these individual units during process operations of OSD-CM could result in unplanned downtime, and further impact product quality or process productivity. Mitigation of such disturbances necessitates continued system verification and the development and implementation of maintenance strategies for reliable operations. Moreover, maintenance considerations are crucial to manage process risks during the product's life cycle.

In this work, CBM is introduced in terms of its rationale for continued verification and sustainment for reliable operations. CBM is a mature maintenance management strategy, intended to proactively monitor and manage the conditions that may lead to failure or diminished functionality of the system, instead of strictly relying on time-based inspection and replacement of components or reacting to unplanned events. The data flow for CBM is comprised of three workflows for data sourcing, analysis for fault detection, and lastly, operations support. Notably,

developments in OSD-CM address multiple aspects of the CBM framework and thereby, facilitate proactive maintenance management. This work builds on these advances in RTPM for OSD-CM and emphasizes the system integration and maintenance aspects for sensor network robustness.

A systems architecture required for the CBM data flow is discussed, and its implementation in a testbed for OSD-CM is illustrated, along with discussing some potential fault scenarios of the infrastructure. The implementation leverages the advances in emerging technologies that are integral to the current wave of Industry 4.0 practices for manufacturing operations management. Ongoing research includes utilizing the infrastructure implemented in the testbed to address consideration of additional failure modes in the sensor network components and the corresponding methods for condition monitoring and subsequent maintenance. With the increase in implementation of continuous manufacturing, frameworks such as CBM, enabled by process knowledge and the availability of real-time data, can directly support continued verification, maintenance, and operational excellence. The proactive use of process data and modern maintenance practices can be effectively exploited in manufacturing operations in the pharmaceutical industry ranging from single unit operation to a series of physically integrated unit operations, whether batch, hybrid or continuous.

7 FUTURE DIRECTIONS

7.1 OSD-CM process development and implementation

The modernization of tablet manufacturing through continuous manufacturing requires the systems integration of numerous unit operations, sensing devices 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. Till late 2018, five drug products produced by early adopters of OSD-CM systems have received FDA approval. Yet, numerous challenges remain to be addressed in the implementation of individual subsystems, sensing methods and data architectures to realize all of the potential benefits of integrated manufacturing systems. Notably, utility of the system necessitates holistic considerations for numerous components such as (i) equipment, (ii) particulate processing, (iii) sensing, (iv) data analytics and automation, (v) information technology, (vi) human factors and (vii) maintenance, repair and support. Consideration for these components is essential for the realization of the potential benefits of integrated systems. It is recommended that each of these components be assessed on manufacturing readiness levels (Office of the Secretary of Defense Manufacturing Technology Program, 2018) so as to bridge the gaps from research to development to implementation for manufacturing.

This work attempted to address some gaps in process monitoring and systems integration for implementing OSD-CM processes. These involved demonstrating an x-ray-based mass flow sensor, investigating the roller compaction for integrated process operations, implementing data architectures for RTPM applications, and introducing condition-based maintenance as a strategy for continued verification of the integrated process. The pursuit of these objectives utilized the Purdue CP3 pilot-scale tablet manufacturing testbed; and resulted in infrastructure developments in the testbed towards achieving the continuous flow of material and data required for OSD-CM operations. In this subsection, opportunities in improving and advancing the outcomes from this work are further highlighted.

Chapter 3 discussed the assessment of the x-ray-based mass flow sensor. While this work demonstrated its utility in the testbed, the practical use of the sensor presented multiple challenges at the location envisioned due to its size. Moreover, the utility of process analyzers for use in the manufacturing process require connectors for both its physical setup, and its communications for utility in the integrated process. While an acrylic box was constructed for the x-ray to overcome the challenges in physical setup, the sensor software is designed for use as a standalone characterization system and presented challenges for data integration into the control system. In building the required data adapters for its use in the process and supporting its use in integrated process runs, it also came to light that the testbed lacked a robust data architecture for RTPM. As a result, further developments for its use in supervisory control was not pursued, and instead the work progressed towards considerations described in Chapters 5 and 6. Through recent advances in the testbed, the x-ray sensor can be investigated for its utility at the exit of the tablet press, as well as in the continuous wet granulation applications. Additional use of the sensor may require a physical rebuild of the device through collaboration with the vendor.

Chapter 4 discussed the technology transfer study for the integration of the roller compactor process into the continuous tableting line. The assessment enabled the demonstration of robust process monitoring systems discussed in (Moreno, 2019). However, the limitations observed in the existing equipment such as hopper design, equipment age, interfacing capabilities with sensors and upstream and downstream units challenged its utility in the continuous line. To this end, through collaborations with the equipment vendor a redesign of the system was pursed. The collaborations to redesign the equipment commenced in May 2018 and the updated unit was received in the testbed in August 2019. Improvements to the hopper design, sensing locations, and the physical interfaces to connect to the upstream and downstream unit operations do enable further end-to-end continuous manufacturing studies. A short study on assessment of the new equipment with the sensors implemented is recommended to be first pursued to evaluate the device level control systems. Additionally, the control system of the device requires integration into the testbed data infrastructure. Establishing this connection following the systems integration framework discussed in Chapters 5 and 6 is a suitable short project to learn the importance of data architectures required for supervisory control.

Chapter 5 discussed the implementation of QbC. A requirement to develop systematic data architectures and maintenance practices surfaced and led to the work discussed in Chapter 6. Notably, Chapter 6 addressed the individual components for maintenance management and emphasized a holistic systems architecture. While an infrastructure is implemented to support the operations management applications, there exists a need to investigate the analysis techniques, methods, and tools within the diagnosis, prognosis, and decision support systems. Furthermore, continuous powder flow and longer durations of equipment use require considerations for safety such as dust handling, equipment cleaning and validation, and subsystem verification. To this end, methods for condition monitoring of equipment and tactical decisions for proactive maintenance can be adopted from published works such as (Márquez, 2007; Moubray, 1999). Furthermore, considerations for probabilistic risk assessment and material tracking are essential to safeguard and track product quality. While methods for addressing these problem features exist, the sensing schemes in OSD-CM require further developments towards technology readiness in process operations. Importantly, the data architectures implemented in the testbed can be used for demonstration of such methods. Ongoing efforts in the testbed to expand the sensing scheme such as the assessment of mass flow rate sensors, Raman sensors and further considerations for equipment health monitoring devices such as for vibration monitoring could significantly advance the holistic maintenance management framework.

Knowledge management systems for capturing metadata information such as equipment parts, raw material properties, lab conditions, operators, cleaning procedures etc. in addition to the time-series data stand to benefit effective process development, troubleshooting, and importantly, predicting and preventing operational losses (Andrews and Nahas, 2018; Joglekar et al., 2017). Importantly, the FDA recently introduced the 'Knowledge-aided assessment & structured applications' initiative to enrich the effectiveness, efficiency, and consistency of regulatory quality oversight through lifecycle management of products and facilities, and information sharing in a standardized and structured format (Yu et al., 2019). Recognizing the need for knowledge management, this work briefly aimed to build a knowledge management system using KProMS with Dr. Girish Joglekar following works such as (Hailemariam and Venkatasubramanian, 2010b; Joglekar et al., 2014; Venkatasubramanian et al., 2006). However, the lack of a data infrastructure in the testbed for systematized implementation of knowledge management workflows motivated

this work to build such an infrastructure discussed in Chapter 6. The systems architecture implemented in the testbed now facilitates the further development of knowledge management systems.

Lastly, data architectures require customization for every process. Chapter 6 provides insights on integrating individual devices into the systems architecture. It is recommended that for the long-term use of the device in the testbed, the data standards be followed. A major requirement to rebuild the infrastructure was lack of standardization and protocols in the setup of the data architecture. This consequently also resulted in a cyberthreat to the lab. Hence, while process analyzers and equipment provide valuable insights for process engineering, research focused on implementation of RTPM requires some basic understanding of the data architectures and associated failure modes. It is hence also important to undergo a minimum training for the use of the automation systems before making changes in the testbed, in addition to the process equipment and instrumentation. Importantly, the tools, technologies and devices used in the testbed will keep evolving, and it is recommended to engage with the technology vendors to ensure intended use of the respective systems.

7.2 Continuous vs. batch: Leveraging digitalization for lean processes

Continuous manufacturing has been receiving increasing attention in the pharmaceutical industry driven by the expectation of achieving reduced operating and capital costs, improved product quality and increased reliability. While this mode of manufacture is new to the pharmaceutical industry, it is widely practiced in many industry sectors, such as refining and petrochemical, bulk chemical, food and minerals processing. It most commonly involves the processing of fluids, liquid or gases, although particulate and granular materials and suspensions are also handled. In these industries the continuous manufacturing plant or line is usually dedicated to a specific product and is typically operated without interruption around the clock with only infrequent shut-down to perform maintenance functions or in case of emergency. A continuous manufacturing line is normally designed for a nominal production rate and while that rate can be reduced within a limited range, typically further reductions lead to unsatisfactory product outputs or damage to equipment. Generally, continuous manufacturing facilities enjoy economies of scale, that is, the investment and operating cost per unit of production decrease as the plant design

capacity is increased. The incentives for continuous manufacturing in the pharmaceutical industry are not the same in all aspects as they may be for the other industry sectors and, thus, it is important to understand what the essential elements of the continuous manufacturing mode are, and which aspects are really introduced to adapt to the needs of a specific industry sector.

With the developments following QbD and PAT, the pharmaceutical discovery, development and manufacturing community continues to embrace digital technologies for product and process engineering, as well as operations management. Integrated continuous manufacturing systems provide a means to manufacture a high-quality drug product; however, the progress towards the digitalization of assets, process operations, and management are applicable to the optimal processing route required for the business case of the product under development. As shown in Figure 7-1, the availability and accessibility of process data enabling the necessitated process automation and operations management strategies are vital to produce the product, for which the process may or may not require a continuous flow of material.

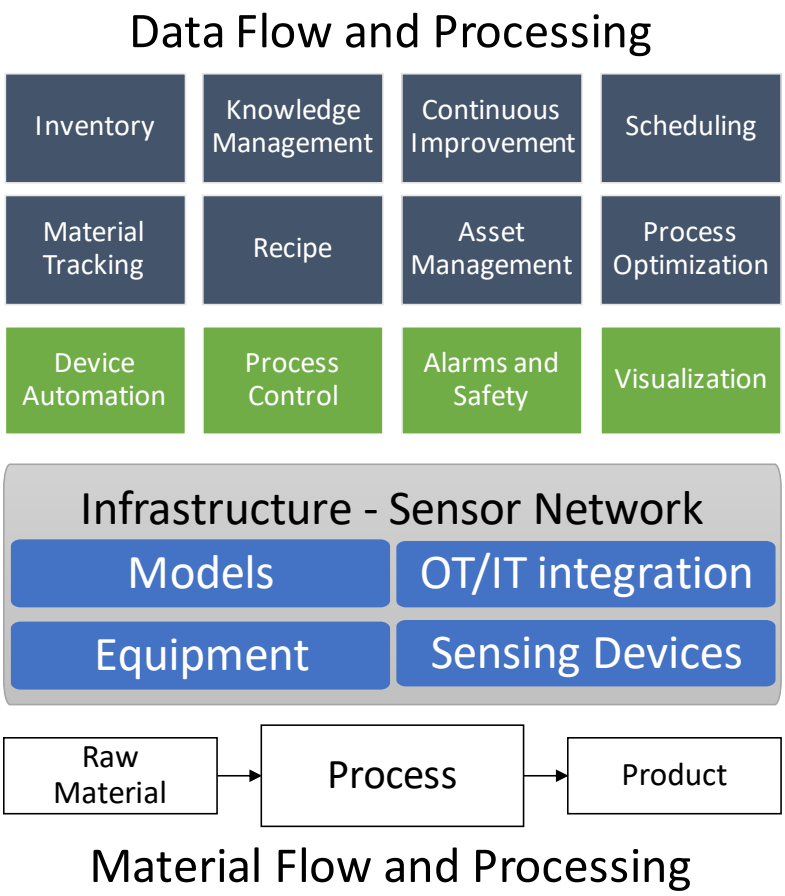


Figure 7-1: The infrastructure for the integration of operations and information technologies enables the continuous flow of material and data required for continuous process operations

Moreover, while innovator companies are selectively adopting continuous processes, the overwhelming majority of pharmaceutical plants employ batch operations. Hence, a challenge lies in enabling the adoption of continuous manufacturing and other advanced manufacturing concepts given the business constraints created by the huge sunk investment in existing batch facilities. Further, while modern process systems engineering tools for advanced manufacturing tools are now coming into prominence, they have not been adopted to any significant extent in pharmaceutical batch manufacturing, especially in the generic sector. A low hanging fruit for modernizing existing batch operations without the penalty of replacing process equipment is to retrofit these facilities with sensors for real-time process monitoring, models for dynamic profile optimization, process controls which ensure that consistent end-points are achieved for each operation and scheduling tools which facilitate effective campaign and change-over management.

Such retrofits have potential to improve product quality, increase process reliability and reduce the cost of manufacture. Depending on case-specifics, this may allow the process to exceed or come close to the benefits which could be achieved by the replacement with a new fully continuous process, while in others it will only bring part of the benefits. Hence, while the advances in data management and analysis is enabling operations management innovations, it is vital to analyze the unit operations for the material processing as a "lean" system comprising of a spectrum of processing alternatives from batch to hybrid batch/continuous to fully continuous based on case-specific technical constraints imposed by material properties, kinetics, and transport phenomena, and processing conditions as well as economics and scale.

APPENDIX A: NETWORK ARCHITECTURES

The process automation systems in the testbed utilize hardware such as programmable logic controllers (PLCs) embedded in process equipment, personal computer controllers to communicate and operate PAT tools, distributed control systems for the integration of the unit operations, and data historians required for holistic process operations management. The reader is referred to (Nixon, 2012; Seborg et al., 2010) for an introductory overview of digital systems for process control.

The network architecture illustrating the configuration of the communication links and the workstations used for the development of a modular and hierarchical network architecture in the testbed discussed in this thesis is presented in Figure A-1. At the process level, the equipment PLCs and personal computers connected to the PAT Tools are configured using suitable communication protocols in the Emerson DeltaV 13.3 distributed control system. The DeltaV controller, DeltaV workstations and the I/O cards installed on the DeltaV base plate form the 'DeltaV Area Control Network.' The communication between the DeltaV controller and the process equipment is established using input-output cards, such as Profibus and EtherNet I/P. For example, as shown in the figure, the Profibus network comprises the three Schenck feeders and the blender, the VIM network comprises the roller compactor, and the VIM2 network comprises the tablet press and the K-Tron feeder. For devices whose communications are not supported in the existing DeltaV setup, such as the personal computer controllers for the PAT tools, additional software tools such as MATLAB, KepServerEx and LinkMaster are configured as suitable data adapters. These data adapters facilitate establishing the required connectivity with the personal computers using the OPC DA 2 or UA communication protocol with the DeltaV Application Stations. The network enabling the OPC communication is configured and illustrated in the figure as the 'DeltaV 2.5 Network'. Such layering of networks is known as a De-Militarized Zone (DMZ) network. These are implemented following cybersecurity guidelines provided in the DeltaV Security Manual and with elementary know-how of IT networking, which can be referred in YouTube courses such as (Eli the Computer Guy, 2013).

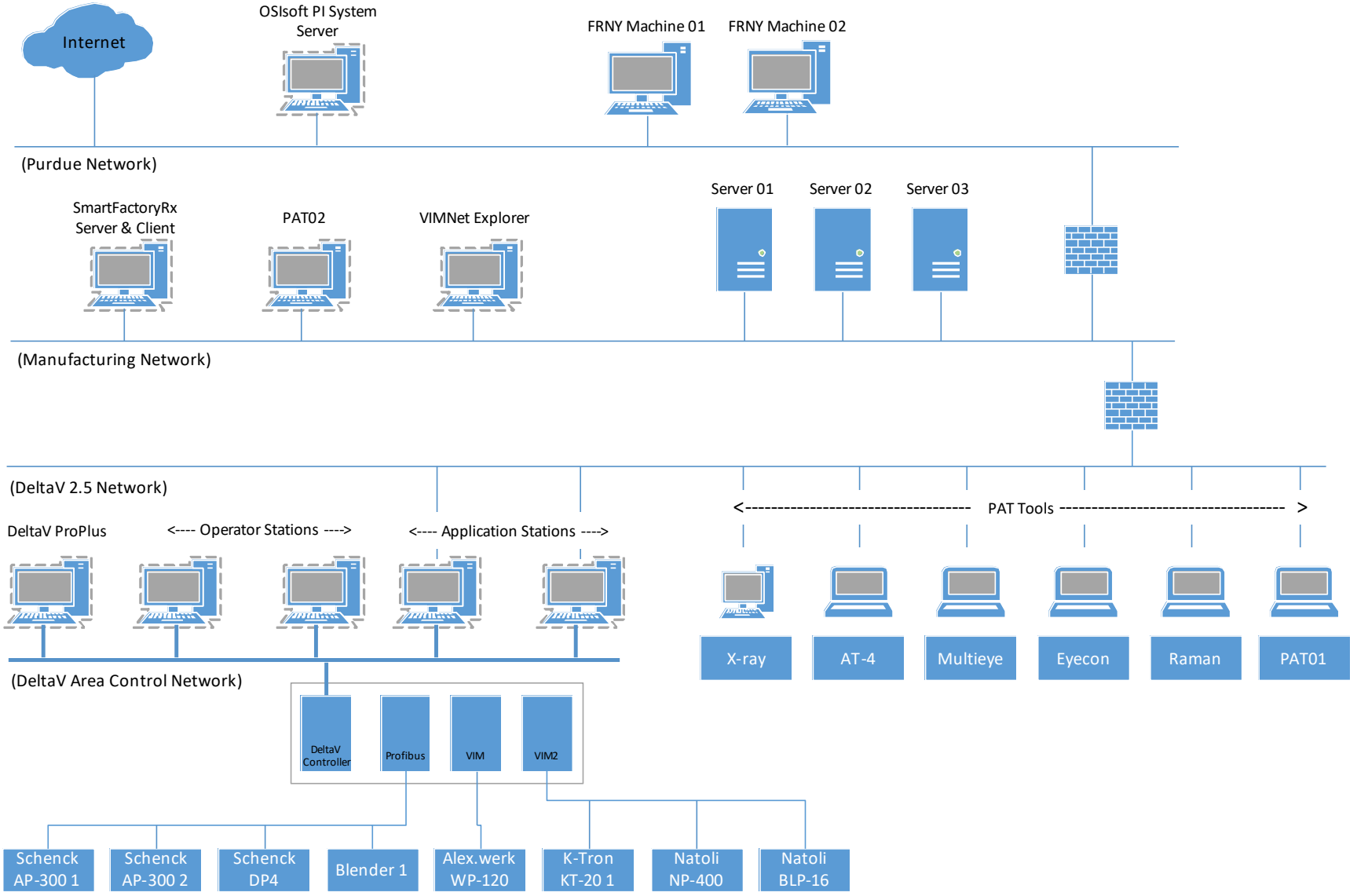


Figure A-1: Network Architecture showing the functionality of the workstations in the testbed

The DeltaV ProPlus is the main DeltaV workstation used for engineering the control system. These include configuring the I/Os, control strategies, operator securities, human-machine interfaces, etc. The DeltaV Application Station is typically the gateway to external communications for the implementation of 3rd party tools and also hosts the DeltaV historian. The DeltaV OPC DA 2 server installation on this workstation enables the read and write access to process data and requires configurations of Microsoft security protocol known as distributed component object model (DCOM). Data from the PAT Tools are communicated through this OPC server for use in the implementation of plant-wide control strategies. The networks are layered using routers to enable the machine-machine communications required for plant-wide control in the manufacturing facility. Such layering also facilitates accessing software licenses for tools such as MATLAB hosted in Purdue's Network without compromising the Windows Securities and DCOM settings required in the implementation of OPC DA communications. Routers are set up between DeltaV 2.5 Network, the Manufacturing Network, and Purdue Network. Further, a workstation with an installation of VIMNet explorer, a tool for configuring the VIM and VIM2 I/O cards, is located on Manufacturing Network. The VIMNet Explorer is also connected to the respective VIM networks to facilitate the configurations.

The DeltaV workstations are set up as virtual machines using VMWare ESXi Type 1 hypervisor. The VMWare ESXi server stations are connected to the 'Manufacturing Network'. The virtual machines are accessed using a vSphere client installed in a computer that is also connected to the same network (Manufacturing Network). Thin client machines are further setup in the Manufacturing Network to enable access to the workstations using the remote desktop protocol. In the current testbed setup, engineering the I/Os, control strategies, deployment, and maintenance of the systems requires access to the relevant hardware, physically located in the testbed facility. The integration of the process equipment, DeltaV I/O and controller, DeltaV workstations, the PAT tools, and their corresponding personal computers and the networking components such as switches, routers, and thin clients together form the 'Process Level Control Room' for the implementation of ISA-95 Levels 0-2 in the tablet manufacturing testbed.

As discussed in Chapter 6, holistic manufacturing operations management also requires the implementation of ISA-95 levels 3 and 4 functions. In the ongoing developments towards

achieving Industry 4.0 functionalities, the accessibility to real-time process data enables the effective implementation and management of Levels 3 and 4 services. To this end, infrastructures such as the OSIsoft PI System and the Applied Materials SmartFactoryRx are configured as representative tools for the corresponding functionalities at the 'Facility Level Control Room.' This is further illustrated in Section 6.3.3. The workstation for the OSIsoft PI System is deployed as a virtual machine in Purdue's ITaP Network as an illustration of a cloud-based workstation. This virtual machine is managed by Purdue's IT resources and is built using Microsoft Hyper V. The PI System is managed by the automation administrator of the testbed and is accessible through Purdue's network using Purdue and Windows credentials. The workstation for the SmartFactoryRx is implemented as a virtual machine using VMWare ESXi and is managed by the testbed admin, similar to the ones hosting the DeltaV workstations.

While Figure A-1 presented the network architecture illustrating the functionality of the workstations and the devices, Figure A-2 shows the hardware infrastructure diagram of the automation infrastructure managed in the testbed facility. These represent the three lab managed servers along with the respective virtual machines hosted in them, the DeltaV controller and I/O cards, and the corresponding the network connections for implementing the numerous local area networks resulting in the integrated system. Notably, a managed switch is used for the configuration of virtual LANs, thereby enabling the use of a single device for managing multiple networks. The IP addresses are hidden in the image for security purposes of the testbed infrastructure. The networks are connected using a pfsense router, also installed as a virtual machine in the lab servers.

It is worth noting here that the DeltaV infrastructure is localized to the tablet manufacturing testbed assets and relies on wired and bus-based communications with the assets. However, the ongoing increase in the use of software-based communications such as OPC using appropriate networking aids and tools such as KepServerEx enables the implementation of OSIsoft PI System and Applied Materials SmartFactoryRx, facilitating the development of a facility-level control room to manage intelligent devices and implement end-to-end control strategies effectively.

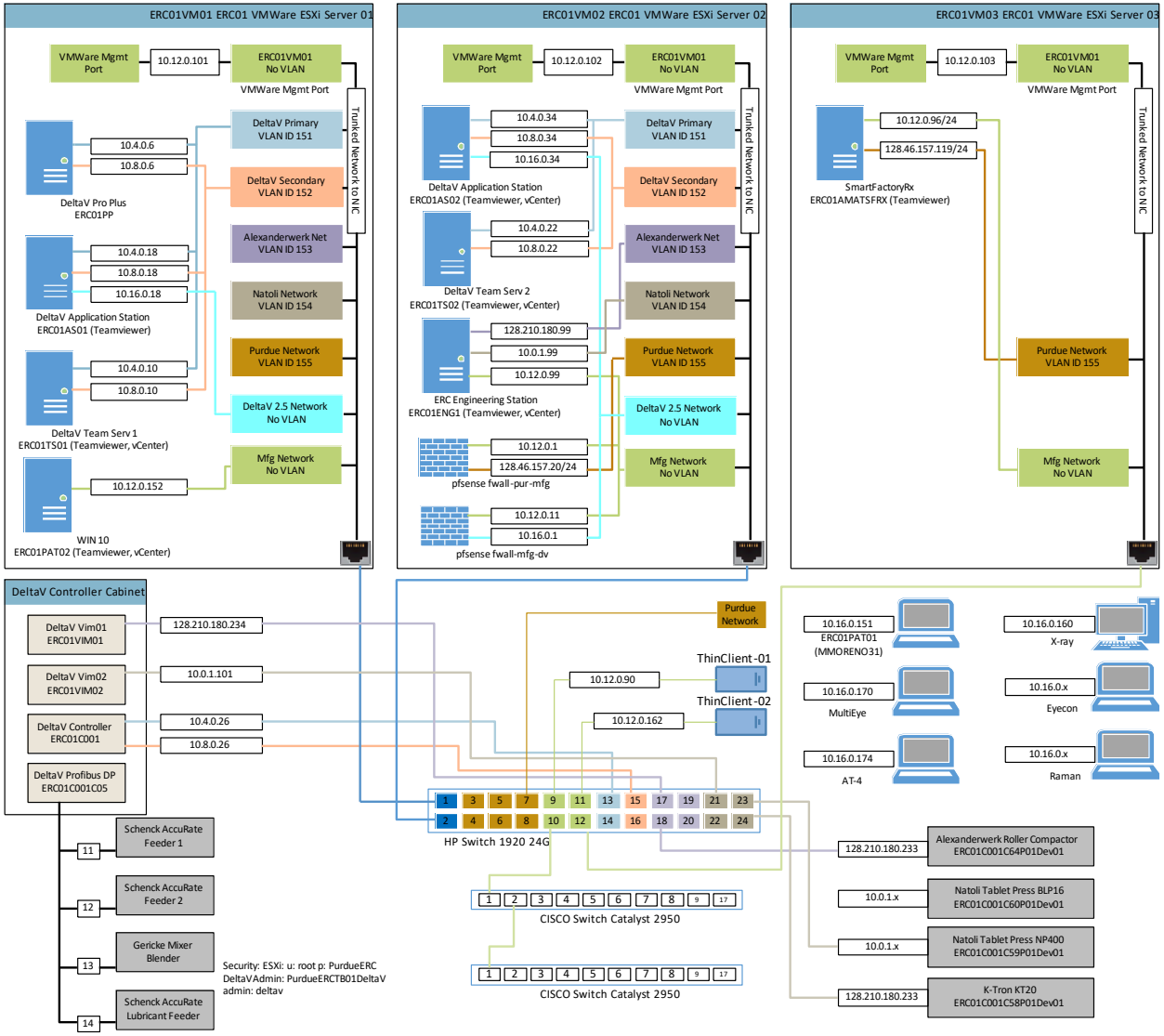


Figure A-2: Hardware configuration of the servers, equipment, PAT Tools and additional systems managed in the testbed

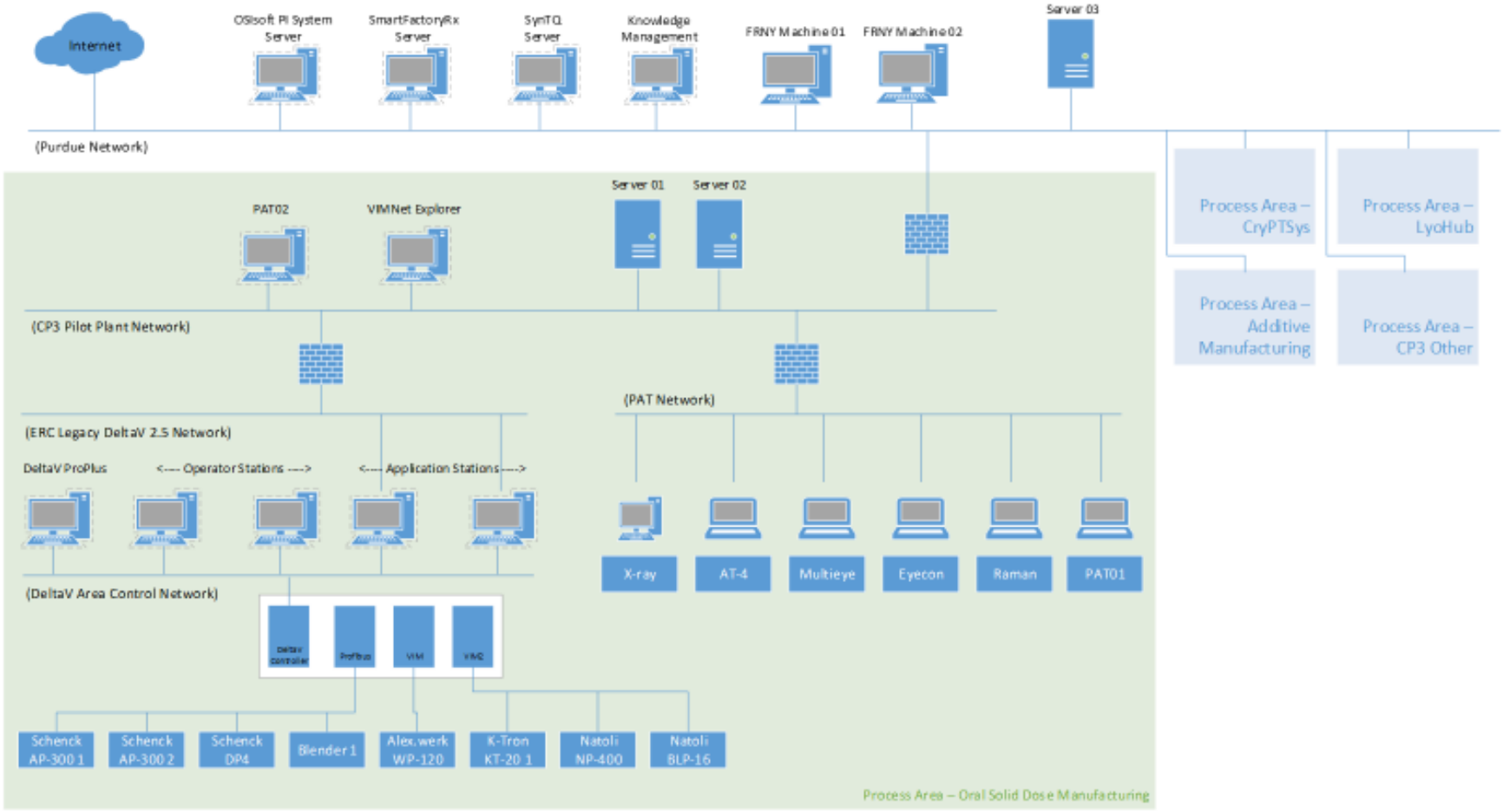


Figure A-3: Suggested reorganization and expansion of the networks to accommodate additional labs under a common digital infrastructure

Figure A-3 presents a proposed change to the architecture as part of the ongoing scaling efforts of the digital infrastructure to support additional pharmaceutical manufacturing processes. While the OSIsoft PI System was already installed for immediate deployment to other research labs, the network configurations of the SmartFactoryRx workstations must be moved from the tablet manufacturing testbed to the enterprise level. Further, additional tools such as SynTQ for PAT data management, gFormulate for implementation of digital twins, and knowledge management systems may be required as part of the standard digital layer supporting operations management research in multiple processes, dispersed geographically across the Purdue campus. The IT architectures developed for the tableting testbed can be replicated in the additional facilities towards the overall goals of standardizing the operations management layer for all of the advanced pharmaceutical manufacturing research labs at Purdue.

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VITA

Sudarshan Ganesh grew up in India in the cities of Mumbai and Pune. He received his B.S. in Chemical Engineering from Institute of Chemical Technology (formerly UDCT/UICT), Mumbai. He joined the PhD program in the School of Chemical Engineering at Purdue in Fall 2014. His PhD was co-advised by Prof Gintaras V. Rex Reklaitis and Prof. Zoltan Nagy.

Sudarshan's graduate work focused on the aspects of solids processing, process monitoring, systems integration and maintenance management for advanced pharmaceutical manufacturing. He had the opportunity to mentor ten undergraduate research assistants in support of his work. He was awarded the Teaching Academy Graduate Teaching Award in 2017, by Center of Institutional Excellence at Purdue University for his teaching assistantship in the Senior CHE Process Control class. He participated as the Purdue representative in the Continuous Manufacturing Community of Practice Subcommittee in ISPE, co-authored over 8 articles, presented at numerous international conferences, represented the CHE Graduate Student Organization in Gradate Committees and organized alumni gatherings. He further got his first opportunity to serve as a co-chair during AIChE Annual Meeting in 2019 through the Next-Gen Manufacturing Topical Conference and PD2M Forum. He was invited to present his contributions to the field at conferences such as the 32nd International Forum for Process Analysis and Control (IFPAC) in Bethesda, 3rd International Symposium for Continuous Manufacturing of Pharmaceuticals in London, and 2019 OSIsoft Users Conference in San Francisco. He has received awards for presenting his work at meetings such as the 8th World Congress on Particle Technology (Orlando, 2018), 33rd IFPAC (Bethesda, 2019) and ASTM E55/LyoHub Meeting (West Lafayette, 2018). He was further selected in the 2018 Focused-on Industry Recruitment of Scientific Talent Workshop and Conference organized by the Proctor and Gamble Company in Cincinnati.

To continue his professional goals towards developing enabling technologies for accessible healthcare and education, Sudarshan accepted a position with Applied Materials, Inc. in Santa Clara, California, and is expected to begin in February 2020. One could get in touch with him at sudarshan.ganesh@gmail.com or through LinkedIn.

PUBLICATIONS

Journal Publications

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Conference Proceedings

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